

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-602/S-010

Trade Name: Velcade

Generic Name: bortezomib

Sponsor: Millenium Pharmaceuticals, Inc.

Approval Date: December 8, 2006

Indications: For injection for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

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APPLICATION NUMBER:

21-602 / S-010

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APPLICATION NUMBER:

21-602 / S-010

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-602/S-010

Millennium Pharmaceuticals, Inc.
Attention: Tanya Lewis
Director Regulatory Affairs
40 Landsdowne Street
Cambridge, Massachusetts 02139

Dear Ms. Lewis:

Please refer to your supplemental new drug application dated June 8, 2006, received June 9th, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Velcade (bortezomib) for Injection 3.5 mg.

We acknowledge receipt of your submissions dated June 16, July 27, August 30, September 21 and 28, October 6, 20, 24 and 25 (2), November 1, 2 and 23, 2006.

This supplemental new drug application provides for the use of Velcade (bortezomib) for injection for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert).

Please submit an electronic version of the FPL. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-602/S-010.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirements for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising and Communications
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Tammie Brent, Regulatory Project Manager, at (301) 796-1409.

Sincerely,

{See appended electronic signature page}

Robert Justice, MD
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosures: Package Insert
Patient Package Insert

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ramzi Dagher
12/8/2006 12:15:42 PM

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:

21-602 / S-010

LABELING

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

2 **PRESCRIBING INFORMATION**

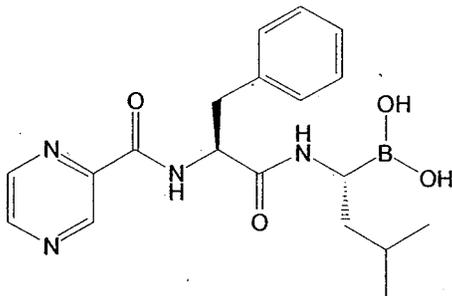
3 **DESCRIPTION**

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

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

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

13 Bortezomib has the following chemical structure:



14

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

18 **CLINICAL PHARMACOLOGY**

19 ***Mechanism of Action***

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

29 ***Pharmacokinetics***

30 Following intravenous administration of 1.0 mg/m² and 1.3 mg/m² doses to 24 patients with
31 multiple myeloma (n=12, per each dose level), the mean maximum plasma concentrations of
32 bortezomib (C_{max}) after the first dose (Day 1) were 57 and 112 ng/mL, respectively. In

33 subsequent doses, when administered twice weekly, the mean maximum observed plasma
34 concentrations ranged from 67 to 106 ng/mL for the 1.0 mg/m² dose and 89 to 120 ng/mL for the
35 1.3 mg/m² dose. The mean elimination half-life of bortezomib upon multiple dosing ranged
36 from 40 to 193 hours after the 1.0 mg² dose and 76 to 108 hours after the 1.3mg/m² dose. The
37 mean total body clearances was 102 and 112 L/h following the first dose for doses of 1.0 mg/m²
38 and 1.3 mg/m², respectively, and ranged from 15 to 32 L/h following subsequent doses for doses
39 of 1.0 and 1.3 mg/m², respectively.

40 ***Distribution***

41 The mean distribution volume of bortezomib ranged from approximately 498 to 1884 L/m²
42 following single- or repeat-dose administration of 1.0mg/m² or 1.3mg/m² to patients with
43 multiple myeloma. This suggests bortezomib distributes widely to peripheral tissues. The
44 binding of bortezomib to human plasma proteins averaged 83% over the concentration range of
45 100 to 1000 ng/mL.

46 ***Metabolism***

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

55 ***Elimination***

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

57 ***Special Populations***

58 ***Age:*** Analyses of data after the first dose of Cycle 1 (Day 1) in 39 multiple myeloma patients
59 who had received intravenous doses of 1.0 mg/m² and 1.3 mg/m² showed that both dose-
60 normalized AUC and C_{max} tend to be less in younger patients. Patients < 65 years of age (n=26)
61 had about 25% lower mean dose-normalized AUC and C_{max} than those ≥ 65 years of age (n=13).

62 ***Gender:*** Mean dose-normalized AUC and C_{max} values were comparable between male (n=22)
63 and female (n=17) patients after the first dose of Cycle 1 for the 1.0 and 1.3 mg/m² doses

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

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

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

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

71 ***Drug Interactions***

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

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

75 Bortezomib is a poor inhibitor of human liver microsome cytochrome P450 1A2, 2C9, 2D6, and
76 3A4, with IC₅₀ values of >30 μM (>11.5 μg/mL). Bortezomib may inhibit 2C19 activity (IC₅₀ =
77 18 μM, 6.9 μg/mL) and increase exposure to drugs that are substrates for this enzyme.

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

80 ***Pharmacodynamics***

81 Following twice weekly administration of 1.0 mg/m² and 1.3 mg/m² bortezomib doses (n=12 per
82 each dose level), the maximum inhibition of 20S proteasome activity (relative to baseline) in
83 whole blood was observed 5 minutes after drug administration. Comparable maximum inhibition
84 of 20S proteasome activity was observed between 1.0 and 1.3 mg/m² doses. Maximal inhibition
85 ranged from 70% to 84% and from 73% to 83% for the 1.0 mg/m² and 1.3 mg/m² dose regimens,
86 respectively.

87 **CLINICAL STUDIES**

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

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

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

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

101
102

Table 1: 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%

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

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

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

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

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

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

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

Efficacy Endpoint	All Patients		1 Prior Line of Therapy		> 1 Prior Line of Therapy	
	VELCADE	Dex	VELCADE	Dex	VELCADE	Dex
	n=333	n=336	n=132	n=119	n=200	n=217
Time to Progression						
Events n (%)	147 (44)	196 (58)	55 (42)	64 (54)	92 (46)	132 (61)
Median ^a (95% CI)	6.2 mo (4.9, 6.9)	3.5 mo (2.9, 4.2)	7.0 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 ^b (95% CI)	0.55 (0.44, 0.69)		0.55 (0.38, 0.81)		0.54 (0.41, 0.72)	
p-value ^c	<0.0001		0.0019		<0.0001	
Overall Survival						
Events (deaths) n (%)	51 (15)	84 (25)	12 (9)	24 (20)	39 (20)	60 (28)
Hazard ratio ^b (95% CI)	0.57 (0.40, 0.81)		0.39 (0.19, 0.81)		0.65 (0.43, 0.97)	
p-value ^{c,d}	<0.05		<0.05		<0.05	
Response Rate						
Population ^e n = 627	n=315	n=312	n=128	n=110	n=187	n=202
CR ^f n (%)	20 (6)	2 (<1)	8 (6)	2 (2)	12 (6)	0 (0)
PR ^f n (%)	101 (32)	54 (17)	49 (38)	27 (25)	52 (28)	27 (13)
nCR ^{f,g} n (%)	21 (7)	3 (<1)	8 (6)	2 (2)	13 (7)	1 (<1)
CR + PR ^f n (%)	121 (38)	56 (18)	57 (45)	29 (26)	64 (34)	27 (13)
p-value ^h	<0.0001		0.0035		<0.0001	
Median Response Duration						
CR ^f	9.9 mo	NE ⁱ	9.9 mo	NE	6.3 mo	NA ^j
nCR ^f	11.5 mo	9.2 mo	NE	NE	11.5 mo	9.2 mo
CR + PR ^f	8.0 mo	5.6 mo	8.1 mo	6.2 mo	7.8 mo	4.1 mo

137

^a Kaplan-Meier estimate.

138

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

139

140

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

141

^d Precise p-value cannot be rendered.

142

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

143

144

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

145

146

^g In 2 patients, the IF was unknown.

147

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

148

149

ⁱ Not Estimable.

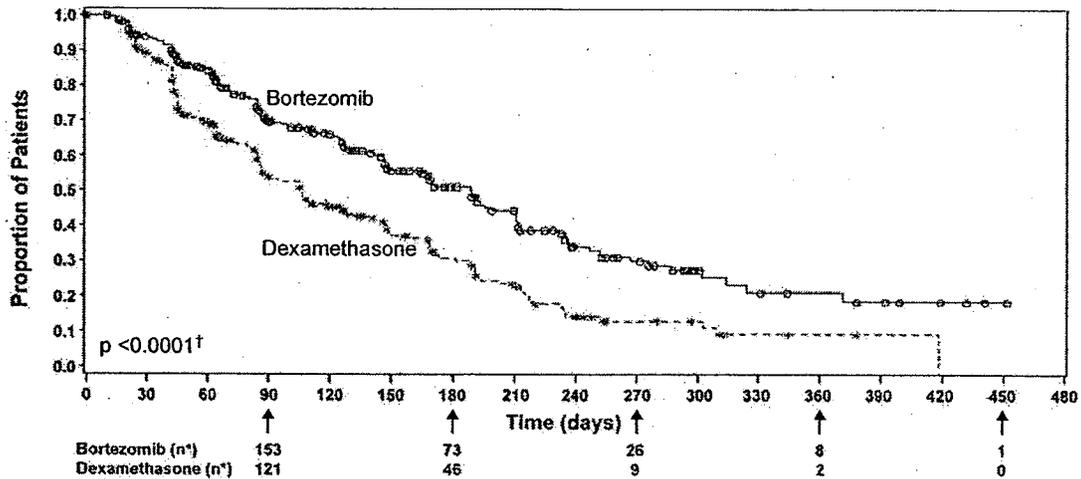
150

^j Not Applicable, no patients in category.

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

152
153

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



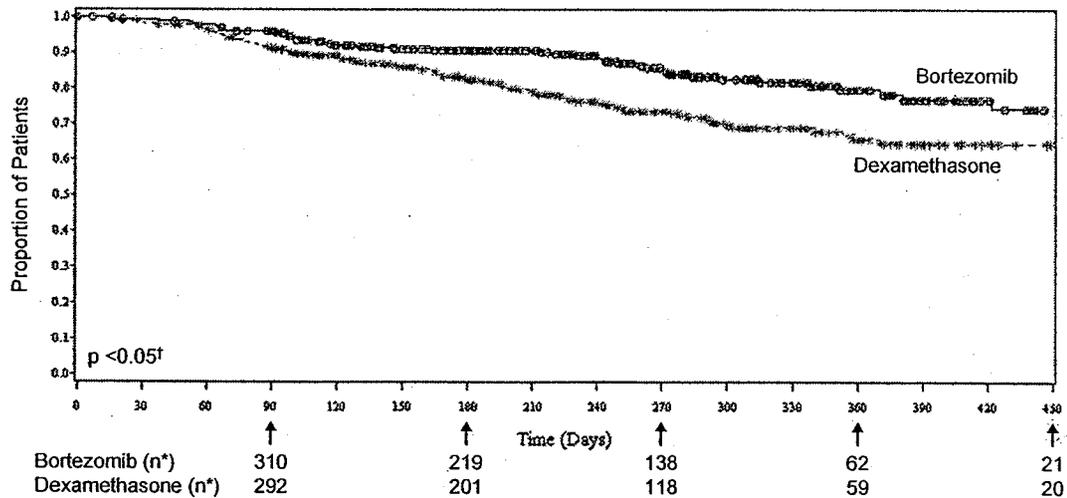
* Patients remaining after the indicated timepoint
† p-value from log-rank test

154

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

157
158

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



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

159

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

162 months) for the 56 responders on the dexamethasone arm. The response rate was significantly
 163 higher on the VELCADE arm regardless of β_2 -microglobulin levels at baseline.

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

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

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

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

Patient Characteristics	N = 202
Median age in years (range)	59 (34, 84)
Gender: Male/female	60% / 40%
Race: Caucasian/black/other	81% / 10% / 8%
Karnofsky Performance Status score ≤ 70	20%
Hemoglobin < 100 g/L	44%
Platelet count $< 75 \times 10^9$ /L	21%
Disease Characteristics	
Type of myeloma (%): IgG/IgA/Light chain	60% / 24% / 14%
Median β_2 -microglobulin (mg/L)	3.5
Median creatinine clearance (mL/min)	73.9
Abnormal cytogenetics	35%
Chromosome 13 deletion	15%
Median Duration of Multiple Myeloma Since Diagnosis in Years	4.0
Previous Therapy	
Any prior steroids, e.g., dexamethasone, VAD	99%
Any prior alkylating agents, e.g., MP, VBMCP	92%
Any prior anthracyclines, e.g., VAD, mitoxantrone	81%
Any prior thalidomide therapy	83%
Received at least 2 of the above	98%
Received at least 3 of the above	92%
Received all 4 of the above	66%
Any prior stem cell transplant/other high-dose therapy	64%
Prior experimental or other types of therapy	44%

176 * Based on number of patients with baseline data available

177 Responses to VELCADE alone are shown in Table 4. Response rates to VELCADE alone were
 178 determined by an independent review committee (IRC) based on EBMT criteria.¹ Response
 179 rates using the Southwest Oncology Group (SWOG) criteria² are also shown. SWOG response
 180 required a $\geq 75\%$ reduction in serum myeloma protein and/or $\geq 90\%$ urine protein. A total of 188
 181 patients were evaluable for response; 9 patients with nonmeasurable disease could not be

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

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

Response Analyses (VELCADE monotherapy) N = 188	N (%)	(95% CI)
Overall Response Rate (EBMT) (CR + PR)	52 (28%)	(21, 35)
Complete Response (CR)	5 (3%)	(1, 6)
Partial Response (PR)	47 (25%)	(19, 32)
Clinical Remission (SWOG) ^a	33 (18%)	(12, 24)
Kaplan-Meier Estimated Median Duration of Response (95% CI)	385 Days	(245, 538)

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

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

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

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

197 An open-label, multicenter study randomized 54 patients with multiple myeloma who had
 198 progressed or relapsed on or after front-line therapy to receive VELCADE 1.0 mg/m² or
 199 1.3 mg/m² IV bolus twice weekly for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-day rest
 200 period (Days 12 to 21). The median duration of time between diagnosis of multiple myeloma
 201 and first dose of VELCADE on this trial was 2.0 years, and patients had received a median of 1
 202 prior line of treatment (median of 3 prior therapies). A single complete response was seen at
 203 each dose. The overall response rates (CR + PR) were 30% (8/27) at 1.0 mg/m² and 38% (10/26)
 204 at 1.3 mg/m².

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

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

216 ***A Phase 2 Single-arm Clinical Study in Relapsed Mantle Cell Lymphoma After Prior therapy***
 217 The safety and efficacy of VELCADE in relapsed or refractory mantle cell lymphoma were
 218 evaluated in an open-label, single-arm, multicenter study of 155 patients with progressive disease
 219 who had received at least 1 prior therapy. The median age of the patients was 65 years (42, 89),
 220 81% were male, and 92% were caucasian. Of the total, 75% had one or more extra-nodal sites of
 221 disease, and 77% were stage 4. In 91% of the patients, prior therapy included all of the
 222 following: an anthracycline or mitoxantrone, cyclophosphamide, and rituximab. A total of thirty
 223 seven percent (37%) of patients were refractory to their last prior therapy. An IV bolus injection
 224 of VELCADE 1.3 mg/m²/dose was administered twice weekly for 2 weeks on Days 1, 4, 8, and
 225 11 followed by a 10-day rest period (Days 12 to 21) for a maximum of 17 treatment cycles. The
 226 study employed dose modifications for toxicity (see **DOSAGE AND ADMINISTRATION**).

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

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

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)

233 **INDICATIONS AND USAGE**

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

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

238 **CONTRAINDICATIONS**

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

241 **WARNINGS**

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

244 **Pregnancy Category D**

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

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

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

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

259 **PRECAUTIONS**

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

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

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

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

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

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

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

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

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

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

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

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

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

Pretreatment Platelet Count*	Number of Patients (N=331)**	Number (%) of Patients with Platelet Count <10,000/μL	Number (%) of Patients with Platelet Count 10,000-25,000/μL
$\geq 75,000/\mu\text{L}$	309	8 (3%)	36 (12%)
$\geq 50,000/\mu\text{L}$ - $<75,000/\mu\text{L}$	14	2 (14%)	11 (79%)
$\geq 10,000/\mu\text{L}$ - $<50,000/\mu\text{L}$	7	1 (14%)	5 (71%)

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

331 ** Data were missing at baseline for 1 patient

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

336 **Hepatic Events**

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

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

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

349 **Animal Toxicity Findings**

350 **Cardiovascular Toxicity**

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

357 **Chronic Administration**

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

364 ***Information for Patients***

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

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

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

374 ***Drug Interactions***

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

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

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

385 ***Drug Laboratory Test Interactions***

386 None known.

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

388 Carcinogenicity studies have not been conducted with bortezomib.

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

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

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

399 ***Pregnancy***

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

401 ***Nursing Mothers***

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

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

406 *Pediatric Use*

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

408 *Geriatric Use*

409 Of the 669 patients enrolled in the phase 3 multiple myeloma study, 245 (37%) were 65 years of
410 age or older: 125 (38%) on the VELCADE arm and 120 (36%) on dexamethasone arm. Median
411 time to progression and median duration of response for patients ≥ 65 were longer on VELCADE
412 compared to dexamethasone [5.5 mo versus 4.3 mo, and 8.0 mo versus 4.9 mo, respectively].
413 On the VELCADE arm, 40% (n=46) of evaluable patients aged ≥ 65 experienced response
414 (CR+PR) versus 18% (n=21) on the dexamethasone arm. The incidence of Grade 3 and 4 events
415 was 64%, 78% and 75% for VELCADE patients ≤ 50 , 51-64 and ≥ 65 years old, respectively (see
416 **CLINICAL STUDIES**).

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

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

423 **ADVERSE REACTIONS**

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

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

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

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

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

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

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

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

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

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Table 7: Most Commonly Reported Adverse Events (≥10% in VELCADE arm), with Grades 3 and 4 Intensity in the Phase 3 Multiple Myeloma Study (N=663)

Adverse Event	Treatment Group					
	VELCADE (n=331) [n (%)]			Dexamethasone (n=332) [n (%)]		
	All Events	Grade 3 Events	Grade 4 Events	All Events	Grade 3 Events	Grade 4 Events
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

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

466 ***The Phase 2 Open-Label Extension Study in Relapsed Multiple Myeloma***

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

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

470 Safety data from phase 2 and 3 studies of VELCADE 1.3 mg/m²/dose twice weekly for 2 weeks
471 followed by a 10-day rest period in 1163 patients with multiple myeloma (N=1008) and mantle
472 cell lymphoma (N=155) were integrated and tabulated. In these studies, the safety profile of
473 VELCADE was similar in patients with multiple myeloma and mantle cell lymphoma.

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

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

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

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

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

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

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

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Table 8: Most Commonly Reported ($\geq 10\%$ 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

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

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

505 ***Gastrointestinal Events***

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

513 ***Thrombocytopenia***

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

523 ***Peripheral Neuropathy***

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

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

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

536 ***Hypotension***

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

545 ***Neutropenia***

546 Neutrophil counts decreased during the VELCADE dosing period (days 1 to 11) and returned
547 toward baseline during the 10-day rest period during each treatment cycle. Overall, neutropenia
548 occurred in 17% of patients and was Grade 3 in 9% of patients and ≥Grade 4 in 3%.
549 Neutropenia was reported as a serious event in <1% of patients and <1% of patients discontinued
550 due to neutropenia. The incidence of neutropenia was higher in patients with multiple myeloma
551 (18%) compared to patients with mantle cell lymphoma (6%). The incidence of ≥Grade 3
552 neutropenia also was higher in patients with multiple myeloma (14%) compared to patients with
553 mantle cell lymphoma (4%) (see PRECAUTIONS).

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

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

559 ***Pyrexia***

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

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

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

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

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

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

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

- 587 ***Ear and labyrinth disorders:*** Hearing impaired, vertigo
- 588 ***Eye disorders:*** Diplopia and blurred vision, conjunctival infection, irritation
- 589 ***Gastrointestinal disorders:*** Ascites, dysphagia, fecal impaction, gastroenteritis, gastritis
- 590 hemorrhagic, hematemesis, hemorrhagic duodenitis, ileus paralytic, large intestinal obstruction,
- 591 paralytic intestinal obstruction, peritonitis, small intestinal obstruction, large intestinal
- 592 perforation, stomatitis, melena, pancreatitis acute, oral mucosal petechiae, gastroesophageal
- 593 reflux
- 594 ***General disorders and administration site conditions:*** Injection site erythema, neuralgia,
- 595 injection site pain, irritation, phlebitis
- 596 ***Hepatobiliary disorders:*** Cholestasis, hepatic hemorrhage, hyperbilirubinemia, portal vein
- 597 thrombosis, hepatitis, liver failure
- 598 ***Immune system disorders:*** Anaphylactic reaction, drug hypersensitivity, immune complex
- 599 mediated hypersensitivity, angioedema, laryngeal edema
- 600 ***Infections and infestations:*** Aspergillosis, bacteremia, urinary tract infection, herpes viral
- 601 infection, listeriosis, septic shock, toxoplasmosis, oral candidiasis, sinusitis, catheter related
- 602 infection
- 603 ***Injury, poisoning and procedural complications:*** Catheter related complication, skeletal
- 604 fracture, subdural hematoma
- 605 ***Metabolism and nutrition disorders:*** Hypocalcemia, hyperuricemia, hypokalemia,
- 606 hyperkalemia, hyponatremia, hypernatremia
- 607 ***Nervous system disorders:*** Ataxia, coma, dysarthria, dysautonomia, encephalopathy, cranial
- 608 palsy, grand mal convulsion, hemorrhagic stroke, motor dysfunction, spinal cord compression,
- 609 paralysis, postherpetic neuralgia, transient ischemic attack, reversible posterior
- 610 leukoencephalopathy syndrome
- 611 ***Psychiatric disorders:*** Agitation, confusion, mental status change, psychotic disorder, suicidal
- 612 ideation
- 613 ***Renal and urinary disorders:*** Calculus renal, bilateral hydronephrosis, bladder spasm,
- 614 hematuria, hemorrhagic cystitis, urinary incontinence, urinary retention, renal failure (acute and
- 615 chronic), glomerular nephritis proliferative
- 616 ***Respiratory, thoracic and mediastinal disorders:*** Acute respiratory distress syndrome,
- 617 aspiration pneumonia, atelectasis, chronic obstructive airways disease exacerbated, dysphagia,
- 618 dyspnea, dyspnea exertional, epistaxis, hemoptysis, hypoxia, lung infiltration, pleural effusion,
- 619 pneumonitis, respiratory distress, pulmonary hypertension
- 620 ***Skin and subcutaneous tissue disorders:*** Urticaria, face edema, rash (which may be pruritic),
- 621 leukocytoclastic vasculitis
- 622 ***Vascular disorders:*** Cerebrovascular accident, cerebral hemorrhage, deep venous thrombosis,
- 623 peripheral embolism, pulmonary embolism, pulmonary hypertension
- 624 ***Post-Marketing Experience***
- 625 Clinically significant adverse events are listed here if they have been reported during post-
- 626 approval use of VELCADE and either they have not been reported in clinical trials, or they have

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

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

632 OVERDOSAGE

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

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

646 DOSAGE AND ADMINISTRATION

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

654 *Dose Modification and Re-initiation of Therapy*

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

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

664
665

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

Severity of Peripheral Neuropathy Signs and Symptoms	Modification of Dose and Regimen
Grade 1 (paresthesias, weakness and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce VELCADE to 1.0 mg/m 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

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

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

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

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

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

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

687 **HOW SUPPLIED**

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

690 NDC 63020-049-01

691 3.5 mg single dose vial

692 **STORAGE**

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

696 **Caution: R_x only**

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

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700 40 Landsdowne Street

701 Cambridge, MA 02139

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

719 **PATIENT INFORMATION**

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

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

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

726 ***Pregnancy/Nursing:***

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

733 ***Dehydration/Hypotension:***

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

739 ***Concomitant Medications:***

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

742 ***Diabetic Patients:***

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

745 ***Peripheral Neuropathy:***

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

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

750 Contact your doctor if you develop a rash.

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

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

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755 40 Landsdowne Street
756 Cambridge, MA 02139
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764 Issued December 2006

Rev 6

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-602 / S-010

SUMMARY REVIEW

Acting Deputy Division Director Summary Review of an Efficacy Supplement

NDA: 21-602/S010

Drug: Velcade (bortezomib) for injection

Applicant: Millenium

Date: December 8, 2006

This efficacy supplement seeks approval of Velcade for the following indication: "VELCADE (bortezomib) for Injection is indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy." The study design and results are summarized in the following excerpts from the agreed upon labeling.

The safety and efficacy of VELCADE in the treatment of patients with relapsed or refractory mantle cell lymphoma were evaluated in an open-label single-arm multicenter study of 155 patients with progressive disease who had received at least 1 prior therapy. In 91% of the patients, prior therapy included all of the following: an anthracycline or mitoxantrone, cyclophosphamide, and rituximab. An IV bolus injection of VELCADE 1.3 mg/m² was administered twice weekly for 2 weeks on Days 1, 4, 8 and 11 followed by a 10-day rest period (Days 12 to 21) for a maximum of 17 treatment cycles.

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

Table 5: 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)

Most Commonly Reported Adverse Events in the Integrated Summary of Safety

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

Table 8: 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	≥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 ^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

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

Clinical Review

The Clinical Review by Robert Kane, M.D., was completed on December 5, 2006. Dr. Kane's recommendation on regulatory action is quoted below.

“Based on this sNDA submission, I recommend that bortezomib (Velcade) receive regular approval for this indication: treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy...

The Velcade responses are convincing for their durability and for their reduction of the disease burden on the responding patients... Toxicity is similar to that observed in the myeloma setting...”

Dr. Kane had no recommendations for postmarketing actions, risk management activity, or phase 4 commitments.

Dr. Ann Farrell, Medical Team Leader, has indicated her concurrence with these findings. She was a signatory to the medical review on December 6, 2006.

Clinical Inspection Summary

A draft clinical inspection summary prepared by J. Lloyd Johnson, Pharm.D. was circulated on December 4, 2006. The overall assessment of findings and general recommendations are provided below.

b(4)

“ In general, based on the inspection of the three clinical sites and the CRO (_____ , LLC) audit for this NDA, it appears that sufficient documentation to assure that study subjects audited at the inspected sites did exist, study eligibility criteria were fulfilled, participants received assigned study medications, and adverse events were adequately reported. Primary endpoints and secondary endpoints were captured in accordance with protocol requirements.”

Statistical Review and Evaluation

The Statistical Review and Evaluation (primary reviewer Chia-Wen Ko, Ph.D., concurrence reviewers Rajeshwari Sridhara, Ph.D. and Aloka Chakravarty Ph.D.) was completed on November 30, 2006. The conclusions and recommendations are quoted below.

“ ...the study results from the submitted Phase II, single-arm, multicenter trial support the claim of efficacy based on response rate and duration of response as the primary outcomes...The results indicate that previously treated relapsed or refractory MCL patients had a 31% response to VELCADE, and the response was durable with a median duration of response of 285 days in complete or partial responders.”

Chemistry Review

The Chemistry Review by Chengyi Liang, Ph.D. was completed on December 7, 2006. The reviewer found the justification to support categorical exclusion from the environmental assessment requirements to be acceptable.

Pharmacology/Toxicology Review and Evaluation

The review by Leigh Verbois Ph.D. with concurrence from David Morse, Ph.D. was completed December 4, 2006. The conclusions and recommendations are excerpted below.

“ In response to Phase 4 commitments, the sponsor has investigated the cardiovascular toxicities associated with bortezomib administration... The differences between dopamine/phenylephrine responses before and after bortezomib administration were not statistically significant however the magnitude of the differences may be biologically relevant. Due to the design of the study, it is not evident if these interventions at 24 hours post-dose would attenuate PS-341 related mortality which is observed after 48 hours sacrifice in a preponderance of animals. Attenuation of mortality is unlikely given the moribundity observed in the pilot study in spite of dopamine and phenylephrine administration. Additionally, the effect of fluid supplementation is unclear...In summary, at this point, we recognize the completion of the non-clinical Phase IV commitments.”

The review recommends that the OVERDOSAGE section of the label should continue to state the lack of a known specific antidote for VELCADE overdose. The reviewer recommends that the description of cardiac toxicity associated with studies in monkeys be amended to include monkeys and dogs.

Clinical Pharmacology Review

The clinical pharmacology review by Sophia Abraham, Ph.D. with concurrence by Brian Booth, Ph.D. was completed on December 6, 2006. The review summarizes findings from a phase IV commitment study which were submitted with this supplement. In study M34103-058, the pharmacokinetics (PK) and pharmacodynamics (PD) of bortezomib were assessed on Days 1 and 11 of each of Cycles 1 and 3 in 24 patients with multiple myeloma at doses of 1.0 mg/m² (n=12) and 1.3 mg/m² (n=12). The reviewer recommends inclusion of findings from this study in the labeling.

Conclusion

I concur with the reviewers' recommendations for approval of this efficacy supplement. The response rate observed, including durable complete and partial responses, supports the use of bortezomib as therapy in patients with mantle cell lymphoma who had received

at least one prior therapy. Although patients receiving bortezomib may experience adverse events including nausea, diarrhea, vomiting, peripheral neuropathy, anemia and thrombocytopenia, these toxicities are outweighed by the demonstrated clinical benefit.

Ramzi Dagher, M.D.
Acting Deputy Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research

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MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-602 / S-010

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA 21-602
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Established Name Bortezomib
(Proposed) Trade Name Velcade
Therapeutic Class Antineoplastic
Applicant Millennium, Inc.

Priority Designation P

Formulation Intravenous
Dosing Regimen 1.3 mg/m² days 1, 4, 8, 11 every 21 days
Indication Treatment of mantle cell lymphoma
Intended Population after at least 1 prior therapy

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Table 1: Abbreviations used in the review

AE	Adverse Event (CTC criteria)
CDER	Center for Drug Evaluation and Research, FDA
CR	Complete response (IWG criteria)
CRu	Complete response unconfirmed (residual masses)
CTCAE	Common Toxicity Criteria, version 3, NCI
DLT	Dose-limiting toxicity
DSMB	Data safety monitoring committee
FISH	Fluorescence in situ hybridization assay
IHC	Immunohistochemistry
IRRC	Independent radiologic review committee
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
ITT	Intention to treat population (all patients' randomized)
IV	Intravenous
IWG	IWRC
IWRC	International workgroup response criteria for NHL
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
MCL	Mantle cell lymphoma
NHL	Non-Hodgkin lymphoma
NOS	Not otherwise specified
ns	not statistically significant
OS	Overall survival
PCR	Polymerase chain reaction assay
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PO	per os, orally
PR	Partial response (IWG criteria)
P.S.	Performance status
SAE	Serious adverse event (CTCAE criteria)
SPD	Sum of the longest perpendicular diameters
TEAE	Treatment-emergent adverse event
TTP	Time to tumor progression
ULN	Upper limit of normal

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1. EXECUTIVE SUMMARY

1.1. Recommendation on Regulatory Action

Based on this sNDA submission, I recommend that Bortezomib (Velcade®) receive regular approval for the indication: treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy. Mantle cell lymphoma is an uncommon disease with an aggressive behavior, typically occurring in older age patients. The standard initial treatment is an intensive combination of several chemotherapy agents. Following this therapy, most patients relapse. No subsequent therapy is of recognized value. No randomized studies have been performed in relapsed MCL patients. In a population of relapsed, progressive, mantle cell lymphoma patients following one or more prior therapies, Millennium and Johnson & Johnson Pharmaceutical Research, Inc., have conducted a single-arm, single-agent study of Velcade in 155 patients accrued from 35 centers in the North America and Europe demonstrating responses, including complete responses, with duration (9-13 months). The overall response rate is 31% (48/155), including 8% (12/155) complete responses and complete responses unconfirmed (see table 7, below). For all responders, the median response duration is 9 months, and durable responses occurred consistently in all subgroups examined. The population of patients enrolled had all received optimal first-line therapy including anthracyclines, cyclophosphamide, rituximab, and many had also received autologous stem cell transplants or dose-intensive chemotherapy.

The Velcade responses are convincing for their durability and for their reduction of the disease burden on the responding patients (e.g., adenopathy and hepatosplenomegaly) and were verified by independent radiologic review of CT scan changes. Toxicity is similar to that observed in the myeloma setting, is already well-described in the existing label, and is familiar to hematology-oncology physicians.

1.2. Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No special risk management activities are required.

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Millennium has conducted several studies of Velcade as a single agent and in combination therapy in various populations of multiple myeloma patients, leading to regular approval of Velcade therapy for myeloma patients after one or more prior therapies (with demonstration of improved TTP and OS).

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This sNDA includes one company-sponsored phase 2 study, a study of the NCI Canada clinical trials group, and three investigator-initiated phase 2 studies in patients with relapsed/refractory mantle cell lymphoma (after at least one prior therapy). In addition to these studies, _____

1.3.2 Efficacy

The study population for analysis comprises 155 MCL patients, median age 65, who had progressive disease after previously receiving optimal available therapy; 77% were stage 4, 75% had extra-nodal disease sites, one-third had elevated LDH, and 37% had received prior "high-intensity" therapy such as stem-cell transplant (SCT) or hyper-CVAD chemotherapy. Historical experience indicates few patients with relapsed MCL would be expected to obtain benefit from further therapies. For this group, Velcade therapy has resulted in:

- A 31% ORR rate, including a CR rate of 8%; ORR median duration 9.3 months
- Duration of response for the CR plus CRu group is 15.4 months
- Duration of response for the PR population is 6 months
- KM estimate of 1 year survival is 100% for the CR plus CRu patients, 94% for all responders and 69% for all patients
- TTP: for all patients, the median is 6.2 months (~ 50% censored)
- PFS, with 35% of events censored, was also 6.2 months

FDA 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 (months)	Median	95% CI
CR + CRu + PR (N=48)	9.3	(5.4, 13.8)
CR + CRu (N=12)	15.4	(13.4, 15.4)
PR (N=36)	6.1	(4.2, 9.3)

Four additional single-arm studies in MCL, not conducted by the applicant, are supportive with similar reported magnitudes of benefit.

1.3.3 Safety

The current labeling for Velcade adequately describes information for safe use. No new, unexpected, or more severe toxicities were observed in this study.

1.3.4 Dosing Regimen and Administration

The single dose level tested in the applicant's study is 1.3 mg/m² on days 1, 4, 8, and 11 every 21 days. This is the same regimen as used in the myeloma approvals and as recommended in the label. The dose adjustments schedule detailed in the label remains satisfactory to guide ongoing therapy.

1.3.5 Drug-Drug Interactions

None were identified in these studies of Velcade as a single agent. The concomitant medications used on study are typical for an advanced cancer population. There is a higher prevalence of prior vinca alkaloid use in this lymphoma population than in the previous myeloma study (95% versus 77%), which may have contributed to the higher neuropathy incidence incurred by the MCL patients.

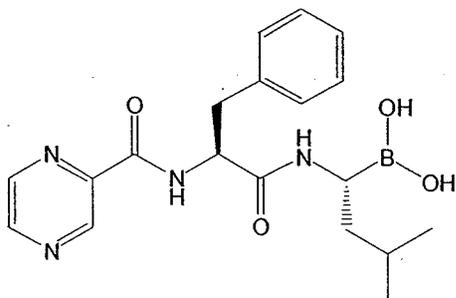
1.3.6 Special Populations

Of the 155 patients, the median age was 65 years; 80% were male, and 92% were White. MCL is not a disease of childhood, and a pediatric waiver was granted. Patients with moderate or severe renal or hepatic impairments at baseline were excluded [baseline limits were aspartate transaminase ≤ 3 x upper limit of normal (ULN), alanine transaminase ≤ 3 x ULN, total bilirubin ≤ 2 x ULN, and creatinine ≤ 2 mg/dL or calculated creatinine clearance ≥ 50 mL/min.]

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Bortezomib is described as a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome, a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. Bortezomib is a modified dipeptidyl boronic acid.



Bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes 3A4, 2C19, and 1A2. The major metabolic pathway is deboronation to form 2 deboronated metabolites that subsequently undergo hydroxylation to several metabolites.

Velcade is given by rapid IV administration. The approved schedule is 1.3 mg/m² on days 1, 4, 8, and 11 every 21 days. Since approval, labeling revisions have added additional safety information.

2.2 Currently Available Treatment for Indications

None

2.3 Availability of Proposed Active Ingredient in the United States

Bortezomib is commercially available in the U.S.

2.4 Important Issues With Pharmacologically Related Products

There are no related products for comparison.

2.5 Presubmission Regulatory Activity

Velcade received accelerated approval in 2003 for multiple myeloma after 2 prior therapies and, in 2005, Velcade received regular approval for the treatment of multiple myeloma after one prior therapy.

For this indication, an EOP2 meeting was held on September 14, 2004. The applicant initially proposed a single arm phase 2 study to assess TTP, response rate, and response duration for previously treated mantle cell lymphoma (MCL) patients. FDA cautioned that interpreting TTP in a single arm study would be problematic. Later, the company amended the protocol to specify that response rate, defined as the proportion of patients achieving CR plus CRu, would be the primary endpoint, and this change was accepted by the Division.

Velcade was granted fast track in November 2004 for relapsed and refractory mantle cell lymphoma, considered to be a serious and life-threatening disease with unmet medical need.

The applicant developed a computer-based algorithm to determine response and progression endpoints. A preliminary data analysis using the applicant's programmed algorithm identified issues requiring revision of the algorithm. These primarily concerned small lymph node measurements which fluctuated between scans but were not reflected in clinical changes. Millennium met with FDA to review their modifications to the algorithm and these were acceptable to FDA. Thus, the algorithm criteria reflect a modified form of the IWRC response criteria but are applied consistently to all patients and appear clinically relevant. A pre-sNDA meeting occurred on January 17, 2006.

Millennium is seeking patent exclusivity for the treatment of mantle cell lymphoma under 21CFR 314.108(b)(5).

2.6 Other Relevant Background Information

The response and progression criteria used in the study were defined by a consensus panel and published in 1999.¹ These criteria, referred to as the International Working Group Response Criteria (IWRC), are included in appendix 10.3. The criteria were modified slightly for this study after initial testing, as noted above. The data elements for assessing response and progression were entered into a computer program algorithm to adjudicate treatment outcomes and provide the protocol-defined outcomes for analysis.

Mantle cell lymphoma is considered an aggressive and incurable but relatively uncommon form of non-Hodgkin lymphoma, accounting for 5-6% of new lymphoma diagnoses in the U.S. (annual incidence of 3,000-4,000 cases each in the U.S. and the European Union). The median age at diagnosis is 60-65 years, and the majority of patients are male. A pathologic diagnosis usually rests on a combination of histology, immunophenotyping (mantle cell lymphoma cells typically express CD5, CD19, and CD20, and are CD23 negative), and either IHC demonstrating overexpression of cyclin D1 or cytogenetics consistent with chromosomal translocation [t(11;14)].² This chromosomal translocation t(11;14)(q13;q32), present in most cases, puts the

cyclin D1 gene, B-cell leukemia/lymphoma-1 (bcl-1), under the control of the immunoglobulin heavy chain enhancer region with subsequent overexpression of cyclin D1.

Most patients present with stage 3 or 4 and respond to initial combination chemotherapy, but patients then relapse with median survivals of 3-4 years from initial diagnosis. Initial therapy may include chemotherapy with R-CHOP, Hyper-CVAD, or FCR regimens, sometimes followed by autologous stem cell transplant (SCT). Involvement of the bone marrow and gastrointestinal tract are common.

Following first relapse, median survival is 1-2 years, and there is no accepted standard therapy of general benefit. Achieving durable complete responses in aggressive hematologic malignancies is a general goal of therapy, since such responses may have the greatest potential to provide a substantial clinical benefit if the toxicity associated with the treatment is manageable. In the relapsed setting for an uncommon cancer, it can be difficult to conduct a randomized study. If the effects are of sufficient magnitude and duration, evidence of treatment effect from single-arm phase 2 studies may be sufficient to support an approval action. This single-arm study examines the effect of Velcade in a population of MCL patients who have already received the effective, available therapies for the disease.

Single arm studies in advanced lymphomas and chronic leukemias have used response rate, in particular complete response (CR), with durability, as a surrogate of benefit in relapsed patients and in conditions with relatively small numbers of patients for study. Regular or accelerated approval may be appropriate. For example, all drugs approved for cutaneous lymphoma all were based on single arm studies. Campath received accelerated approval in 2001 for CLL, previously treated, based on an overall response rate (ORR) of 31% including 2% CRs. Nelarabine was approved in 2005 for T-cell lymphoblastic leukemia-lymphoma after prior therapy failure based on response rate with duration. When a disease process is known to proceed rapidly in the absence of effective therapy, a response endpoint may be clinically meaningful and sufficient evidence for an approval.

When a randomized study is performed, progression-free survival (PFS) allows the assessment of a treatment effect among all patients in the study, and this PFS comparison between study arms is usually more informative than considering the responder subgroup of a single-arm study population. Recently, in phase 3 randomized studies, rituximab received approval for use in combination with chemotherapy first-line or following chemotherapy induction for low-grade or follicular lymphomas based on improved PFS endpoints. In diffuse large cell lymphoma, rituximab is approved for first-line treatment along with chemotherapy based on improvements in PFS, event-free survival, and OS in randomized phase 3 trials.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

3.2 Animal Pharmacology/Toxicology

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The network path is: \\CDSESUB1\N21602\S_010\2006-06-08 consisting of modules 1, 2 and 5. The applicant submitted electronic datasets, narratives, CRFs and clinical study reports (CSRs). In addition, the sponsor was queried for additional data, and literature reports for the four additional phase 2 studies were assessed for concordance with the submitted information.

4.2 Tables of Clinical Studies

Table 2: Reviewer summary table of clinical studies for the sNDA

Study	Sponsor	N	population	Dose ^a
M34103-053	Millennium	155	1-2 prior therapies	1.3 mg/m ²
	NCIC	29	0 (n=13) -2 prior	1.3 mg/m ²
Goy	MD Anderson	33	1 or more prior	1.5 mg/m ²
O'Connor	MSKCC	42	0 -3 prior	1.5 mg/m ²
Straus/Lister	London, UK	24	1 or more	1.3 mg/m ²

Dose^a: Given on days 1, 4, 8, 11, every 3 wks

NCIC: NCI Canada clinical trials group

MSKCC: Memorial Sloan Kettering Cancer Center

All studies are single-arm, single-agent, with response as the primary endpoint.

4.3 Review Strategy

The statistical and clinical reviewers plan is to ascertain the actual number of CR, CRu, and PR patients and the duration of the responses from the applicant's study. Discrepancies between the algorithm adjudication and investigator determinations will be examined. Three of the highest enrolling sites will be audited by DSI. The independent radiologic review contractor, _____ will also be audited. The clinical reviewer will examine the actual bone marrow

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specimens for the CR and CRu patients. AEs were examined for any new events or differences in frequency from those previously described.

4.4 Data Quality and Integrity

For the Millennium study:

1. All scans were read by an independent and blinded radiologic review contractor, _____
_____ Each image was to be assessed for overall quality and for similarity of acquisition techniques to prior studies. Lesions were to be labeled (numbered) and listed as per location. No more than 10 measurable sites of disease were to be included. Each lesion was to be measured using electronic calipers across the longest dimension and perpendicular to the longest dimension. If there was disagreement on a previously measured lesion, the measurement was to be reviewed with the lead radiologist.
2. To determine response to treatment and the date of response and PD for each patient, the sponsor developed a SAS algorithm that applied the IWRC, as specified in the protocol. The algorithm used data on the identity and size of lymphoma sites as derived from the independent radiology review, as well as clinical and laboratory data provided on the CRF, such as assessments of bone marrow, symptoms of MCL, serum LDH, and appearance of new sites of disease. In addition, if the investigator used physical examination to follow a neck lesion or detect a new site of disease in the neck, and the neck was not imaged in the scans available to the independent radiologists, then the investigator assessments of the neck lesion(s) were to be used by the algorithm. This assured that sites of disease in the neck were not excluded from the sponsor assessments of response and PD since the protocol did not require neck CTs.
3. Central pathology review was performed but not required by the protocol.

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4.5 Compliance with Good Clinical Practices

All protocols received IRB review and approval. All patients provided written informed consent. Accruing sites were monitored periodically during the study.

4.6 Financial Disclosures

Among the studies submitted, there were 450 investigators with no financial interests to the applicant, 24 investigators who did not provide the financial disclosure statements, and 5 investigators reporting a financial interest in or funding by the applicant. One of these sites, with one of the 11 CR/CRu responders, has been selected for audit by DSI. In addition, the applicant reports that 100% data verification of the enrolled patients at each of the investigators' sites has been performed by Millennium. The potential for bias appears to be minimal.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

5.2 Pharmacodynamics

5.3 Exposure-Response Relationships

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

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

6.1.1 Methods

SAS data files were examined with the statistical reviewer. The original protocol, protocol amendments, and modules 2 and 5 of the eCTD were the data sources for this review. Please see the statistical review by Dr. Chia-wen Ko for data calculations.

6.1.2 General Discussion of Endpoints

Assessment of response and progression in MCL generally use the criteria of an international consensus working group (IWRC) which are detailed in appendix 10.3 below. In brief:

- CR – complete response: disappearance of all evidence of disease
 - Nodes initially > 1.5 cm must decrease to 1.5 cm or less
 - Nodes initially 1.1 – 1.5 cm must decrease to 1.0 cm or less
- CRu – complete response except for either:
 - A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass; or
 - Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia)
- PR – at least 50% decrease in the 6 largest measurable lesions and in spleen/liver nodules, and no new disease sites
- PD – any new lesions, or an increase of 50% to 1.5 cm of nodes <1.0 cm or an increase of 50% of any residual masses, measured from nadir

6.1.3 Study Design

Study M34103-053 is a single-arm, single-agent, phase 2, prospective study of Velcade in previously treated patients with progressive MCL.

The original version of the protocol was dated April 9, 2003. (Forty-six patients were enrolled under this version.)

Protocol amendment 1, dated November 4, 2003, made minor revisions. (Seventy-nine patients were enrolled under this version.)

Protocol amendment 2, dated October 20, 2004, changed the timing of some later response assessments and added the eligibility requirement for patients previously to have received rituximab. (Thirty patients were enrolled under this version.)

Study Objectives:

Originally, the primary objective of this study was to determine if Velcade increases median time to progression (TTP) compared to historical controls in patients with MCL who have documented relapse or progression following 1 or 2 prior lines of antineoplastic therapy.

Secondary objectives were the following:

- To evaluate the rates of complete response (CR), CR unconfirmed (CRu), and overall response (CR + CRu + partial response [PR])
- To determine if Velcade increases median survival compared to historical controls
- To evaluate duration of response

An appropriate cohort of historical controls could not be found for comparison to the results of this study, and thus the formal statistical comparisons of TTP and survival specified in the protocol could not be performed. Therefore, the efficacy analyses performed in in this report are non-comparative (single-arm) assessments of response rate, duration of response, TTP, and survival. This change was made in 2006.

The major inclusion criteria were:

1. Male and female patients 18 years or older
2. Pathologically confirmed MCL including expression of cyclin D1 or evidence of t(11;14) by cytogenetics, FISH or PCR; with independent pathology review
3. Documented relapse or progression following 1 or 2 prior lines of anti-neoplastic therapy of which at least 1 must have included an anthracycline or mitoxantrone, cyclophosphamide, and at least 1 must have included rituximab. Relapse or progression since previous therapy must be documented by new lesions or objective evidence of progression of existing lesions.
4. At least 1 measurable or assessable site of disease that has not been previously irradiated, or has grown since previous irradiation.
5. KPS \geq 50% (ECOG 0-2)

The major exclusion criteria were:

1. Previous treatment with Velcade
2. Anti-neoplastic or experimental therapy within 3 weeks before Day 1 of Cycle 1.
3. Nitrosoureas within 6 weeks before Day 1 of Cycle 1.

4. Radioimmunoconjugates or toxin immunoconjugates such as ibritumomab tiuxetan (Zevalin™) or tositumomab (Bexxar®) within 10 weeks before Day 1 of Cycle 1.
5. Rituximab, alemtuzumab (Campath®) or other unconjugated therapeutic antibody within 4 weeks before Day 1 of Cycle 1.
6. Radiation therapy within 3 weeks before Day 1 of Cycle 1.
7. Major surgery within 2 weeks before Day 1 of Cycle 1.

Removal of patients from protocol treatment:

Velcade was to be permanently discontinued for subjects meeting any of the following criteria:

- Completion of 4 cycles beyond the date of initial documentation of CR or CRu
- Completion of 17 cycles (ie, approximately 12 months) of treatment
- PD (progressive disease)
- Occurrence of an unacceptable toxicity
- Decision by subject or investigator

Treatment:

All patients receive Velcade 1.3 mg/m² IV bolus on days 1, 4, 8, and 11 every 21 days. Dose adjustments or discontinuation for toxicities were provided similar to previous Velcade studies. Corticosteroids including dexamethasone were prohibited, except for prednisone at a dose \leq 15 mg per day or its equivalent were allowed for treatment of adrenal insufficiency. Prophylactic use of leukocyte growth factors also was prohibited.

Lesion Assessments:

- **Eligibility:** For entry into the study, patients were to have at least 1 measurable or assessable site of disease that had not been previously irradiated, or had grown since previous irradiation.
- **Timing:** Patients had clinical and scan assessments every 6 weeks through week 18 then every 12 weeks thereafter until PD. Patients who discontinued treatment prior to PD were to be evaluated for PD at short-term follow-up visits every 6 weeks through Week 18 and every 12 weeks thereafter.
- **Size:** Measurable lesions by scan had to be at least 1.5 cm in 2 dimensions and at least 1.0 cm in 2 dimensions by physical examination.

Independent data review:

- **Pathology:** An independent pathologist review included stained and previously unstained tissue slides (for repeat IHC), flow cytometry, FISH, PCR, and cytogenetics. A pathology CRF was completed and submitted to the sponsor.
- An independent, blinded radiologic assessment of the CT scans was performed by World Care, Inc. all radiologists were blinded to all patient identifiers as well as site assessment of disease. As well, each radiologist was blinded to his/her own previous assessments. The charter and operations policies were reviewed and accepted by the Division of Medical Imaging and Hematology Products, CDER.

Patient populations and censoring as defined by the applicant in the study report:

- The All Treated Population (ATP) was defined as all patients who received any amount of Velcade. The data listings were based on the ATP; patients who were screen failures or withdrew before treatment started are not included in the listings. Safety and efficacy data (with the exception of response) were analyzed for the ATP.
- The Response Population for Final Analysis (RP-Final) was defined as patients included in the ATP who had measurable disease at Screening and at least 1 post-baseline tumor assessment (including measurable or assessable lesions). Response and duration of response data were analyzed for the RP-Final.
- The Per-Protocol Population (PPP) was defined as patients included in the ATP who were confirmed to have MCL by independent pathology review and had prior therapy including rituximab, anthracycline/mitoxantrone, and an alkylating agent (such as cyclophosphamide). Prior therapy with an alkylating agent was not required for eligibility in this study; however, this criterion was included for the PPP based on advice from the FDA at the end of phase 2 meeting on 14 Sept 2004.
- While the RP-final and the PPP are each subgroups of the ATP, they are not subgroups of each other.
- Efficacy analyses, with the exception of disease response, were presented for the PPP by the applicant.
- The Refractory Population was defined as a subset of the ATP who had not responded (CR, CRu, or PR) to their last prior line of therapy, or who responded to their last prior line but had a TTP that was <6 months (measured from the initiation of their last prior line of therapy). Efficacy analyses were presented for the Refractory Population.
- TTP was defined as the duration in days from the date of first dose of Velcade to the date of PD, or relapse for patients who experience CR or CRu. Kaplan-Meier methods were used for the analysis.
- Censoring for TTP: Patients who died, or were lost to follow-up before documentation of PD, or who discontinued VELCADE and started alternate antineoplastic therapy without documentation of PD within 2 weeks of the start of alternate antineoplastic therapy were censored at the last documented SD or better response prior to antineoplastic therapy for TTP analyses. Patients who did not have any post-baseline response assessments were censored at the date of first dose for TTP analyses.
- PFS was defined similarly to TTP except that death prior to PD was an event. The Kaplan-Meier method was used to estimate the distribution of PFS.
- Censoring for PFS: Analyses were similar to that for TTP analyses, except that death before documentation of PD was considered an event on the date of death.
- Survival was defined as the duration in days from date of first dose of Velcade to date of death. Survival analysis was performed using Kaplan-Meier methods. Patients who did not have death information recorded at the time of database lock for this study were censored at the date they were last known to be alive for survival analyses.

Reviewer comment: Although the study was initially planned to be a comparison of TTP with an historical group, the study did require measurable disease for entry and serial assessment of disease status. Thus, for regulatory purposes, the entire population of 155 patients is considered the appropriate group for response and toxicity assessments.

Statistical assumptions for the study:

The parameters used in the calculations of sample size were: 2-sided test, $\alpha = 0.05$ (significance level of the statistical test), $\beta = 0.20$ (corresponding to power of 80%), an estimated median TTP of approximately 14 months for patients treated with Velcade on this study and approximately 9 months for historical controls (ratio of median TTP of 1.50), a patient accrual period of 14.5 months (approximately 10 patients/month), and a planned analysis approximately 15.5 months after the last patient was accrued. The proportional hazards model was used and 5% losses to follow-up were accounted for in the calculations. Based on this calculation, the total number of events of progressive disease required was 192 (96 events from patients treated with VELCADE on this study and 96 events from historical controls), and approximately 152 patients treated with Velcade on this study were expected to be sufficient to reach 96 events. The expected time to complete the study excluding long-term follow-up was approximately 30 months from first patient enrolled. The primary analysis was to be performed when the number of patients treated with Velcade on this study with PD reached 96. The final plan was based on statistical power to define an undesirable response rate of 25% and a desirable response rate of 40%. The data cutoff date for all analyses was December 1, 2005.

6.1.4 Efficacy Findings

Table 3: Reviewer's response analysis for the applicant's phase 2 MCL 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)

See statistical review also.

Reviewer comments: The 95% CI upper bound happens to be equal to the median duration of response in CR+CRu responders (n=12) because of the high percentage of censoring (8 out of the 12 responders did not experience disease progression or death). Only four events of progression or death were observed in CR+CRu responders at 45, 143, 409, 470 days since their first response. The response rate and duration of response were calculated as proposed in the

protocol; namely, overall response rate (ORR) is the proportion of subjects exhibiting CR+Cru+PR as their best response on Velcade and duration of response is the time from first response to progressive disease (PD) or censoring. The results were calculated using the algorithm-determined response and duration of response in all 155 patients (applicant's ATP population), except for patient 010-001, for whom the investigator-determined response and duration of response were used to assess response. This is consistent with the protocol-specified analysis plan for all patients enrolled. The medical reviewer agreed with the algorithm-determined responses with the exception of the above patient who was added to the response population (see below).

Duration of response in months is calculated as duration of response in days / 30.5.

Efficacy data in this phase 2, single-arm study include response and time to event information. Response, as defined by the IWRC, is a composite endpoint requiring all of: CT scan results, disease-related symptom assessment, physical examination of non-scanned areas, disease-related biochemistry (LDH), and bone marrow. The applicant's primary means of determining response in this study is the computer algorithm analysis, merging the above elements.

Patient Disposition:

In the phase 2 study (M34103-053) among 35 study sites, 162 patients were screened and 155 were enrolled and received at least the first dose of Velcade. The first patient was enrolled in June 2003. At the time of the data cutoff (1 December 2005), 55 patients (35%) were off-study, including 52 deaths. Of the 155, 72 (46%) patients had stopped treatment due primarily to disease progression and 41 (26%) patients stopped for adverse events.

Protocol violations and deviations:

There were 26 protocol violations for inclusion/exclusion criteria: Most were minor and were permitted as exemptions by the study monitor. Six of these patients had received 3 prior lines of therapy but were considered otherwise eligible. One patient each had received radiation therapy and rituximab within the proscribed time interval. Three patients had not previously received an anthracycline or mitoxantrone. No patients were withdrawn for protocol deviations, which were most commonly related to missed evaluations.

Reviewer comment: These violations are unlikely to have altered the study results.

Demographics:

Table 4: Applicant's table of demographic characteristics (CSR table 10-5)

Demographic and Baseline Characteristic	N=155
Age (years)	
Mean (Std Dev)	64.9 (9,32)
Median	65.0
Minimum, Maximum	42, 89
Sex [n (%)]	
Male	125 (81)
Female	30 (19)
Race [n (%)]	
White	142 (92)
Black	6 (4)
Hispanic	4 (3)
Asian or Pacific Islander	3 (2)
KPS [n (%)]	
< 50	0
50-60	7 (5)
70-80	37 (24)
90-100	109 (71)
Missing	2

Reviewer comment: The population studied is representative of a relapsed MCL patient group.

Table 5: Applicant table of baseline disease characteristics (CSR, table 10-6)

Prognostic Factor	N=155
Time Since Initial Diagnosis to First Dose (years)	
Mean (Std Dev)	2.7 (1,88)
Median	2.3
Minimum, Maximum	0.2, 11.2
Diagnosed < 3 years Prior to First Dose [n (%)]	103 (66)
Diagnosed ≥3 years Prior to First Dose [n (%)]	52 (34)
MCL Stage at Screening [n (%)]	
Stage I	5 (3)
Stage II	7 (5)
Stage III	24 (15)
Stage IV	119 (77)
IPI [n (%)]	
0-1	34 (23)
2	48 (33)
3	48 (33)
4-5	17 (12)
Missing	8
LDH [n (%)]	
Normal	95 (64)
High (above upper limit of normal)	54 (36)
Missing	6
Number of Involved Extra-nodal Sites [n (%)]	
0	38 (25)
1	64 (41)
2	32 (21)
3 or more	21 (14)
Bone Marrow Evaluation (biopsy and/or aspirate)	
Positive Results	84 (55)
Negative/Indeterminate Results	70 (45)
Missing	1

Table 6: Applicant's table of prior therapy received by the MCL patients

Number of Prior Lines of Therapy	
1	84 (54)
2	65 (42)
3 or more	6 (4)
Received Prior Regimen Containing	
Anthracycline/Mitoxantrone	152 (98)
Alkylating Agents	150 (97)
Rituximab	149 (96)
Received at Least 2 of the Above 3	155 (100)
Received All of the Above 3	141 (91)
Received Prior High-Intensity Therapy ^a	58 (37)
Received Prior High-Intensity Therapy as Last Prior Regimen ^a	47 (30)
Number of Patients with Prior Radiation Therapy	29 (19)

^a High intensity prior regimen defined as Hyper-CVAD; R-hyper-CVAD; ICE/ESHAP/DHAP with or without rituximab; and SCT

Regarding prior therapy, median TTP on last prior therapy for all patients in this study was 12 months (366 days, table 14.2.1.7). Best response on prior therapy was CR, CRu or PR in 96 (62%) of the 155 patients.

Reviewer comments: The study population appears representative of a treated population with mantle cell lymphoma, although possibly slightly younger and healthier than a community-based sample. This is expected by the study design and referral center nature of the study sites.

Table 7: Applicant summary of best response findings in the applicant's response-population

	Sponsor Algorithm- Derived	Investigator determined
Response	N=141 n (%)	N = 141 n (%)
CR+CRu+PR 95% C.I.	47 (33%) (26, 42)	57 (40%) (32, 49)
CR + CRu 95% C.I.	11 (8%) (4, 14)	11 (8%) (4, 14)
CR	9 (6)	8 (6)
CRu	2 (1)	3 (2)
PR	36 (26)	46 (33)
SD	47 (33)	46 (33)
PD	35 (25)	37 (26)
No Post- baseline Assessment	12 (9)	1 (<1)

(See CSR table 11-1 for applicant's data)

Reviewer comments:

The FDA results are presented in table 3 at the beginning of section 6.1.4 and are based on all 155 patients. In the applicant's analysis, patients were censored for lack of baseline or follow-up assessments, resulting in 141 evaluable patients. This analysis was not accepted by FDA for regulatory review.

Based on the sponsor algorithm, the 12 patients with no post-baseline assessments were classified by the applicant as non-responders (9 of these 12 were assessed as PD by the investigator, and 9 had no post-baseline scans for review by the IRRC).

The response endpoint was pre-specified as a composite of radiologic, clinical, symptom resolution (for the CR categories), and lab findings. The applicant's algorithm determination was the pre-specified determinant of response rate. The protocol provided for inclusion of investigator-determined response in the neck region if no CT scans were obtained for this body area.

While not exhaustively validated, the applicant's proprietary algorithm had been tested and slightly modified in agreement with FDA before the formal analysis of this study. FDA had judged the algorithm as acceptable as an estimate of the true response result. In this review, the purpose of comparing the investigator assessment with the algorithm result is to examine a sensitivity analysis for the algorithm-determined outcomes.

For the CR plus CRu patients, the sponsor-derived algorithm and the investigator assessment each identified 11 patients; however, these were not the same 11 patients (see applicant table 11-7, CSR page 108). There were a total of 14 patients fulfilling the CR or CRu definition between the two methods of assessment. For 6 patients, the assessments agreed. For one patient, there was

no assessment made by the — based on the disease location confined to the neck without CT examinations of this area. Based on the investigator's assessment of resolution by measurement and the IWRC criteria defined per-protocol, this patient qualifies as a CR.

b(4)

The applicant was asked to provide a reconciliation of the 8 patients found to be discordant for CR between the two methods of assessment:

Table 8: Applicant table of reconciliation of discordance in CR

Patient	Sponsor using independent radiology review		Investigator using local radiology review	
	Response	Comment	Response	Comment
002-002	CR	algorithm reports CR at Cycle 10. All measurable lesions regressed to normal size, all assessable lesions resolved, LDH normal, no disease symptoms, no splenomegaly, bone marrow follow-up not required (negative at baseline). This evaluation meets all CR criteria.	PR	Investigator reports PR at Cycle 2 and subsequent evaluations. Measurable lesions meet criteria for CR on several evaluations. Per the investigator one assessable lesion (left para-aortic in the mediastinum) remains at each evaluation. This prevents any evaluation from being considered CR, but all PR criteria are met. Note that chest, abdomen and pelvis CTs were reviewed by — each visit, and all lesions were considered resolved.
006-003	CR	algorithm reports CR at Cycle 6. All measurable lesions regressed to normal size, LDH normal, no disease symptoms, no splenomegaly, bone marrow follow-up negative after positive at baseline. This evaluation meets all CR criteria.	CRu	Investigator reports CRu at Cycle 6. All measurable lesions regressed to normal size, LDH normal, no disease symptoms, no splenomegaly, bone marrow follow-up negative after positive at baseline. The investigator assessed CRu despite the fact that this eval meets all CR criteria.
010-001	None	No response could be determined for MPI-derived algorithm. This patient had disease primarily of the neck assessed by physical examination and baseline scans sent to independent radiology review did not include the neck, therefore response could not be assessed.	CR	Investigator reports CR at Cycle 4 and several subsequent evaluations. All measurable lesions resolve completely, LDH normal, no disease symptoms, splenomegaly at baseline resolved, bone marrow follow-up not required (negative at baseline). This evaluation was based upon physical examination.

b(4)

014-004	PR	algorithm reports PR at Cycle 2 and several subsequent evaluations. Measurable lesions do not all regress to normal size, preventing any evaluation from being considered a CR, but all PR criteria are met.	CR	Investigator reports CR at end of treatment visit, after Cycle 14. All measurable lesions resolve completely, LDH remains abnormal throughout study (investigator considers this unrelated to lymphoma), bone marrow positive at baseline, but only follow-up (at Cycle 7) is also positive. LDH and bone marrow prevent any evaluation from being considered CR, but all PR criteria are met.
014-005	CRu	algorithm reports CRu at Cycle 6 and Cycle 10. Measurable lesions do not all regress to normal size, but do decrease > 75% in product of transverse dimensions. This prevents either evaluation from being considered CR, but all CRu criteria are met.	CR	Investigator reports CR at Cycle 6 and several subsequent visits. Measurable lesions assessed by investigator to resolve completely, LDH normal, no disease symptoms, no splenomegaly, bone marrow follow-up not required (negative at baseline). This evaluation meets all CR criteria.
015-004	CR	algorithm reports CR at Cycle 4 and Cycle 6. All measurable lesions regressed to normal size, all assessable lesions resolved, LDH normal, no disease symptoms, no splenomegaly, bone marrow follow-up not required (negative at baseline). This evaluation meets all CR criteria.	PR	Investigator reports PR at Cycle 2 and subsequent evaluations. By cycle 6, all measurable lesions assessed by investigator regressed to normal size, but assessable lesions (bilateral lower lobe lung nodules and a retroperitoneal lymph node) are still present. This prevents any evaluation from being considered CR, but all PR criteria are met. Note that chest, abdomen and pelvis CTs were reviewed by — at each visit, and all lesions were considered resolved.

b(4)

018-001	PR	algorithm reports PR at Cycle 2 and subsequent evaluations. From Cycle 6 through Cycle 17, all measurable lesions regressed to normal size, LDH normal, no disease symptoms, bone marrow indeterminate at baseline, but no follow-up data available. Lack of follow-up bone marrow prevents any evaluation from being considered CR or CRu, but all PR criteria are met.	CRu	Investigator reports CRu at Cycle 17 and subsequent evaluations. All measurable lesions regressed to normal size, LDH normal, no disease symptoms, bone marrow indeterminate at baseline, but no follow-up data available. Lack of follow-up bone marrow prevents any evaluation from being considered CR or CRu, but all PR criteria are met.
042-003	CR	algorithm reports CR at Cycle 4 and subsequent evaluations. All measurable lesions regressed to normal size, all assessable lesions resolved, LDH normal, no disease symptoms, no splenomegaly, bone marrow follow-up not required (negative at baseline). This evaluation meets all CR criteria.	PR	Investigator reports PR at Cycle 4 and subsequent evaluations. Measurable lesions (subcarinal and peripancreatic lymph nodes) assessed by investigator do not all regress to normal size and assessable lesions (para-aortic in the mediastinum and axillary lymph nodes) remain present. This prevents any evaluation from being considered CR or CRu, but all PR criteria are met. Note that chest, abdomen and pelvis CTs were reviewed by _____ at each visit, and all lesions were considered resolved.

b(4)

Reviewer Comments: For all patients except 010-001, the algorithm-determined result is consistent with the study protocol and is acceptable. Patient 010-001 should be included as a CR because the sites of disease all regressed completely per the IWRC. The measurable lesions were in the neck and were not evaluable by the _____ but were acceptable for assessment per protocol and IRWC criteria.

b(4)

The bone marrow findings were independently reviewed as well for the response determination. To ascertain response in the marrow, only patients whose baseline marrows were positive (at study entry) were required to have repeat exams.

Table 9: Applicant table of baseline bone marrow findings among the patients judged as CR or CRu

Center- Subject	MPI Best Response	Site Best Response	Screening			
			Aspirate		Biopsy	
			Date	Result	Date	Result
001-004	CR	CR		Negative		Negative
002-002	CR	PR		Negative		Negative
006-002	CR	CR		Negative		Negative
006-003	CR	CRu		Positive		Positive
008-001	CR	CR		Negative		Negative
010-001		CR		Negative		Negative
010-003	CR	CR		Negative		Negative
011-001	CRu	CRu		Negative		Negative
014-004	PR	CR		Negative		Positive
014-005	CRu	CR		Negative		Negative
015-004	CR	PR		Negative		Negative
018-001	PR	CRu		Negative		Indeterminate
042-003	CR	PR		Negative		Negative
049-005	CR	CR		Negative		Negative

b(6)

Reviewer comment:

Of the algorithm-determined CR or CRu patients, only two (2/12) initially had a positive bone marrow at the time of study entry, while 55% of the entire group were reported to have positive marrows at baseline. One of the two initially positive patients cleared the marrow on follow-up examination.

Patient 006-003, with a baseline positive marrow in _____ had a repeat marrow on _____ with both the aspirate and biopsy negative for lymphoma and achieved a CR.

Patient 014-004, with a positive marrow initially, had a repeat bone marrow exam in _____ with a positive biopsy and thus was scored as a PR.

Patient 018-001, initially judged as indeterminate, did not have a follow-up marrow reported but was otherwise a PR.

This reviewer examined the above described bone marrow slides provided by the applicant for the baseline and post-therapy patients and agrees with the applicant's determinations.

b(6)

TTP:

For both the algorithm-derived and the investigator-determined progressions, the median time-to-progression for all 155 patients was 189 days (6.2 months), and the 95% confidence intervals are very similar (123, 211 and 132, 210).

Table 10: Applicant's table of time to progression for all patients (CSR table 11-3)

	Algorithm-Derived	Investigator-Determined
Kaplan-Meier Results:	N=155	N=155
Number of Events [n (%)]	75 (48)	96 (62)
Number Censored [n (%)]	80 (52)	59 (38)
25th Percentile (95% CI)	43 (38, 83)	48 (38, 93)
Median (95% CI)	189 (123, 211)	189 (132, 210)
Reason for Censoring	(N=80 censored)	(N=59 censored)
Alternate Therapy	39 (49)	23 (39)
Death	8 (10)	8 (14)
Study Cut-off (within 90 days)	15 (19)	22 (37)
Not Evaluated	2 (3)	1 (2)
PD by investigator (no more scans performed)	3 (4)	0
Lost to Follow-up/Data Not Available	13 (16)	5 (8)

See reviewer's table 3.

Reviewer comment: Of all 155, 52% of patients were censored for the TTP analysis by the applicant, for the reasons shown above. Initiation of alternate therapy and unsubstantiated diagnosis of PD by the investigator were not considered evidence of PD. While this approach resulted in a smaller number of PD events compared to that using the investigator assessments, PD was assessed uniformly among the 35 investigative sites and PD events were based on objective evidence of disease progression. Despite the difference in the number of events and percent censored observations between the 2 methods, the median TTP in both analyses was 6.2 months and the Kaplan-Meier curves of TTP for the 2 methods were similar.

Figure 1: Applicant's Kaplan-Meier curve of time to progression for all patients

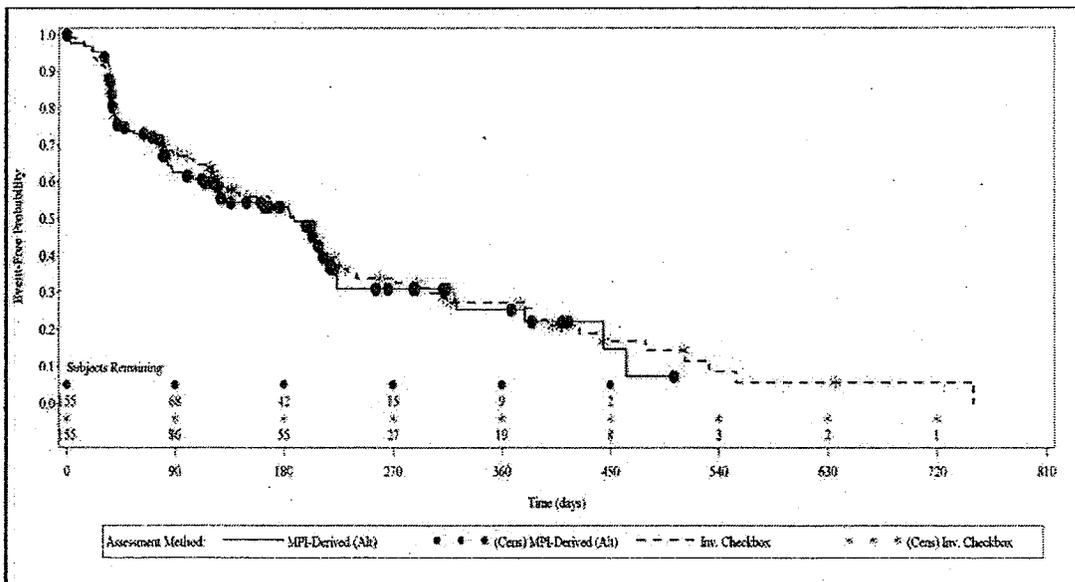


Figure 11-2, CSR, page 103

Patients without post-baseline assessments were censored at date of first dose of Velcade (treatment day 1). In total, 52% of patients were censored at the time of analysis. The curve in red depicts the algorithm-based results. The curve in blue depicts the investigator-determined result.

Reviewer comment: The FDA analysis agrees with the applicant's findings. This treatment effect is noted to be more modest than the anticipated effect used in planning the study.

Figure 2: Applicant's Kaplan-Meier curve for overall survival

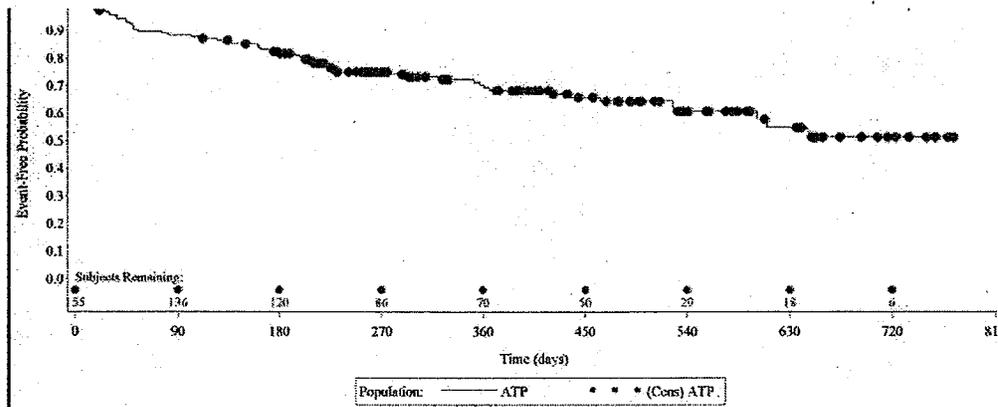


Figure 11-4, CSR, page 106

Table 11: Applicant table of survival results (table 14.2.3.1 CSR)

Survival (days)	ATP
	N=155
Number of Events N (%)	52 (34)
Number of Censored Events N (%)	103 (66)
25th Percentile (95% CI)	278 (194, 438)
Median (95% CI)	NE (601, NE)
75th Percentile (95% CI)	NE
Min, Max	10, 774*
Kaplan-Meier Estimates (a)	
6 Months	81.7% (n=119)
12 Months	69.3% (n=69)
Reason for Censor:	
Study Cutoff (Last Known Alive Date Within 90 Days of 01DEC2005)	97 (94)
Lost to Follow-up	6 (6)
Median Duration of Follow-up for Surviving Subjects (days)	407

Reviewer comment: Approximately 2/3 of the survival events are censored at this time. While preliminary, the median survival is encouraging. In general time-to-event analyses are not interpretable without a concurrent control group. Dr. Ko, the statistical reviewer has examined and confirmed both the TTP and OS findings. Please see her review for additional details.

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

The primary study population for analysis comprises 155 MCL patients, essentially all of whom had progressive disease after previously receiving optimal available therapy; 77% were stage 4, median age 65, 75% had extra-nodal disease sites, one-third had elevated LDH, and 37% had received prior "high-intensity" therapy of SCT or hyper-CVAD. In this group, historical experience indicates few patients would be expected to obtain benefit from further therapies. For this group, Velcade therapy has resulted in:

- A 31% ORR rate, including an 8% CR plus CRu rate
- Duration of response for the ORR population is 9.2 months
- Duration of response for the CR plus CRu group is 13.5 months
- KM estimate of 1-year survival is 100% for the CR plus CRu patients, 94% for all responders and 69% for all patients
- TTP: for all patients, the median is 6.2 months (with ~ 50% censored)
- PFS, with 35% of events censored, was also 6.2 months

Some specific features of this study and the associated regulatory considerations are restated here:

- The Applicant has provided a single-arm, single-agent study, with 4 additional supportive studies
- This is an sNDA for a marketed product with clinical experience
- MCL is an uncommon condition
- A randomized study in the second line population is challenging to conduct considering the low frequency of the disease, nature of the illness, extensive yet varied prior therapy, and co-morbidities in an older age population
- Response rate of adequate magnitude and duration for a single agent in a population without alternative therapies may be persuasive
- Velcade is being actively studied in another lymphoma, follicular lymphoma, in a randomized add-on design with rituximab
- The study does not provide comparative TTP, PFS, OS information due to its design
- Velcade toxicity is already well characterized

Table 12: Reviewer summary of MCL studies

Sponsor	N	population	Dose ^a	ORR ^b	CR+CRu
Millennium	155	1-2 prior therapies	1.3 mg/m ²	31%	8%
NCIC	14/29	0 (n=13) - 2 prior	1.3 mg/m ²	-	-
MD Anderson	29	1 or more prior	1.5 mg/m ²	41%	21%
MSKCC	37	0 - 3 prior	1.5 mg/m ²	41%	8%
London, UK	24	1 or more	1.3 mg/m ²	29%	4%

From applicant's table 3-11, page 33

a: Dose- Given on days 1, 4, 8, 11, every 3 wks

b: ORR; CR + CRu + PR

NCIC: NCI Canada clinical trials group (13/29 received Velcade as first-line therapy. Responses were observed in both groups of patients.)

MSKCC: Memorial Sloan Kettering Cancer Center

Reviewer comments: While the additional studies were not reviewed for this sNDA, the findings are from multiple independent sources and appear consistent with the Millennium results.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety in this study was evaluated by the incidence, severity, and type of AEs, and by changes from baseline in patients' physical examination findings, vital signs, and clinical laboratory data.

Overall summary data are provided in the applicant's table 12-3 and summarized here.

Table 13: Applicant summary of adverse events for all patients (table 12-3, CSR page 138)

Category	N=155 n (%)
At least 1 adverse event (AE)	152 (98)
At least 1 study drug-related adverse event	145 (94)
At least 1 \geq Grade 3 adverse event	108 (70)
At least 1 \geq Grade 4 adverse event	26 (17)
At least 1 serious adverse event	60 (39)
At least 1 adverse event leading to study drug discontinuation	46 (30)
On-study deaths a	12 (8)

a On-study deaths were defined as those that occurred within 28 days after the last study drug dose, regardless of attribution, and those that occurred >28 days after the last study drug dose but were considered to be study drug-related. (No deaths occurred >28 days after the last study drug dose that were considered to be study drug-related.)

Reviewer comment: These findings are not unusual for this condition and stage of therapy.

7.1.1 Deaths

Twelve patients died within 28 days of the last dose of Velcade. For six, the cause was reported as disease progression. For three, sepsis was an antecedent SAE. One patient with extensive prior cardiovascular disease had an acute myocardial infarction 8 days after his second dose of Velcade in cycle 1, one patient died in respiratory failure likely related to a pulmonary embolism, and one patient died of unknown cause on day 11, after the cycle 1 day 8 dose.

7.1.2 Other Serious Adverse Events (SAEs)

Among the 155 patients, 39% were reported as experiencing at least one SAE. The AEs reported are consistent with the current label and Velcade experience. The most commonly reported events leading to discontinuation, regardless of relationship to study treatment, were peripheral neuropathy reported in 15 (10%) patients, fatigue reported in 9 (6%) patients, disease progression NOS reported in 6 (4%) patients, sepsis NOS reported in 4 (3%) patients, and

weakness reported in 3 (2%) patients. All other events leading to discontinuation of VELCADE were reported in <1% of patients (data available in applicant table 12-14, CSR page 177).

7.1.3 Dropouts and Other Significant Adverse Events

AEs resulting in drug discontinuation occurred in 30% of the patients and were consistent with prior Velcade experience. The most common AE associated with drug discontinuation was neuropathy (see section 7.1.5).

7.1.4 Other Search Strategies

The current Velcade label was reviewed. The sponsor's supportive studies were reviewed for unexpected or unique AEs.

7.1.5 Common Adverse Events

The most commonly reported treatment-emergent adverse events were asthenic conditions, including fatigue, weakness, worsening fatigue (MedDRA preferred term fatigue aggravated), malaise, lethargy, and asthenia (112 patients; 72%). The incidence of asthenic events in this study was slightly higher than that reported in previous studies of Velcade in patients with multiple myeloma (Studies M34101-039 and M34101-040) in which the incidence was ~60%. Other commonly reported adverse events in this study included peripheral neuropathies (85 patients; 55%), constipation (77 patients; 50%), diarrhea (73 patients; 47%), nausea (68 patients; 44%), and appetite decreased (60 patients; 39%). Treatment-emergent events of \geq Grade 3 severity were reported in 108 (70%) of the 155 patients and were primarily reports of asthenic conditions (29 patients, 19%); peripheral neuropathies (20 patients, 13%); thrombocytopenia (17 patients, 11%); disease progression, and diarrhea (11 patients each, 7%); and abdominal pain and syncope (8 patients each, 5%).

Overall, 85 (55%) patients experienced peripheral neuropathy during the study; the event was considered Velcade-related for all but 1 patient. A total of 20 (13%) patients had peripheral neuropathy of Grade 3 intensity. Grade 4 peripheral neuropathy was reported in 1 patient (<1%). A total of 15 (10%) patients permanently discontinued Velcade because of peripheral neuropathy. This was the most common adverse event leading to Velcade discontinuation. The incidence of peripheral neuropathy in the current study (55%) was higher than that seen in the multiple myeloma Studies M34101-039 and M34101-040 (37% each), which included a total of 572 patients treated with Velcade.

Table 14: Applicant table of treatment-emergent AEs in \geq 10% of patients by MedDRA term

	N=155
MedDRA Preferred Term	n (%)
Asthenic conditions	112 (72)
Peripheral neuropathies	85 (55)
Constipation	77 (50)

Diarrhea NOS	73 (47)
Nausea	68 (44)
Appetite decreased	60 (39)
Rash NOS	43 (28)
Vomiting NOS	42 (27)
Dizziness (excluding vertigo)	36 (23)
Dyspnea NOS	35 (23)
Insomnia	33 (21)
Thrombocytopenia	33 (21)
Musculoskeletal pain	31 (20)
Edema lower limb	31 (20)
Cough	30 (19)
Pyrexia	30 (19)
Anemia NOS	27 (17)
Headache NOS	26 (17)
Abdominal pain NOS	24 (15)
Upper respiratory tract infection NOS	24 (15)
Weight decreased	24 (15)
Lower respiratory tract and lung infections	22 (14)
Arthralgia	20 (13)
Pruritus NOS	19 (12)
Abdominal distension	18 (12)

Table 12-4, CSR page 142)

Table 15: Applicant table of severe (grade 4 and 5) AEs, by MedDRA term for all patients

N = 155	Grade = 4	Grade = 5
MedDRA SOC / Preferred Term	n (%)	n (%)
Patients with at least 1 adverse event	22 (14)	5 (3)
General disorders	7 (5)	3 (2)
Disease progression NOS	4 (3)	3 (2)
Infections and infestations	4 (3)	0
Sepsis NOS	4 (3)	0
Blood and lymphatic system disorders	8 (5)	0
Thrombocytopenia	6 (4)	0
Neutropenia	3 (2)	0

Table 12-7, CSR page 148

Reviewer comments: The frequency and severity of AEs observed are consistent with prior experiences with Velcade and with the disease and prior therapy received by these patients. No unexpected findings were observed. Febrile neutropenia was reported in only one patient. The applicant's guidance for dose adjustments and interruption appear to be satisfactory in minimizing AEs from this therapy.

7.1.6 Less Common Adverse Events

Pulmonary edema was observed in two patients, one of whom was reported as consistent with the non-cardiogenic form. Nine patients reported grade 3 dyspnea. No grade 4 cases occurred. Three patients were reported as having an SAE of dyspnea. No patients were reported to have discontinued Velcade for breathing difficulties. The applicant was queried further on these cases. For each of these three, the dyspnea was in association with disease progression involving malignant pleural effusions and or mediastinal lymphadenopathy.

Reviewer comments:

Interstitial lung disease: (ILD) is not a MedDRA term so it is not captured directly. MedDRA does use a category termed parenchymal lung disorders NEC, and 3 patients were reported under this term, one of whom discontinued drug. The applicant was queried further on these cases. One patient was reported to develop pulmonary alveolar hemorrhage in association with severe thrombocytopenia and sepsis. One patient experienced pulmonary emboli and progressive mediastinal lymphadenopathy. The third patient also had progressive disease. These outcomes are not typical for the ILD syndrome.

Extravascular Fluid Retention: In the NCIC study, there were 3 fatal events associated with extravascular fluid retention associated with Velcade therapy. The applicant performed an analysis of adverse events considered to be representative of extravascular fluid retention in this study. Based on this analysis, 64 (41%) patients were identified as experiencing some type of extravascular fluid retention during the study. Two were considered serious (SAE), and three had pleural effusions grade ≥ 3 . However, most events were Grade 1 and 2 in severity, and none resulted in treatment discontinuation. Of the 60 patients for whom an exact date of onset was reported, 42 (70%) experienced the first onset of a potential extravascular fluid retention event in cycle 1 or cycle 2.

Fluid retention syndromes are adequately described in the current label, including pleural effusion, ascites, edema, congestive heart failure, and respiratory distress.

7.1.7 Laboratory Findings

Blood counts and chemistry profiles were performed weekly or at the start of each cycle and are adequate. No new adverse laboratory events were observed. In general, blood counts routinely returned to baseline by the start date of subsequent cycles.

7.1.7.1 Special assessments

Not applicable.

7.1.8 Vital Signs

Vital signs were recorded at the start of each cycle of treatment. No notable deviations were observed.

7.1.9 Electrocardiograms (ECGs)

ECGs were not performed in this study.

7.1.10 Immunogenicity

Not applicable

7.1.11 Human Carcinogenicity

See prior NDA reviews.

7.1.12 Special Safety Studies

None were performed.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

None

7.1.14 Human Reproduction and Pregnancy Data

Not applicable

7.1.15 Assessment of Effect on Growth

Not applicable

7.1.16 Overdose Experience

No additional cases of overdose occurred in this study. Overdose is described in the current label.

7.1.17 Postmarketing Experience

The applicant has submitted the following additions to the safety section:

There have been rare reports of pulmonary hypertension, temporally associated with VELCADE administration, in the absence of left heart failure or significant pulmonary disease. This addition is acceptable and is supported by IND safety reports in which evaluations did not identify alternative causes of the condition.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): There have been rare reports consistent with RPLS in patients receiving VELCADE in clinical trials and in post-marketing experience. RPLS is a rare, reversible, neurological disorder which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably MRI (Magnetic Resonance Imaging), is used to confirm the diagnosis. In patients developing RPLS, discontinue VELCADE. The safety of reinitiating VELCADE therapy in patients previously experiencing RPLS is not known. This addition is acceptable and is supported by IND safety reports in which evaluations did not identify alternative causes of the condition.

This reviewer suggests the following addition to the Administration section because of two overdose events in which the patient was given the entire contents of a vial rather than a dose based on body surface area: "The drug quantity contained in one vial (3.5 mg) may exceed the usual single dose required."

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The 155 patients in the applicant's study, supplemented by summary information in the additional supportive studies noted, are the source of the safety review.

7.2.1.1 Study type and design/patient enumeration

This information is provided in the efficacy section 6.1.4.

7.2.1.2 Demographics

This information is included in the efficacy section also.

7.2.1.3 Extent of exposure (dose/duration)

Patients were to receive 4 doses of Velcade 1.3 mg/m² in each treatment cycle on days 1, 4, 8, and 11; a total of 5.2 mg/m² in each 3-week cycle. The median dose administered during treatment Cycles 1 through 6 was 5.1 to 5.2 mg/m²; the median dose administered was lower in all subsequent cycles, ranging from 2.9 to 4.1 mg/m² from Cycles 7 through 17, related to dose reductions and interruptions. Through the first 5 cycles, patients received a median of greater than 90% of the pro forma dose (see applicant table 14.5.1.3, CSR). Responders received a median of 8 cycles.

The proportion of patients treated with Velcade within a given cycle who missed at least one dose in that cycle for adverse event ranged from 6% to 10% in Cycles 1 through 5. The

proportion of patients with doses held for other reasons was low in all cycles (< 5%). No patients had a dose reduction during Cycle 1; dose reductions were reported in 4% to 6% of patients in Cycles 2 through 7 and in < 2% of patients in all remaining cycles. Dose delays also were unusual (< 5% of doses).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The AERS data was searched for ILD and cardiac AEs during this review. No unexpected or unusual signals were identified.

7.2.2.1 Postmarketing experience

The Velcade label has had 3 safety updates since the original approval in 2003 and currently reflects accurately the known safety profile of the drug. See also 7.1.17

7.2.2.2 Literature

No relevant additional literature sources are informative for this drug.

7.2.3 Adequacy of Overall Clinical Experience

The clinical experience is adequate to estimate the effect of Velcade in this disease in a relapsed-refractory population, given the uncommon frequency of this disease setting.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable

7.2.5 Adequacy of Routine Clinical Testing

Blood counts and chemistry profiles were performed weekly or at the start of each cycle and results are adequate for assessing hematologic tolerance. No new adverse events were observed.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Not applicable

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

7.2.8 Assessment of Quality and Completeness of Data

In conjunction with the phase 3 myeloma studies, the safety profile of Velcade is reasonably well described. A similar dose and schedule have been used in most of the clinical trials and exposure has been adequate to assess appropriate dose levels for the majority of treated patients. The applicant has made appropriate efforts to examine the safety of the drug and has been proactive in updating the label.

7.2.9 Additional Submissions, Including Safety Update

Since the study data were mature, no safety update was provided or requested.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

No specific additional safety issues have been observed in the studies contributing to this sNDA.

7.4 General Methodology

The exploration of Velcade therapy in a single arm study design in patients with advanced and previously treated MCL does not provide a precise assessment of all safety concerns but is sufficient to endorse approval of the product for this condition primarily based on its efficacy.

7.4.1 Explorations for Predictive Factors

The AE profile of Velcade overall is similar for patients with myeloma or MCL, previously treated.

7.4.2 Causality Determination

The similarity in AE profile is most likely causally related to the effects of the Velcade.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

While 2 dose regimens have been evaluated in the studies provided, there is no evidence of superiority for the higher dose schedule and the applicant has selected the 1.3 mg/m² on days 1, 4, 8, and 11 every 21 days for the indication. This is the same as the myeloma schedule. The label dose-adjustments schedule remains satisfactory to guide ongoing dosing.

8.2 Drug-Drug Interactions

None were identified in these studies of Velcade as a single agent. The concomitant medications used on study are typical for an advanced cancer population. There was a higher prevalence of prior vinca alkaloid use in this lymphoma population than in the previous myeloma study (95% versus 77%) which may have contributed to the higher neuropathy incurred in the MCL patients.

8.3 Special Populations

Of the 155 patients, the median age was 65 years; 80% were male, and 92% were White. MCL is not a disease of childhood, and a pediatric waiver was granted. Patients with moderate or severe renal or hepatic impairments at baseline were excluded (baseline limits were aspartate transaminase ≤ 3 x upper limit of normal (ULN), alanine transaminase ≤ 3 x ULN, total bilirubin ≤ 2 x ULN, and creatinine ≤ 2 mg/dL or calculated creatinine clearance ≥ 50 mL/min).

8.4 Pediatrics

MCL is not a disease of childhood.

8.5 Advisory Committee Meeting

No advisory committee meeting was held.

8.6 Literature Review

The applicant's literature review was complete and satisfactory.

8.7 Postmarketing Risk Management Plan

No additional measures are warranted by these study results.

8.8 Other Relevant Materials

Dr. Alexandra Levine, ODAC member, was cleared by the Advisors and Consultants staff and reviewed the protocol and results. Dr. Levine's conclusions were:

- The achievement of PR in relapsed/refractory MCL is a meaningful treatment effect, indicating clinical benefit, especially in patients with organ involvement/impingement, which could be substantially improved with attainment of PR status, and the duration of PR is clinically meaningful at 6-7 months; the responses were achieved across all patient characteristics and therapeutic history. Thus, as stated in the briefing document, similar rates of PR were seen in both relapsed and *refractory* patients, and across all other sub-groups
- The CR (plus CRu) rate of 8% is clinically meaningful and indicative of clinical benefit.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy is demonstrated by the responses and the durability of these responses, obtained with Velcade in this population of MCL patients who had exhausted all available therapy. Such patients would otherwise be expected to experience progressive deterioration and death within a relatively short time interval. Safety is adequate in the context of this disease state and is not materially different than that found in the myeloma experience. The current label provides the information necessary for safe and appropriate use of Velcade.

Regular approval is appropriate for the applicant's indication.

9.2 Recommendation on Regulatory Action

This section duplicates section 1.1

9.3 Recommendation on Postmarketing Actions

This section duplicates section 1.2

9.3.1 Risk Management Activity

This section duplicates section 1.2.1

9.3.2 Required Phase 4 Commitments

This section duplicates section 1.2.2

9.3.3 Other Phase 4 Requests

This section duplicates section 1.2.3

9.4 Labeling Review

Detailed labeling review has been conducted by the review team. See section 7.1.17 for postmarketing experience to be added to the current label.

9.5 Comments to Applicant

10 APPENDICES

10.1 Review of Individual Study Reports

10.2 Line-by-Line Labeling Review

A line-by line review was conducted.

10.3 IWG Response criteria (Cheson et al, J Clin Oncol 1999)

Table 16: IWG Response Criteria for Non-Hodgkin's Lymphoma

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
CRu	Normal	Normal	Normal	Indeterminate
	Normal	Normal	> 75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥ 50% decrease	≥ 50% decrease	Irrelevant
	Decrease in liver/spleen	≥ 50% decrease	≥ 50% decrease	Irrelevant
Relapse/progression	Enlarging liver/spleen; new sites	New or increased	New or increased	Reappearance

Note that Gallium, PET, and other isotope scans are not part of these response criteria.

The following text is from the IWG article.

The following criteria are considered anatomic definitions (Table above). In the future, as additional radiographic, laboratory, and functional studies become more widely available and clearly demonstrate predictive value, they may be recommended as well.

CR requires the following:

1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities (eg, lactate dehydrogenase [LDH]) definitely assignable to NHL.
2. All lymph nodes and nodal masses must have regressed to normal size (< 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to < 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).
3. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size. For

instance, spleens thought to be of normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes. The determination of splenic volume or splenic index by CT scan is cumbersome and not widely used. Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.

4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site. The sample on which this determination is made must be adequate (> 20 mm biopsy core). Flow cytometric, molecular, or cytogenetic studies are not considered part of routine assessment to document persistent disease at the present time. These studies should only be incorporated into trials examining important research questions.

CR/unconfirmed (CRu) includes those patients who fulfill criteria 1 and 3 above, but with one or more of the following features:

1. A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.
2. Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

PR requires the following:

1. > 50% decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from as disparate regions of the body as possible, and (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase in the size of the other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by at least 50% in the SPD.
4. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.
5. Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified in the report, eg, large-cell lymphoma or low-grade lymphoma (ie, small, lymphocytic small cleaved, or mixed small and large cells).
6. No new sites of disease. Stable disease is defined as less than a PR (see above) but is not progressive disease (see below).

Relapsed disease (CR, CRu) requires the following:

1. Appearance of any new lesion or increase by > 50% in the size of previously involved sites.
2. > 50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

Progressive disease (PR, nonresponders) requires the following:

1. > 50% increase from nadir in the SPD of any previously identified abnormal node for PRs or nonresponders.
2. Appearance of any new lesion during or at the end of therapy.

Response Assessment

Response is currently assessed on the basis of clinical, radiologic, and pathologic (ie, bone marrow) criteria.

1. CT scans remain the standard for evaluation of nodal disease. Thoracic, abdominal, and pelvic CT scans are recommended even if those areas were not initially involved because of the unpredictable pattern of recurrence in NHL. Studies should be performed no later than 2 months after treatment has been completed to assess response. This interval may vary with the type of treatment, eg, a longer period may be more appropriate for biologic agents where the anticipated time to response may be greater.
2. A bone marrow aspirate and biopsy should only be performed to confirm a CR if they were initially positive or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear.

End Points

The major end points of interest in clinical trials should include event-free survival (time to treatment failure), which includes failure or death from any causes, freedom from progression, and overall survival (Table 3). These outcomes are more relevant in NHL than response rates. Overall survival and failure-free survival are measured from entry onto a trial until death from any cause, or until death or progression of disease, respectively. Progression-free survival for all patients is taken from the time of entry onto study until disease progression or death from NHL. This end point is more important in aggressive NHL, where it correlates better with survival than in follicular NHL.

Secondary end points such as response duration, disease-free survival, or cause-specific survival may also be included, but only when the other end points have been reported. Disease-free survival for patients in CR or CRu is measured from the first assessment that documents that response to the date of disease progression, generally within 2 months of completion of therapy. For patients with an indolent NHL, response duration may be less clinically important than the point at which initiation of treatment is necessary; however, uniform criteria should be used for that end point. These include disease-related symptoms, threatened end-organ function, cytopenias secondary to NHL, massive bulk disease, or steady progression over at least 6 months

Table 17: Applicant's modifications to algorithmic definition of Progressive Disease

Criterion	Original PD definition	Revised PD definition
#1	Appearance of any new assessable site of lymphoma or a positive bone marrow aspirate/biopsy has appeared, when it was negative or indeterminate at baseline.	Same as original algorithm
#2	At least 50% increase in the product of the perpendicular dimensions for any single measurable lesion.	At least 50% increase in the product of the perpendicular dimensions for any single measurable lesion, and that lesion is greater than 1.0 cm in both perpendicular dimensions at the time of PD, and the absolute increase in either dimension is at least 0.5 cm.

#3	At least 50% increase in the longest dimension of any measurable lesion.	At least 50% increase in the longest dimension of any measurable lesion, and that lesion is greater than 1.0 cm in both perpendicular dimensions at the time of PD, and the absolute increase in the longest dimension is at least 0.5 cm.
#4	At least 50% increase in the size of any previously identified, assessable (not measurable) site of lymphoma.	Same as original algorithm

Applicant's Table 2.7.3-2

a In all cases the smallest prior measurement is used as the baseline for comparison when evaluating for progressive or relapsed disease.

11 REFERENCES

¹ Cheson BD, Horning SJ, Coiffier B, Shipp M, Fisher R, Connors J, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. *J Clin Oncol* 1999; 17: 1244-1253.

² Harris NL, Jaffe ES, Stein H, Banks P, Chan JKC, Cleary M et al. A Revised European-American Classification of Lymphoid Neoplasms: A Proposal from the International Lymphoma Study Group *Blood* 1994; 84:1361-1392.

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/s/

Robert Kane
12/5/2006 09:08:19 PM
MEDICAL OFFICER

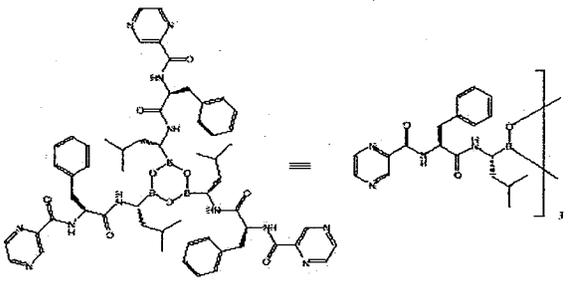
Ann Farrell
12/6/2006 08:05:54 AM
MEDICAL OFFICER
I concur.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-602 / S-010

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW		1. ORGANIZATION ONDQA		2. NDA NUMBER 21-602	
3. NAME AND ADDRESS OF APPLICANT (City and State) Millennium Pharmaceuticals, Inc. 75 Sidney St. Cambridge, MA 02139				4. AF NUMBER	
6. NAME OF DRUG VELCADE		7. NONPROPRIETARY NAME bortezomib for injection		5. SUPPLEMENT (S) NUMBER(S) DATES(S) SEI-010 7/8/2006	
8. SUPPLEMENT PROVIDES FOR: new indication of mantle cell lymphoma				9. AMENDMENTS DATES	
10. PHARMACOLOGICAL CATEGORY Antineoplastic		11. HOW DISPENSEDRX OTC <input checked="" type="checkbox"/>		12. RELATED IND/NDA/DMF None	
13. DOSAGE FORM(S) Injection		14. POTENCY 3.5 mg/vial			
15. CHEMICAL NAME AND STRUCTURE [(1R)-3-Methyl-1-[[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]boronic acid $C_{19}H_{25}BN_4O_4$, MW = 384.24				16. RECORDS AND REPORTS	
				CURRENT YES <input checked="" type="checkbox"/> NO	
				REVIEWED YES <input checked="" type="checkbox"/> NO	
17. COMMENTS In this efficacy supplement, the applicant claimed that all the CMC information is same as those in the approved NDA 21-602 and no new chemistry, manufacturing and control information was needed to submit. The requirement of filing categorical exclusion for environment assessment was waived by agency.					
18. CONCLUSIONS AND RECOMMENDATIONS Approval is recommended based on the CMC information provided in this application.					
NAME Chengyi Liang, Ph.D.		SIGNATURE			DATE 12/7/2006
DISTRIBUTION	ORIGINAL NDA	DIVISION FILE	Reviewer: C.Y. Liang	CSO:	H. Patel Branch Chief

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this page is the manifestation of the electronic signature.**

/s/

Chengyi Liang
12/7/2006 12:30:15 PM
CHEMIST

Liang Zhou
12/7/2006 01:40:08 PM
CHEMIST

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-602 / S-010

PHARMACOLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-602
SERIAL NUMBER: 010
DATE RECEIVED BY CENTER: 7/8/06
PRODUCT: VELCADE®
INTENDED CLINICAL POPULATION: Relapsed and refractory multiple myeloma
SPONSOR: Millennium Pharmaceuticals, Inc.
DOCUMENTS REVIEWED: Vol. 4
REVIEW DIVISION: Division of Drug Oncology Products
PHARM/TOX REVIEWER: S. Leigh Verbois, Ph.D.
PHARM/TOX SUPERVISOR: David Morse, Ph.D.
DIVISION DIRECTOR: Robert Justice, M.D.
PROJECT MANAGER: Tammie Brent-Steele

Date of review submission to Division File System (DFS): December 4th, 2006

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-602

Review number: 2

Sequence number/date/type of submission: 003/June 8th, 2006/SE1

Information to sponsor: Yes () No (X)

Sponsor and/or agent: Millennium Pharmaceuticals, Inc.

Manufacturer for drug substance: Ash Stevens, 18655 Krause Street,
Riverview, MI 48192

Reviewer name: S. Leigh Verbois, Ph.D.

Division name: Division of Drug Oncology Products

Review completion date: 12/1/06

Drug:

Trade name: VELCADE®

Generic name: Bortezomib

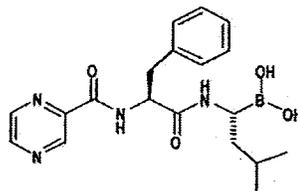
Code name: PS341

Chemical name: N-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic acid

CAS registry number: 179324-69-7

Molecular formula/molecular weight: C₁₉H₂₅BN₄O₄ / 384.24

Structure:



Relevant INDs/NDAs/DMFs: IND 56,515

Drug class: Proteasome Inhibitor

Intended clinical population: Relapsed and refractory multiple myeloma

Clinical formulation: Sterile lyophilized powder in single dose vial containing 3.5 bortezomib and
/ mg mannitol. b(4)

Route of administration: Bolus IV injection

Proposed use: The recommended dose of VELCADE is 1.3 mg/m²/dose administered as a bolus intravenous injection twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21).

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

2.6.2.3 Pharmacology**Title: Western Blot Analysis for the Presence of Proteinase K-Resistant Forms of Prion Protein After Proteasome Inhibition of Neuronal Cell Lines *In Vitro***

Testing Facility: Millennium Pharmaceuticals, Inc., Cambridge, MA.

The study was started 20 May 2003 and was completed on 12 December 2003.

Objective: To determine if pharmacologically relevant concentrations of bortezomib results in the accumulation of normal or detergent-insoluble and proteinase K-resistant forms of protein isoforms of the prion protein (PrP) in the cytosol of non-transfected mouse (N2A, GT-1) and human (NT-2) neuronal cells *in vitro*.

1. Determine pharmacologically relevant concentration ($\leq 80\%$ proteasome inhibition) of bortezomib in N2A, GT-1, and NT-2 cells.

Methods:

Expose each cell line to bortezomib at concentrations ranging from 0.001 μM to 10 μM for 16 hours. Proteasome activity was measured as described in Lightcap et al. with a small modification. Protein concentration was determined by the Bradford assay and the 20S specific activity of the proteasome (chymotryptic) was calculated as pmol LLVY-AMC/second/mg protein.

Results:

Greater than 75% inhibition was attained with < 10 nM concentrations of bortezomib for all neuronal cell lines examined (see table 2).

Table 2 Bortezomib Concentrations Causing 75% Proteasome Inhibition in GT-1, NT-2, and N2a Cell Lines Following a 16-Hour Incubation

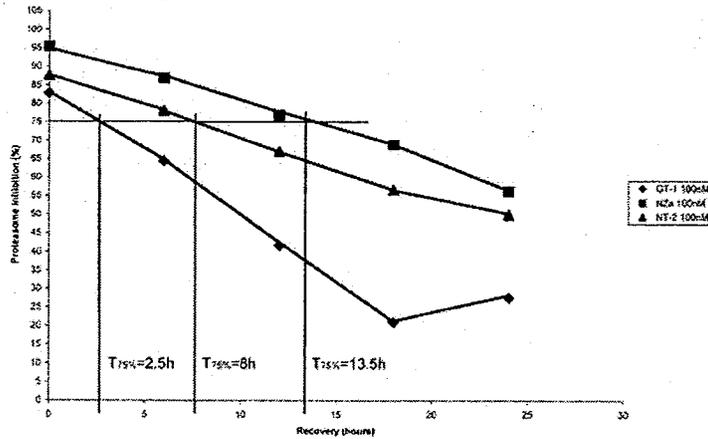
Cell Type	Concentration of Bortezomib (nM) That Yields 75% Proteasome Inhibition
GT-1	6.5
NT-2	8
N2a	6.5

-Based on these results, for each experiment, 10 nM bortezomib was used as the pharmacologically relevant concentration.

-To examine suprapharmacologic concentration of bortezomib on human neuronal cell lines, NT-2 cells were treated with 100 nM bortezomib for 16 hours.

2. To examine transient inhibition and recovery, proteasome inhibition after 2 hours of exposure and a 24-hour washout period was determined at ~75% inhibition.

Recovery of Proteasome Activity in Cell Lines Treated With 100 nM Bortezomib for 2 Hours



- Seventy-five percent proteasome inhibition was observed up to a 2.5-, 8-, and 13.5-hour washout for GT-1, NT-2, and N2a cells, respectively.
- Based on these results, in experiments with murine GT-1 and N2a cells, extracts were collected from cells harvested after either a 3-hour (GT-1) or 13.5 hour (N2a) washout.

3. The inhibition levels for lactacystin (10 μM), epoxomicin (5 μM), MG-132 (10 μM), and bortezomib (0.01 μM) in NT-2 cells were determined

Table 3 Inhibition (%) of the Proteasome with Various Proteasome Concentrations in NT-2, Differentiated Human Neuroblastoma Cells for 16 Hours

Inhibitors	Concentration (μmoles)	Inhibition (%)
Control	0	0
Lactacystin	10	89.2
Epoxomicin	5	98.5
MG-132	10	87.2
MG-132	50	86.6
Bortezomib	10	97.0
Bortezomib	0.1	96.8
Bortezomib	0.01	83.8

- >80% inhibition of the proteasome was achieved in NT-2 cells.
- Results indicate comparable inhibition of the proteasome for chosen concentrations of proteasome inhibitors lactacystin, epoxomicin, MG-132, and bortezomib.

Detection of PrP Method Validation

Validation of PrP^C and PrP^{Sc} detection was conducted using human tissue extract as a control (see Figure 1 below).

- Human PrP^C was detectable prior to protease digestion (Lane 1, Figure 1).
- Detection of PrP^{Sc} occurred after treatment with proteinase K and deglycosylase (PNGase F) (Lane 2, Figure 1), yielding a single, unglycosylated, proteinase K-resistant fragment ~16-Kd that was detectable with the 3F4 antibody at the specified dilution. This band was more intense than other detectable bands.

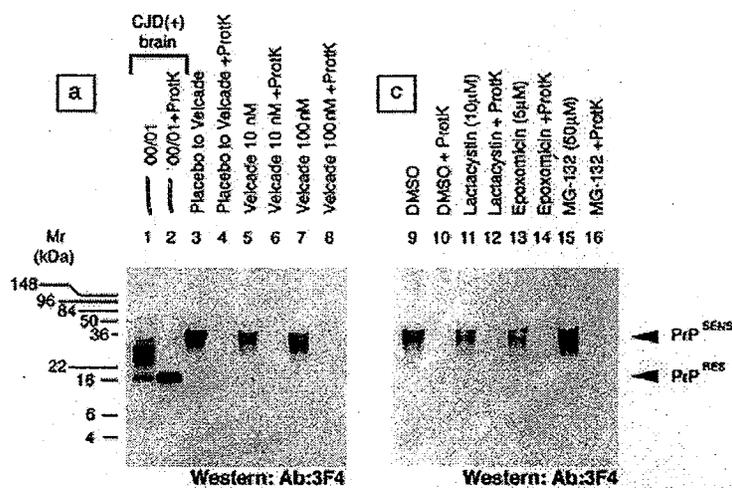
Human NT-2 Results

Methods:

Human neuronal cell lines, NT-2 cells, were treated with protease inhibitors (bortezomib, lactacystin, epoxomicin, or MG-132) at doses that induce >80% protease inhibition for 16 hours and processed for Western analysis.

- Mouse and human brain extracts were used as controls for endogenous PrP^C.
- Protein extract from a Creutzfeldt-Jakob disease (CJD) patient after proteinase K plus deglycosylase (PNGase F) treatment served as the positive control for PrP^{Sc}.
- Protein load was verified by staining gels with coomassie brilliant blue and analysis of constitutive β-actin.
- Verification of proteasome inhibition was demonstrated by accumulation of c-jun after exposure of each cell line to bortezomib, lactacystin, epoxomicin, or MG-132 treatments.

Results:



b(6)

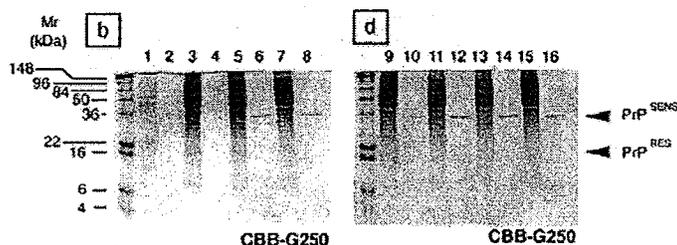
- Lanes 1 and 2 (Figure 1a) are representative of a protein extract from CJD patient (— T00/01) before and after proteinase K plus deglycosylase (PNGase F) treatment. A protease-resistant fragment is seen ~16 kDa.
- Using Western analysis, NT-2 cells were shown to have abundant endogenous PrP (PrP^C) expression.
- Both 10 nM and 100 nM treatments of bortezomib (Lanes 5–8) did not produce a protease resistant fragment and do not show an accumulation of PrP^C as compared to placebo (Lane 3) or DMSO (Lanes 9–10) controls. Although this is not a quantitative assay, it is noteworthy that may be a dose-related increase in bortezomib-induced PrP^C staining compared to the placebo control.

b(6)

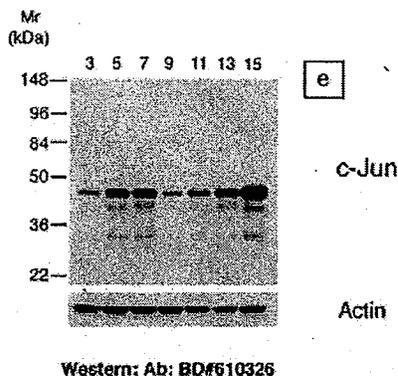
- Similarly, lactacystin at 10 μ M (Lanes 11 and 12), epoxomicin at 5 μ M (Lanes 13 and 14), and MG-132 at 50 μ M (Lanes 15 and 16) did not induce a proteinase K-resistant fragment. These protease inhibitors do not show a significant accumulation of PrP^C as compared to placebo (Lane 3) or DMSO (Lanes 9-10) controls. Although this is not a quantitative assay, it is noteworthy that MG-132-induced PrP^C staining appears greater compared to the DMSO control.

The Sponsor claims that, under the conditions of these assays, there does not appear to be an increase in the amount of PrP^C or the conversion of normal PrP^C into a proteinase K-resistant PrP^{Sc}-like form upon proteasome inhibition treatment with bortezomib, lactacystin, epoxomicin, or MG-132 in human NT-2 cells. At the moment, we cannot concur with this assessment (please refer to conclusions).

Coomassie brilliant blue staining of gels indicated comparable amounts of protein loading (Figure 1b, d).



Validation of proteasome inhibition was conducted evaluating the same extracts for concentration of c-jun, a known target for the ubiquitin-proteasome degradation pathway that accumulates when proteasome function is compromised.



- Compared to control extracts, there is an accumulation of c-jun protein after proteasome inhibition by bortezomib, lactacystin, epoxomicin, and MG-132 (Figure 1e).
- Under control and DMSO conditions, c-jun levels are barely detectable.
- The lower bands of the c-jun blot may be indicative of degradation products of both the non-ubiquitinated and ubiquitinated forms of c-jun, but other secondary modifications can also play a role.

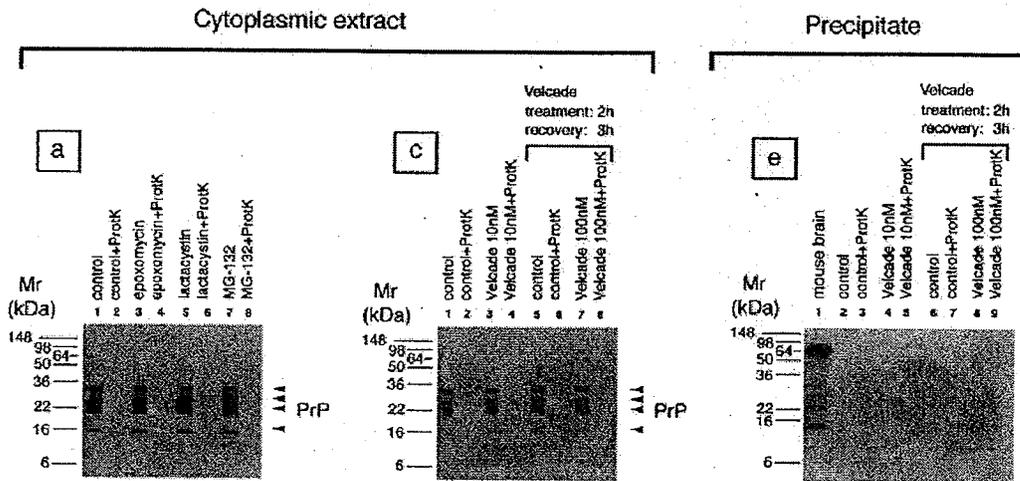
Murine GT-1 Results

Methods:

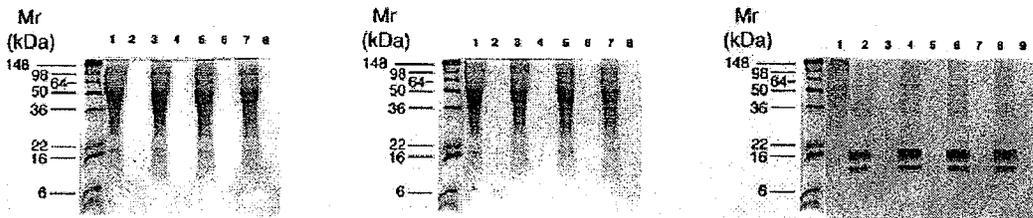
Extracts were collected from cells harvested after 3-hour washout.

Results:

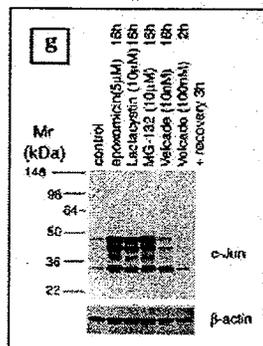
- GT-1 cells had abundant endogenous PrP expression.
- Bortezomib, epoxomicin, lactacystin, and MG-132 treatments all showed comparable pattern of PrP expression compared to control (Figure 2a).
- Western blot analysis for GT-1 cells treated with proteasome inhibitors did not produce a proteinase K fragment in all treatment groups.
- PrP pattern of staining in GT-1 mouse line is different to the pattern of staining in mouse line N2a and human line NT-2. There is an additional band at 16 kDa in GT-1 cell line under all conditions. If that band is the unglycosylated form of PrP^C, that suggest its existence in all conditions, including control and drug treated. Further suggesting that PrP protein expression is different in mouse and human.



Bortezomib, epoxomicin, lactacystin, and MG-132 treatments showed comparable protein load as indicated by coomassie brilliant blue protein stained gels.

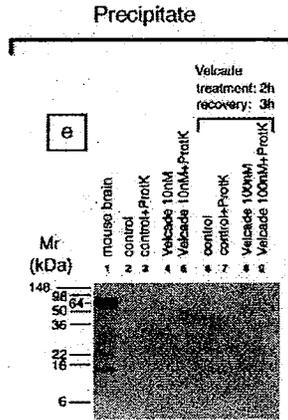


Compared to control levels, there is an accumulation of c-jun after proteasome inhibition induced by bortezomib, lactacystin, epoxomicin, and MG-132 treatments (Figure 2g).



Precipitates were also processed to show that PrP, under this extract protocol, does not remain insoluble in the precipitate (Figure 2e).

- Using mouse brain extract as a positive control, precipitates did not yield detectable levels of PrPC or a proteinase K-resistant form.



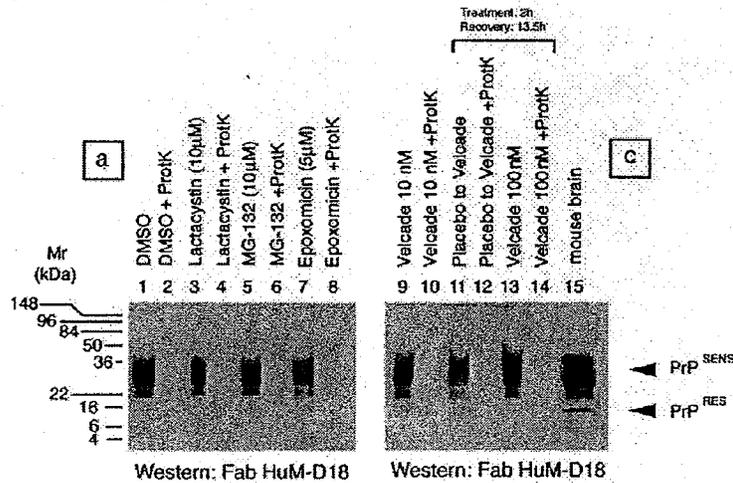
Murine N2a Results

Methods:

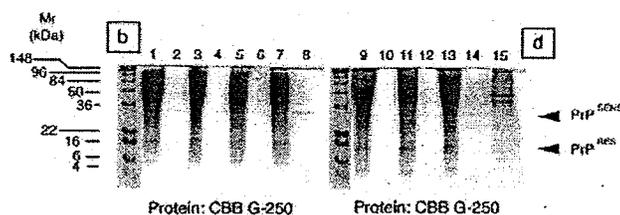
Extracts were collected from cells harvested after 13.5 hour (N2a) washout.

Results:

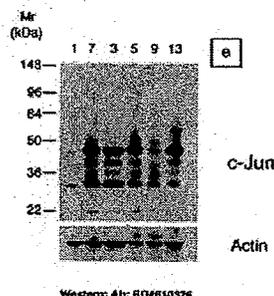
- N2a cells had abundant endogenous PrP expression. Endogenous PrP was observed in all treatment groups and control groups as validated by mouse brain extract control (Lane 15).
- The Sponsor reports that in N2a cells treatment with proteasome inhibitors did not yield an increase of PrP or the generation of a protease K-resistant fragment as indicated by Western analysis (Figure 3a, c). However, PrP expression appears greater in bortezomib treated samples (both doses) compared to the placebo control.



Protein load was verified by coomassie brilliant blue staining (Figure 3b, d).



Compared to constitutive β -actin, there is an accumulation of c-jun after proteasome inhibition induced by bortezomib, lactacystin, epoxomicin, and MG-132 treatments (Figure 3e).



Conclusions:

The Sponsor concludes that, under the conditions of these assays, murine GT1 and N2a and human NT-2 cell lines showed abundant endogenous PrP (PrP^C) expression. In these three nontransfected cell lines, there does not appear to be an increase in the amount of endogenous PrP^C or the conversion of normal PrP^C into a proteinase K-resistant PrP^{Sc}-like form after treatment with bortezomib, lactacystin, epoxomicin, or MG-132 as measured by Western analysis. Furthermore, the Sponsor states that these results with bortezomib are in agreement with recent publications indicating no PrP^{Sc}-like formation after proteasome inhibition with other prototypical proteasome inhibitors in nontransfected neuronal cell lines or in primary neurons of rodent or human origin at pharmacologically relevant levels of proteasome inhibition.

However, these issues may need to be clarified if the patient population includes treatment of patients with a longer life expectancy.

1. The Sponsor states that detection of PrP^{Sc} occurred after treatment with proteinase K and deglycosylase (PNGase F), yielding a single, unglycosylated, proteinase K-resistant fragment that was detectable with the 3F4 antibody at the specified dilution. This is based on western blot analysis of a protein extract from a CJD patient after proteinase K plus deglycosylase (PNGase F). Clarification of how the methods utilized herein differ from the general literature which reports PrP^{Sc} as a band of ~28kDa, not 16kDa, will need to be provided.
2. The pattern of PrP expression appears different between GT-1 and N2a neuroblastoma cell lines. Specifically, there is a 16kDa band in the GT-1 cell line that is absent in the N2a cell line. This band, according to the sponsor's assessment, would represent the unglycosylated, proteinase resistant form of PrP or PrP^{Sc}.
3. We note that the Sponsor did not attempt any quantitative or semi-quantitative analysis of protein expression. Nonetheless, it is noteworthy that in NT-2 cells, there may be a dose-related increase in bortezomib-induced PrP^C staining compared to the DMSO control. Additionally, it is unclear what the "placebo to Velcade" is. The sponsor should clarify whether placebo means saline control. Also in NT-2 cells, there appears to be an increase

in MG-132-induced PrP expression compared to the DMSO and placebo controls. In general, these results suggest an increase in PrP^C expression in nontransfected NT-2 cells treated with bortezomib and MG-132. The absence of any bands after proteinase K and PNGase F would suggest that PrP^{Sc} is not present in the supernatant of this protein extract. However, since the precipitate was not evaluated for this experiment, it cannot be concluded that PrP^{Sc} has become insoluble and is not present after treatment with these compounds.

4. In GT-1 cells, bortezomib, epoxomicin, lactacystin, and MG-132 treatments all showed comparable pattern of PrP expression compared to control. However, the levels of expression appears slightly higher, especially the ~29 kDa band, in drug-treated samples compared to control. In the absence of a quantitative assessment, an increase in PrP expression cannot be ruled out.
5. The Sponsor reports that in N2a cells treatment with proteasome inhibitors did not yield an increase of PrP. However, PrP expression appears greater in bortezomib-treated samples (both doses) compared to the placebo control. Similar to NT-2 cells, the absence of any bands after proteinase K and PNGase F would suggest that PrP^{Sc} is not present in the supernatant of this protein extract. However, since the precipitate was not evaluated for this experiment, it cannot be concluded that PrP^{Sc} has become insoluble and is not present after treatment with these compounds.

Discussion

Normal or cellular prion proteins (PrP^C) are cell surface glyco-proteins found in neurons. It has been proposed that this protein may have a role in normal brain copper metabolism (Brown DR. Copper and prion disease. *Brain Res Bull.* 2001 May 15;55(2):165-73]. Prion diseases are (spongiform encephalopathies) a group of closely-related neurodegenerative conditions of animals and humans that occur as sporadic, inherited, or transmissible forms. Prion diseases are believed to result from the conversion of PrP^C, the normal, α -helical rich, protease-sensitive form of PrP, to PrP^{Sc}, a misfolded, β -rich, and protease-resistant isoform of the protein (Prusiner SB. Prions. *Proc Natl Acad Sci USA.* 1998; 95:13363-83). Examples include Creutzfeldt-Jakob disease (CJD) in humans and bovine spongiform encephalopathy (BSE). CJD generally presents as progressive dementia, whereas scrapie of sheep and BSE are generally manifest as ataxic illnesses. (Wells GA, Scott AC, Johnson CT, Gunning RF, Hancock RD, Jeffrey M, Dawson M, Bradley R. A novel progressive spongiform encephalopathy in cattle. *Veit Rec.* 1987 Oct 31;121(18):419-20; Prusiner SB *PNAS* 1998) These pathologies are characterized by large vacuoles in the cerebral cortex and cerebellum, neuronal loss, and cerebral accumulation of a protease-resistant form of prion protein. (Ma J, Lindquist S. Conversion of PrP to a self-perpetuating PrP^{Sc}-like conformation in the cytosol. *Science.* 2002;298(5599):1785-88.)

Near the time of the bortezomib (VELCADETM) NDA submission, two manuscripts were published which suggested a potential theoretical link between inhibition of the proteasome and prion disease as indicated by the accumulation and cytotoxicity of an unglycosylated and proteinase K-resistant form of PrP (PrP^{Sc}-like) in the cytoplasm of wildtype PrP transfected cells. (Ma J, Lindquist S. Conversion of PrP to a self-perpetuating PrP^{Sc}-like conformation in the cytosol. *Science.* 2002;298(5599):1785-88 and Yedidia Y, Horonchik L, Tzaban S, Yanai A, Taraboulos A. Proteasomes and ubiquitin are involved in the turnover of wild-type prion protein. *EMBO J.* 2001;20(9):5383-91.) The role of the proteasome in PrP processing and the cytotoxic potential of

cytosolic PrP remains controversial. However, since the clinical relevance of these observations was not clear, Millennium Pharmaceuticals, Inc., and the FDA agreed to the following Phase 4 commitment. "Conduct an additional *in vitro* study in mammalian cells transfected with the normal PrP gene to determine if pharmacologically relevant concentrations of bortezomib result in the accumulation of normal, misfolded, or detergent insoluble and proteinase resistant forms of PrP protein in the cytosol, similar to results obtained with other proteasome inhibitors as reported by Ma and Lindquist, 2002. As appropriate, further investigations should be undertaken to understand the implications of any observed effects."

Recent literature (Drisaldi et al., 2003; Roucou et al., 2003) has questioned the relevance of the PrP transfected cell model since the findings of Ma and Lindquist were not duplicated in nontransfected normal wild- type PrP-expressing neuronal cell lines or in primary neurons of both rodent and human origin. Investigators (Drisaldi B, Stewart RS, Adles C, Stewart LR, Quaglio E, Biasini E, et al. Mutant PrP is delayed in its exit from the endoplasmic reticulum, but neither wild- type nor mutant PrP undergoes retrotranslocation prior to proteasomal degradation. *J Biol Chem.* 2003; 278: 21732- 43 and Biasini E, Fioriti L, Ceglia I, Invernizzi R, Bertoli A, Chiesa R, et al. Proteasome inhibition and aggregation in Parkinson's disease: a comparative study in untransfected and transfected cells. *J Neurochem.* 2004; 88(3): 545- 53) have attributed this discrepancy between transfected and nontransfected cells to proteasome inhibitors selectively altering transcription from expression constructs carrying a heterologous viral promoter resulting in abundant PrP mRNA and an elevated protein synthetic rate. These findings have been extended to other proteins expressed from a heterologous promoter (Biasini E, Fioriti L, Ceglia I, Invernizzi R, Bertoli A, Chiesa R, Forloni G. *J Neurochem.* 2004 Proteasome inhibition and aggregation in Parkinson's disease: a comparative study in untransfected and transfected cells Feb;88(3):545-53) suggesting that studies with proteasome inhibitors, in systems where proteins are expressed from a heterologous promoter, are subjected to potential artifacts that need to be considered. Thus, the potential artifact observed when using proteasome inhibitors in PrP-transfected cells makes meaningful interpretation of results difficult. In consideration of the recent literature regarding the limitations of the PrP- transfected *in vitro* cell system, Millennium conducted studies in nontransfected murine N2a and GT-1, and human NT- 2 cell lines.

In addition, cytosolic PrP was not cytotoxic in primary murine and human cerebellar granular neurons, indicating that the toxic potential of cytosolic PrP is cell- type specific. (Drisaldi et al., 2003; Roucou et al., 2003). Moreover, the observed phenomenon of the conversion of PrP^C to PrP^{Sc}- like prion protein is not unique to proteasome inhibitors. Cyclosporin A, an inhibitor of the cyclophilin family peptidylprolyl isomerases (PPIases) involved in protein folding, has caused a similar accumulation of proteinase K- resistant forms of PrP in transfected N2a cells. (Cohen E, Taraboulos A. Scrapie- like prion protein accumulates in aggresomes of cyclosporin A- treated cells. *EMBO J.* 2003; 22(3): 404- 17). In addition, the reducing, dithiothreitol (DTT), and tunicamycin, which reduced glycosylation in PrP transfected N2a cells, resulted in accumulation of proteinase K- resistant forms of PrP. (Ma J, Lindquist S. De novo generation of a PrP^{Sc}- like conformation in living cells. *Nat Cell Biol.* 1999; 6: 358- 61).

To accomplish the aims of the Phase 4 commitment, the pharmacologically-relevant concentration (up to ~ 75% proteasome inhibition) of bortezomib was determined *in vitro*. The percent 20S proteasome inhibition was determined after 16 hours of incubation with bortezomib for each cell line studied. Greater than 80% inhibition was attained with 7.5-10 nM concentrations of bortezomib for

all neuronal cell lines examined. For each experiment, 10nM bortezomib was used as the pharmacologically-relevant concentration. In order to examine inhibition levels of other proteasome inhibitors, NT- 2 cells were exposed to 10 μ M lactacystin, 5 μ M epoxomicin, and 10 and 50 μ M MG- 132 for 16 hours; inhibition was shown to be comparable to that induced by bortezomib. This approach appears acceptable.

Due to the discrepancy in the literature between results obtained with proteasome inhibitors in PrP-transfected and nontransfected cells, possibly related to altered transcription from expression constructs carrying a heterologous viral promoter, the Sponsor decided to investigate the effect of bortezomib on nontransfected neuronal cells. This approach appears acceptable.

In Report RPT-003015, the Sponsor states that nontransfected murine N2a and GT-1 and human NT-2 cell lines were utilized according to the procedures of Ma and Lindquist. However, the Sponsor needs to clarify on the apparent discrepancy in band size as related to the identification of PrP^{Sc}. The Sponsor states that there was no increase in PrP^C expression or detergent insoluble and proteinase-resistant forms of PrP protein as determined by Western analysis when nontransfected murine N2a, GT- 1, or human NT- 2 cells were treated with high concentrations of epoxomicin, lactacystin, MG- 132, or bortezomib. Please refer to conclusions section.

In summary, at this point, we recognize a good faith attempt on the part of the Sponsor to complete their Phase IV commitment.

To date, VELCADE™ (bortezomib) is indicated for the treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy. In this context, the theoretical risk of encephalopathy's resulting from an interaction of bortezomib and PrP^C or the potential exacerbation of the conversion of PrP^C to PrP^{Sc} does not outweigh the risk:benefit assessment. This risk-benefit ratio may need to be reassessed if the indication for bortezomib was to include treatment of patients with a longer life expectancy.

2.6.2.4 Safety pharmacology**Cardiovascular effects:****Study title: Investigative cardiovascular safety study following IV administration of bortezomib in telemetered male beagle dogs****Key study findings:****Pilot Study:**

- ≥ 0.25 mg/kg-Mortality (28-53 hrs post-dose) with concomitant \uparrow HR, \downarrow BP (MAP, diastolic, systolic), \downarrow Left Ventricular BP, and \downarrow contractility.
- Positive inotropic and pressor effects were detected following administration of dopamine and phenylephrine. \downarrow HR occurred concomitantly with \uparrow MAP and contractility.

Definitive Study:

- Mortality not observed, but animals were euthanized per protocol at ~ 48 hours postdose.
- Bortezomib resulted in \downarrow BP (diastolic, systolic, MAP, LV Systolic, LV End Diastolic and Pulse pressure), \uparrow HR, and \downarrow Contractility.
- Positive inotropic and pressor effects were detected following challenges with dopamine and phenylephrine.
- Responses to dopamine and phenylephrine were not significantly different following bortezomib administration compared to prior to bortezomib administration, indicating that cardiac reflexes are intact.
- The effects of fluid administration cannot be determined due to the study design.

Study no.: _____ #:N102643, Millenium #: DSD-00100161

b(4)

Volume #, and page #: 4.2.1.3

Conducting laboratory and location: _____

Date of study initiation: April 6th, 2004

GLP compliance: Yes

QA report: yes (X) no ()

Drug, lot #, and % purity: Bortezomib, D7-1-1, not included

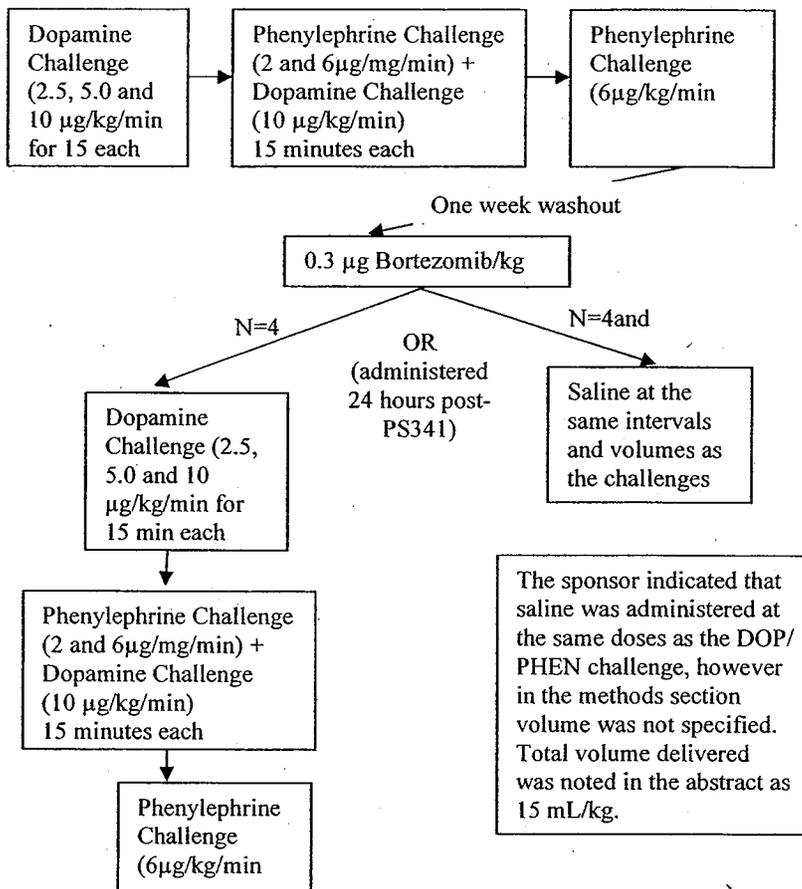
Methods

Doses/Schedule:

Pilot study: 0.25 (n=2) and 0.30 mg/kg (n=3), following a demonstration of CV effect, animals were administered dopamine at 2.5, 5.0, or 10 μ g/kg/minute to "achieve positive CV effect".

Additionally, animals were administered 15 minute infusions of phenylephrine in escalating doses of 2 and 6 μ g/kg/minute along with maintenance infusion of dopamine at 10 μ g/kg/minute, and finally a 15 minute infusions of phenylephrine alone at 6 μ g/kg/minute. Challenge dose volumes were not reported.

Definitive study: See Flow chart for study dosing description



Species/strain: Dog/Beagle

Age: 15-30 months

Weight: 6-14 kg

Unique study design or methodology (if any): All dogs were implanted with radiotelemetry transmitters which contained one pair of ECG leads and two pressure catheters, one implanted in the ascending aorta and the other in the left ventricle through the apex of the heart. For pilot animals ECG leads were implanted SC. For the definitive study animals, the pilot lead was attached to the left ventricular epicardial surface and the negative epicardial lead placed SC. The telemetry unit was implanted underneath the latissimus dorsi muscle. An ultrasonic flow probe was placed on the descending aortic. The flow probe lead wire was routed percutaneously in the subscapular region.

Observations and times:

Mortality: twice daily during dosing, otherwise once/day

Clinical signs: twice daily during dosing, otherwise once/day

Body weights: recorded each dosing day prior to administration

Hemodynamic and blood flow data: systemic arterial blood pressures (systolic, diastolic, mean), left ventricular pressures (systolic and diastolic), HR, ECG and body temperature)

Pilot phase: collected continuously and stored in 10 sec averages. ECGs collected continuously as waveforms from at least 12 hours predose to 24 hours postdose. Flow probe data was collected when animals were in the restraint slings during the dopamine and phenylephrine challenges and prior to study termination.

Definitive phase: Same as above but data was collected 24 hours predose to 24 hours postdose and at least 30 minutes of flow probe data was collected when the animals were in restraints.

Statistical analysis was conducted on systolic, diastolic, mean and pulse pressure, HR, contractility, systolic and diastolic left ventricular blood pressure, aortic blood flow, peripheral vascular resistance, ECG parameters (RR, QT, PR, QRS, and QTc (van de Water)

The objectives were to determine if there was a difference between the two groups based on a 10 minute interval basis within the five hour period commencing with the dopamine/phenylephrine or saline challenges (2) to determine whether significant differences existed between Week 1 (Baseline) and Week 2 (Post-Bortezomib) separately for each group (3) to determine whether differences existed between baseline averages (occurring prior to challenges), separately for each group (4) and for ECG the objectives were to determine if significant differences existed between post-bortezomib and baseline.

Results

Mortality:

Pilot Study: Both animals treated with 0.25 mg/kg were moribund at 53-54 hours post-dose. The 3 animals treated with 0.30 mg/kg were euthanized moribund at 28, 49 and 52 hours.

Definitive study: Mortality was not observed in the definitive study. However, animals were sacrificed (regardless of condition) approximately 48 hours following the administration of bortezomib.

Clinical signs:

Pilot Study: Observations included emesis, labored breathing, salivation, diarrhea, dehydration, lethargy and dehydration at both doses and occurred 6-8 hours post-dose.

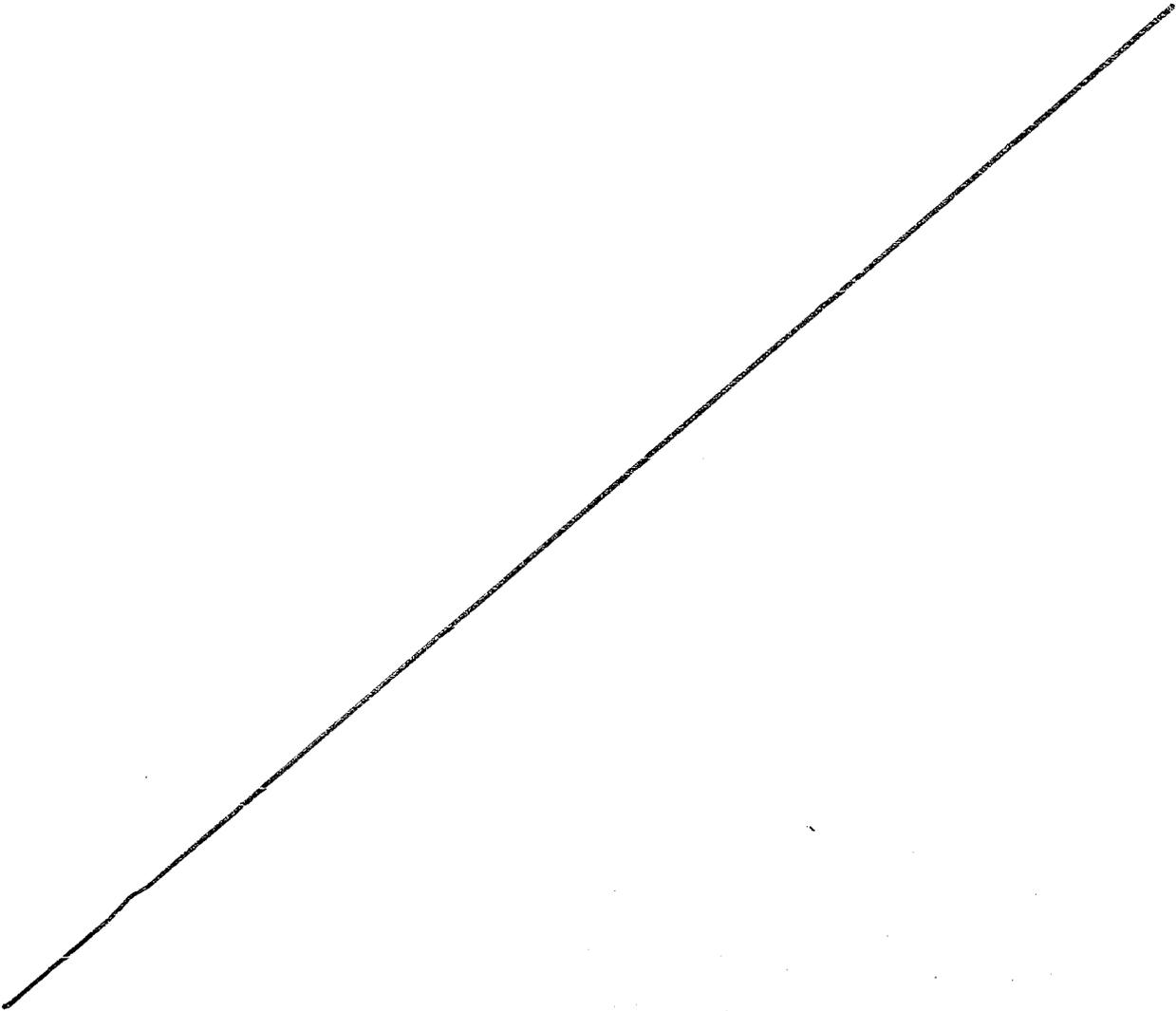
Definitive Study: Emesis and panting were noted and occurred approximately 24 hours post-dose.

Food consumption: qualitative decreases in food consumption noted in all animals

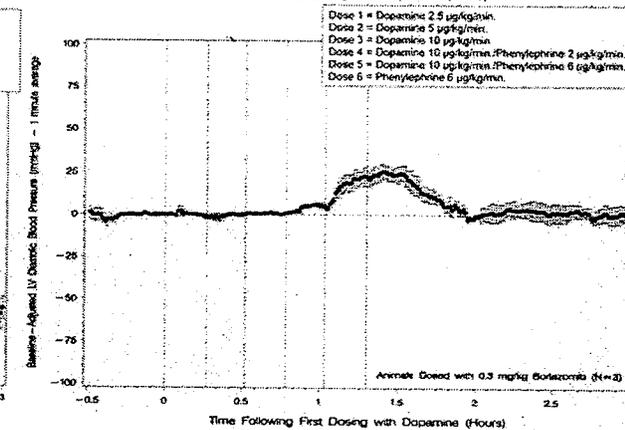
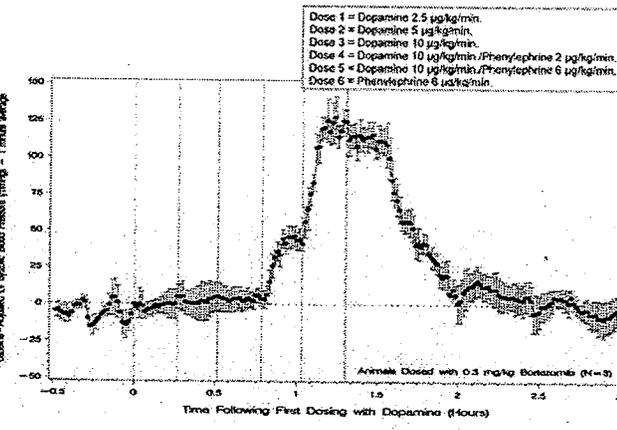
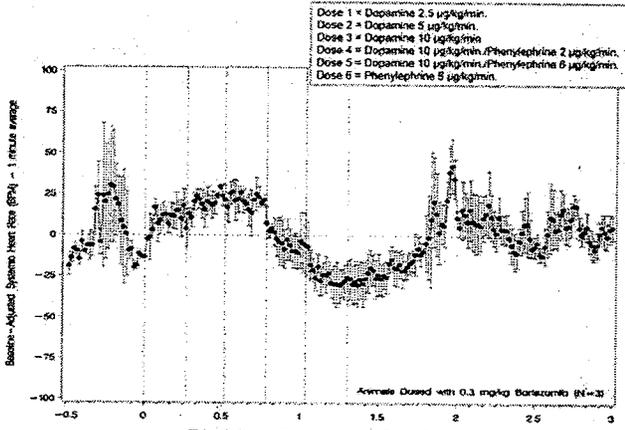
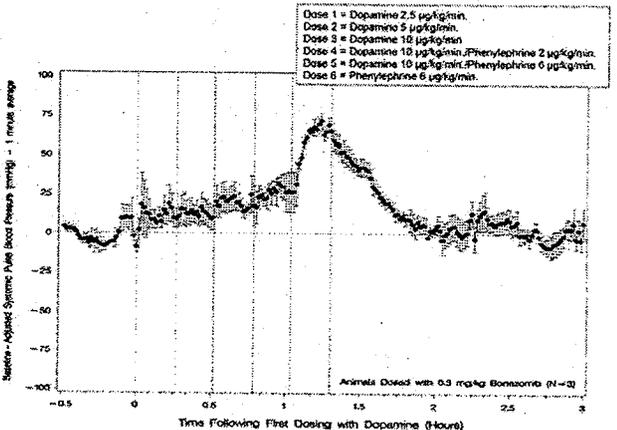
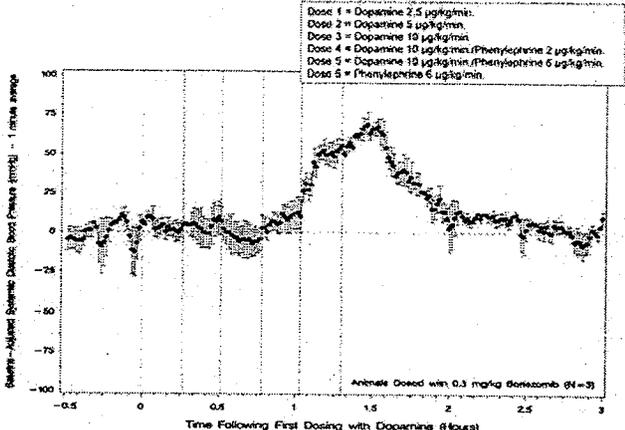
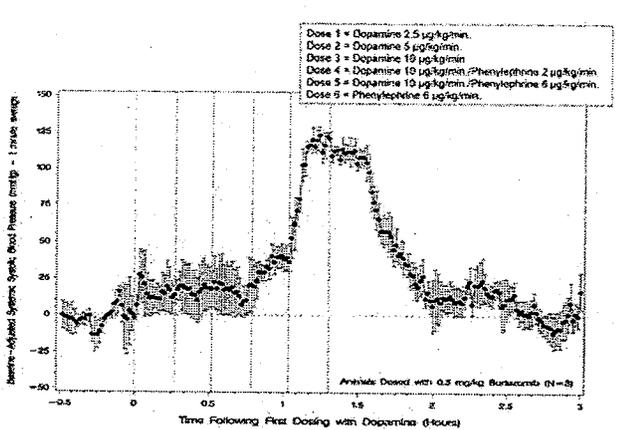
Hemodynamic and blood flow data:

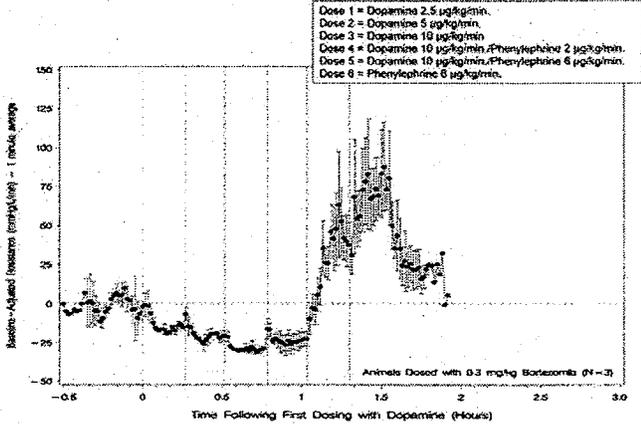
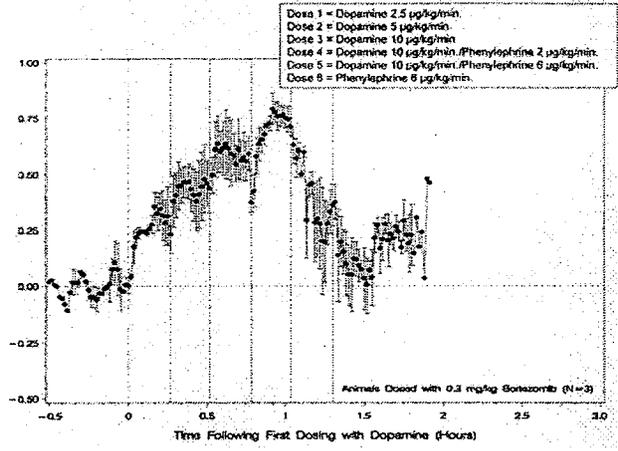
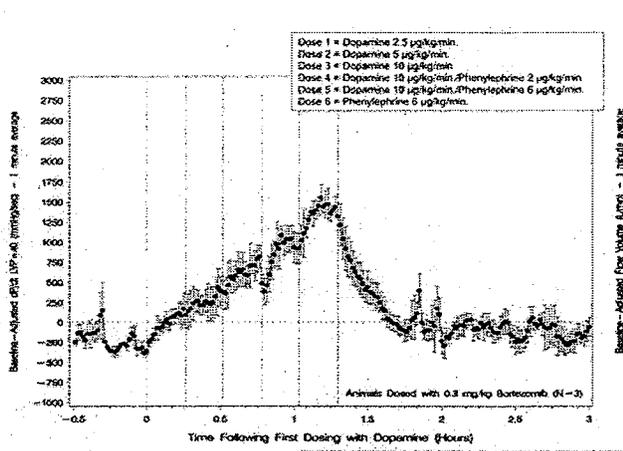
Pilot study:

Following 0.25 and 0.30 mg/kg, reductions in systemic BP, systemic pulse pressure, LV_{BP}, and contractility (dP/dt) were noted at approximately 5 hours postdose and following challenges with dopamine and phenylephrine. See graphs below for representations of these changes (excerpted from the sponsor's submission).



b(4)



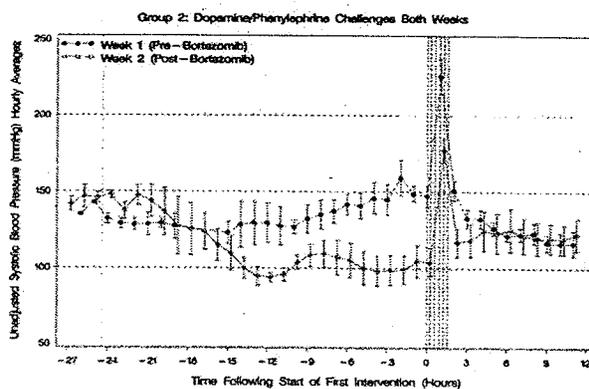
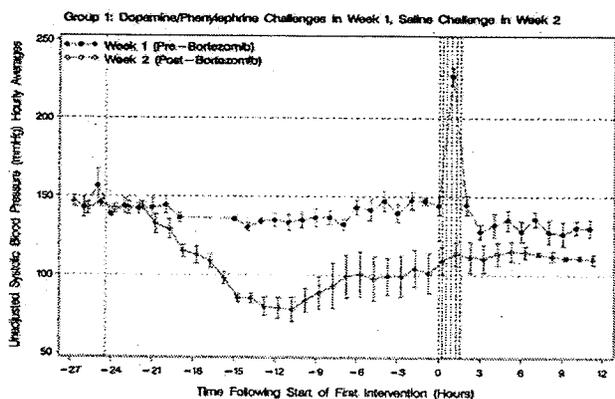


Definitive Study:

(graphs included below were excerpted from the sponsor's submission; first vertical hashed line indicates administration of BTX, additional vertical hashed lines indicate the administration of challenge agents.)

Systolic Blood Pressure:

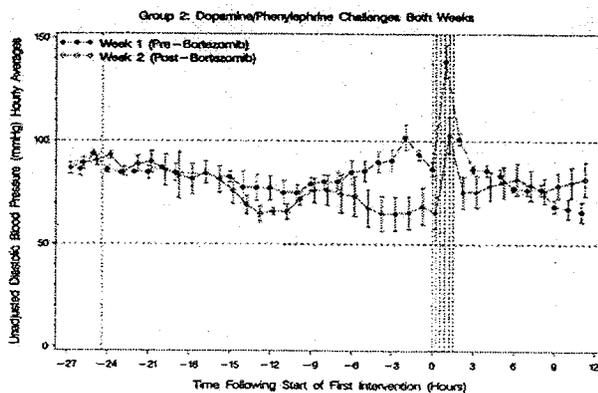
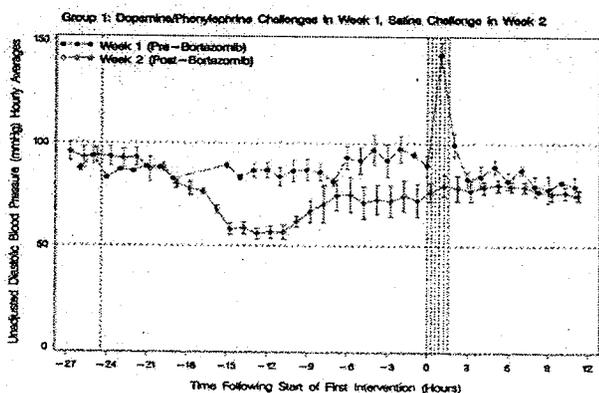
- Systolic BP decreased significantly (25 to 44%) following 0.3 mg/kg bortezomib administration beginning as early as 4 hours post-dose and continuing until 24 hours post dose (the time at which challenge agents were administered). The maximal effect was noted between 10-11 hours postdose.
- Significant differences in DOP/PHEN induced responses between weeks were not observed based on the magnitude of change in systolic BP. However, differences (up to 28%, non-significant) in absolute systolic BP were observed between weeks.



Diastolic Blood Pressure:

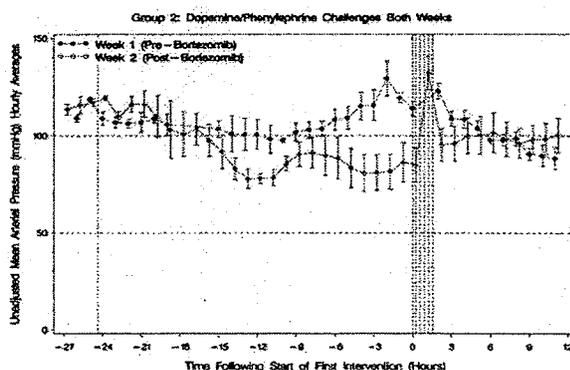
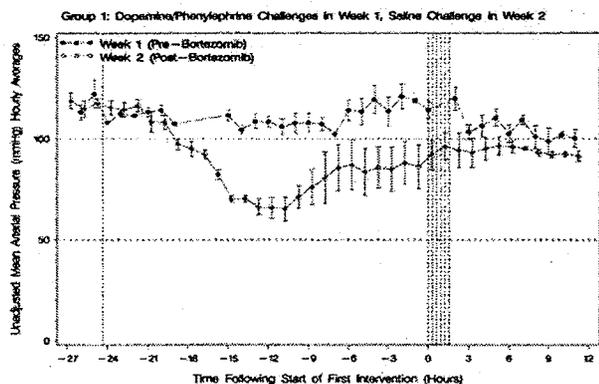
BP Statistically significant differences in diastolic BP

- Maximal decreases of 27% diastolic blood pressure, which were not statistically significant, were not noted following 0.3 mg/kg. The maximal effect was noted between 9 and 15 hours.
- Significant differences in DOP/PHEN induced responses between weeks were not observed based on the magnitude of change in diastolic BP. However, differences (up to 50%) in absolute diastolic BP were observed between weeks (pre/post bortezomib).



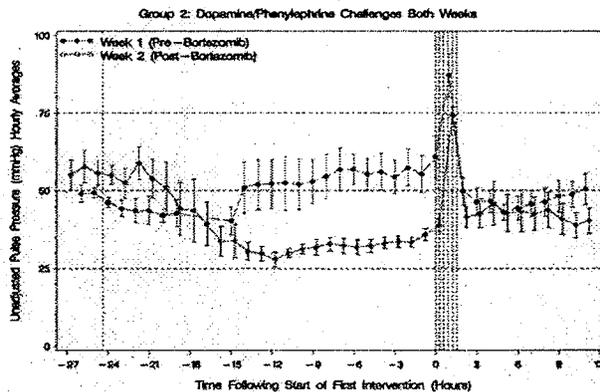
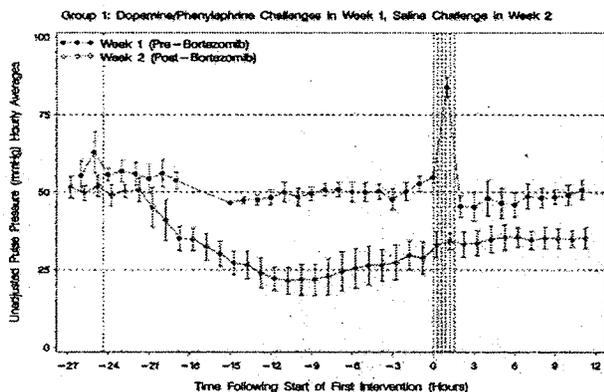
Mean Arterial Pressure:

- MAP decreased significantly (25 to 32%) following 0.3 mg/kg bortezomib administration as early as 8 hours post-dose continuing until 24 hours post dose (the time of challenge). Maximal effect was observed at 12-13 hours postdose, but the magnitude was primarily consistent across timepoints.
- Significant differences in DOP/PHEN between weeks were not observed.



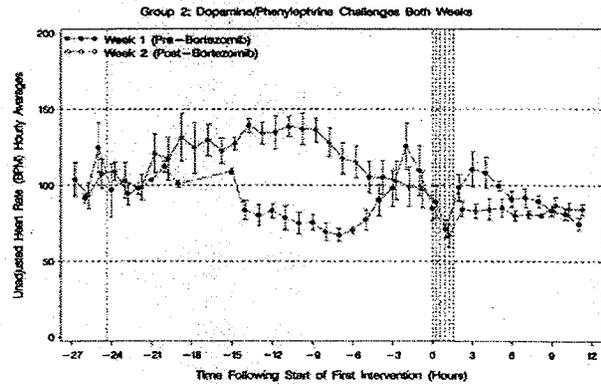
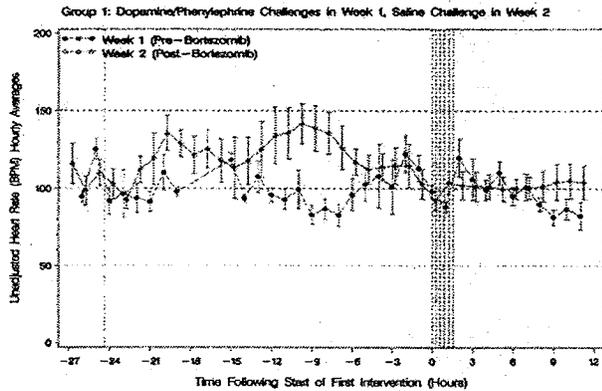
Pulse Pressure:

- Pulse pressure decreased significantly (30-50%) following 0.3 mg/kg bortezomib administration as early as 8 hours post-dose continuing until 24 hours post dose (the time of challenge). Maximal effect was observed at 12 -13 hours postdose.
- Significant differences in DOP/PHEN induced responses between weeks were not observed based on the magnitude of change in Pulse Pressure. However, differences (up to 22%, non-significant) in absolute pulse pressure were observed between weeks.



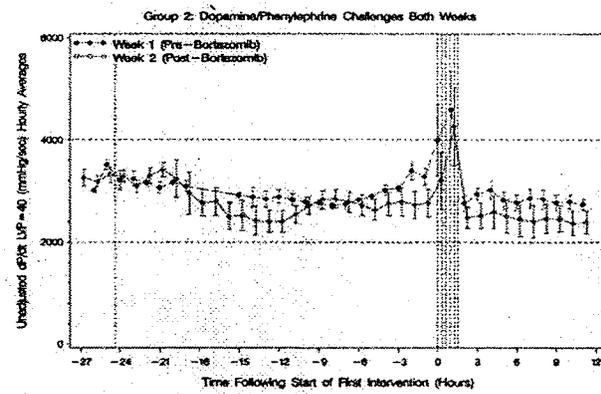
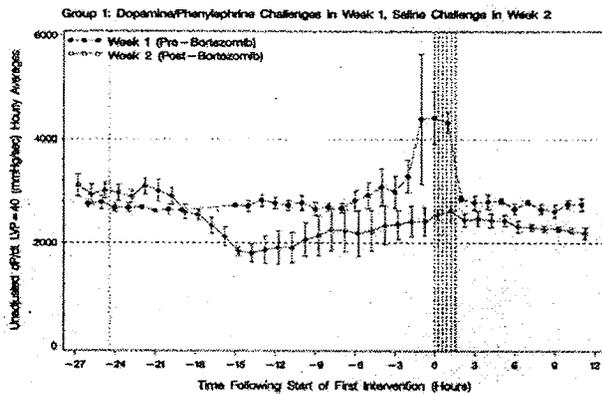
Heart Rate:

- Heart Rate increased significantly (10-72%) following 0.3 mg/kg bortezomib administration as early as 1 hours post-dose continuing until 22 hours post dose. Maximal effect was observed at 13-14 hours postdose
- Significant differences in DOP/PHEN induced responses between weeks were not observed based on the magnitude of change in HR or absolute HR.



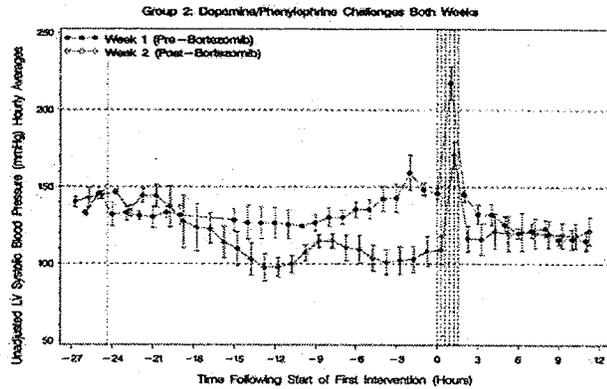
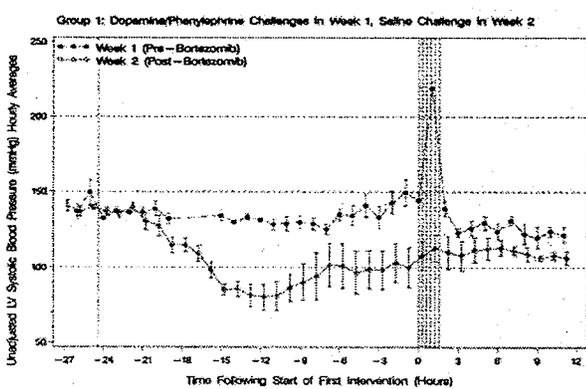
Cardiac Contractility:

- Cardiac contractility decreased significantly (28-33%) following 0.3 mg/kg bortezomib administration 23-24 hours post-dose. Although not statistically significant, decreases of up to ~25% were noted from 9 hours to 23 hours.
- Significant differences in DOP/PHEN induced responses between weeks were not observed based on the magnitude of change in contractility. However, differences (up to 15%, non-significant) in absolute contractility were observed between weeks.



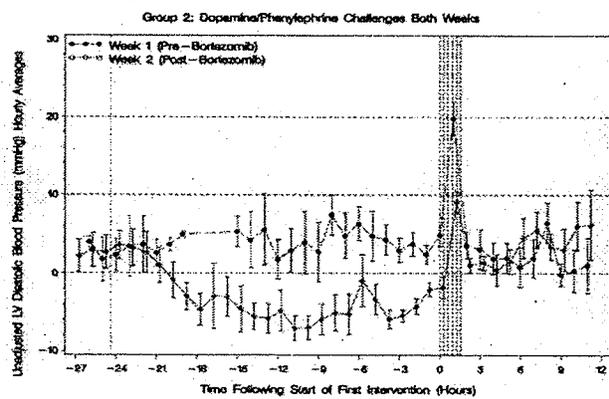
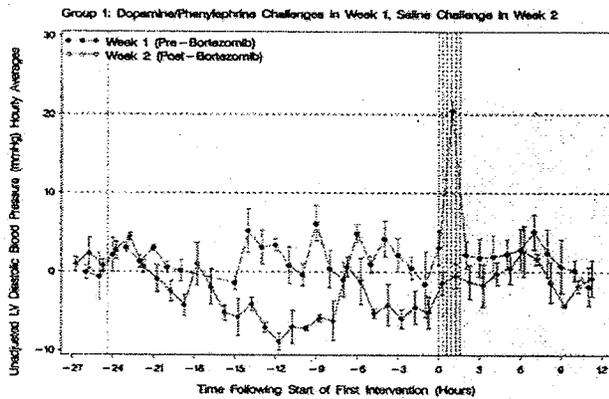
Left Ventricular Systolic Blood Pressure:

- Left ventricular systolic blood pressure decreased significantly (25-32%) following 0.3 mg/kg bortezomib administration beginning as early as 8 hours post-dose and continuing until 24 hours post dose (the time of challenge). The effect was consistent throughout analysis. (Week 1 baselines were not obtained from 6-9 hours postdose, therefore it is unclear if physiological differences would have occurred earlier.)
- Significant differences in DOP/PHEN induced responses between weeks were not observed based on the magnitude of change in left ventricular systolic blood pressure. However, differences (up to 25%, non-significant) in absolute LV systolic BP were observed between weeks.



Left Ventricular End Diastolic Pressure:

- Left ventricular end diastolic pressure decreased significantly (as much as 350%; expressed as change from baseline) following bortezomib administration at 4-21 hours post dose. Maximal effect was observed at 13-14 hours postdose.
- Significant differences in DOP/PHEN induced responses between weeks were not observed based on the magnitude of change in left ventricular end diastolic pressure. However, differences (up to 66%, non-significant) in absolute left ventricular end diastolic pressure were observed between weeks.



ECG Interval Parameters:

- RR intervals decreased and trended downward from pre-dosing levels, consistent with HR.
- QT interval was significantly increased 46.2 msec at 22 hours compared to baseline
- PR intervals initially decreased and then increased progressively with the 22 hour values 9 msec longer than baseline at 22 hours.
- QRS interval increased progressively with the 22 hour values 5.2 msec longer than baseline.
- QTc increased progressively from baseline. QTc was prolonged 20.6 and 48.9 msec at 12 and 22 hours respectively.

Table G-33. ECG Interval Parameter: Means (and Standard Errors), Calculated Across All Study Animals, of the Baseline Averages and Unadjusted and Baseline-Adjusted Post-Dosing Measurements and Results of Statistical Comparisons from Baseline at Each Post-Dosing Time Point

Hours Following Bortezomib Dosing	Unadjusted ECG Intervals (msec) (N=8)					Baseline-Adjusted ECG Intervals (msec) (N=8)				
	RR	QT	PR	QRS	Corrected QT ^a	RR	QT	PR	QRS	Corrected QT ^a
Baseline	693.3 (35.5)	216.0 (4.9)	89.0 (2.9)	38.9 (2.3)	242.7 (3.0)					
6	522.5 (33.6)	204.1 (7.8)	80.1 (2.6)	38.2 (3.1)	245.6 (5.7)	-170.8* (37.7)	-12.0 (4.4)	-8.9 (3.5)	-0.7 (1.4)	2.9 (3.7)
12	496.0 (41.9)	219.4 (10.2)	82.5 (4.2)	42.1 (3.0)	263.3 (7.0)	-197.4* (49.3)	3.4 (7.6)	-6.5 (4.7)	3.2 (1.2)	20.6* (5.1)
22	661.9 (52.8)	262.2 (11.0)	98.1 (4.2)	44.1 (1.5)	291.6 (8.5)	-31.4 (79.6)	46.2* (11.1)	9.0* (3.8)	5.2* (1.8)	48.9* (7.3)

a. QT correction was performed using the Van de Water formula.

* Significantly different from zero (i.e., significantly different from baseline), based upon tests performed within a repeated measures ANOVA on the baseline-adjusted measurements. For each parameter, significance was determined at each time point after adjusting the p-value by the Benjamini and Hochberg approach to controlling the false discovery rate to no higher than 0.05 across all three post-dosing time points simultaneously.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Initial review of NDA 21602 in 2003 indicated that administration of bortezomib resulted in significant effects on cardiovascular function. These results indicated that bortezomib caused: (1) a dose dependant decrease in MAP (mean arterial pressure), (2) a 10-40% increase in HR, and (3) increased CO (cardiac output) following the acute administration of bortezomib at doses between 0.3 mg/kg and 0.5 mg/kg doses in multiple species. In these same studies, there was a dose dependant increase in ventricular contractility following administration of 0.03 mg/kg-0.5 mg/kg. These data suggested that there is a significant potential for adverse cardiovascular events following the administration of PS-341 at doses of 0.25 mg/kg or greater (3.0 mg/m² and above). The unknown etiology of cardiovascular effects seen in multiple non-clinical studies and the occurrence of cardiovascular adverse events in the clinic warranted further investigation into the pathophysiology of cardiovascular toxicities and given the narrow margin of safety, the potential treatments for PS-341 induced toxicity.

To address cardiovascular function and responses to positive inotropic (dopamine) and pressor (phenylephrine) agents following IV dosing with bortezomib, the sponsor conducted a GLP study in beagle dogs. Bortezomib-induced toxicity in the pilot study included hypotension and tachycardia at both 0.25 and 0.30 mg/kg. Progressive decline in pressures and contractility associated with administration of bortezomib was observed. When challenged with dopamine and phenylephrine (at approximately 6-10 hours post-dose), an increase in contractility and blood pressure was observed. Progressive decline of the animals was observed (emesis, diarrhea, and dehydration), which resulted in moribundity at no later than 53 hours post-bortezomib dose. Based on this pilot study a definitive study was designed.

The definitive study utilized eight surgically instrumented dogs divided into two groups (n=4). 0.3 mg/kg was chosen as the dose to be utilized in all animals given that consistent cardiovascular alterations were associated with this level. Animals were administered challenges of dopamine and/or phenylephrine to determine baseline responses to the inotropic and pressor agents. After a one week washout period, 0.3 mg/kg bortezomib was administered to all animals. At 24 hours post-bortezomib, challenges were re-administered.

In the definitive study, blood pressures (systolic, diastolic, mean, and pulse) was significantly lower and remained below the control beginning 4 hours post dose through the 24-hour post-dosing period. Although not statistically significant, cardiac contractility trended below control beginning 6 hours post-dose and remained decreased through the post-dose period, this is in contrast to previously reviewed studies. Left ventricular end diastolic pressure was significantly decreased throughout the 24-hour post-dosing period.

The sponsor asserted that the fluid received during the challenges (15 mL/kg) was sufficient to increase pressures (including left ventricular end diastolic) and decrease heart rates towards nominal values. However, given the design of the study, it is not feasible to determine if fluid supplementation statistically resulted in a normalization of blood pressures, although slight increases in pressures were noted throughout the challenge periods.

When challenged with dopamine and phenylephrine (at 24 hours post-bortezomib), an increase in contractility and blood pressures were observed. These changes were noted in the challenge period

prior to bortezomib administration and following bortezomib administration, which is indicative of intact cardiac reflexes.

At 0.3 mg/kg, ECG intervals PR, QRS, QT, and QTc were all significantly prolonged by 12 to 22 hours. Additionally, the sponsor asserts that ECG changes may in part be due to electrolyte disturbances resulting from deterioration of the clinical condition; however electrolytes were not evaluated and the effects of supplementation were not assessed in this study.

Conclusions:

In response to Phase 4 commitments, the sponsor has investigated the cardiovascular toxicities associated with bortezomib administration. The administration of bortezomib, 24 hours prior to dopamine and phenylephrine administration did not alter tissue responsiveness to dopamine and phenylephrine. However, mean group values for blood pressure (systolic, diastolic), pulse pressure, heart rate, left ventricular systolic pressure and left ventricular diastolic pressure remained depressed versus dopamine/phenylephrine responses without prior administration of bortezomib. The differences between dopamine/phenylephrine before bortezomib and dopamine/phenylephrine after bortezomib administration were not statistically significant however the magnitude of the differences may be biologically relevant. Due to the design of the study, it is not evident if these interventions at 24 hours post-dose would attenuate PS-341 related mortality which is observed after the 48 hour sacrifice in a preponderance of animals. Attenuation of mortality is unlikely given the moribundity observed in the pilot study in spite of dopamine and phenylephrine administration as early as 28 hours post-bortezomib administration. Additionally, the effect of fluid supplementation is unclear due to the design of the current study.

In summary, at this point, we recognize the completion of the non-clinical Phase IV commitments.

Based on this information, the Overdosage section of the label should state:

OVERDOSAGE

There is no known specific antidote for VELCADE overdose. (see **PRECAUTIONS and DOSAGE AND ADMINISTRATION**).

In humans, fatal outcomes following the administration of more than twice the recommended therapeutic dose have been reported, which were associated with the acute onset of symptomatic hypotension and thrombocytopenia. In the event of an overdose, the patient's vital signs should be monitored and appropriate supportive care given.

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

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/s/

Leigh Verbois
12/5/2006 02:28:48 PM
PHARMACOLOGIST

David Morse
12/8/2006 10:11:06 AM
PHARMACOLOGIST

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-602 / S-010

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/Serial Number: N021602 / SE1-010

Drug Name: Velcade (bortezomib), 1.3 mg/m²/dose, for injection

Indication(s): Relapsed or Refractory Mantel Cell Lymphoma

Applicant: Millennium Pharmaceuticals, Inc.

Date(s): Submission date: June 08, 2006
PDUFA due date: December 08, 2006
Review completion date: November 29, 2006

Review Priority: Priority

Biometrics Division: Division of Biometrics 5 (HFD-711)

Statistical Reviewer: Chia-Wen Ko, Ph.D.

Concurring Reviewers: Rajeshwari Sridhara, Ph.D., Team Leader
Aloka Chakravarty, Ph.D., Division Director

Medical Division: Oncology Drug Products (HFD-150)

Clinical Team: Robert Kane, M.D. & Ann Farrell, M.D.

Project Manager: Mrs. Tammie Brent-Steele

Keywords: open-label, intent-to-treat, per protocol, evaluable patients, time to progression, response rate, duration of response, survival analysis, Kaplan-Meier curve, missing data, censoring, multiple endpoints, interim analyses, subgroup analyses, sensitivity analyses, historical control

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1. EXECUTIVE SUMMARY

This is a supplemental NDA submission seeking indication for relapsed or refractory mantle cell lymphoma (MCL) in patients with prior therapies. Included in this submission are: full report with data on study M34103-053; study report on National Cancer Institute of Canada Clinical Trials Group study NCIC CTG IND-150; summary of three investigator-initiated studies in MCL; and reports of post-marketing experience. Among the clinical studies that the sponsor conducted or supported, study M34103-53 is the only one with the target population for this indication, and therefore will be the basis of this review.

1.1 Conclusions and Recommendations

In this reviewer's opinion, the study results from the submitted Phase II, single-arm, multi-center trial supports the claim of efficacy based on response rate and duration of response as the primary outcomes for the treatment of relapsed or refractory mantle cell lymphoma in patients with prior therapies. The results indicate that previously treated relapsed or refractory MCL patients had a 31% response to VELCADE, and the response was durable with a median duration of response of 285 days in complete or partial responders. Whether lacking appropriate controls for comparison, inclusion of partial response for overall response rate, and the size and durability of response are adequate for approval will be a clinical decision.

1.2 Brief Overview of Clinical Studies

This review is mainly based on the clinical study M34103-053. Study M34103-053 is a single arm, open-label clinical trial in patients with relapsed or refractory mantle cell lymphoma. The study enrolled a total of 155 patients from 35 centers in North America and Europe to evaluate the efficacy of VELCADE in terms of time to progression (TTP) as the primary endpoint, and response rate, duration of response, progression free survival, and survival as the secondary endpoints. Each patient had screening assessments, received VELCADE 1.3 mg/m²/dose as a bolus intravenous (IV) injection on Days 1, 4, 8, and 11 of every 21-day treatment cycle for up to seventeen treatment cycles (approximately 1 year of treatment), then was followed up for disease progression, alternative therapies, and death.

The study was originally proposed to demonstrate the drug's efficacy by comparing TTP and response rate to historical controls from three academic centers. The Agency had not agreed to use TTP as the primary endpoint, nor had the Agency agreed to compare VELCADE to historical controls for demonstrating treatment effects. Out of 258 identified historical controls, only 15 were determined to be comparable to the indicated population. The study report and analyses by the sponsor was, therefore, based on estimates from study participants, and no comparisons with historical controls were made.

1.3 Statistical Issues and Findings

This is a supplemental NDA submission seeking indication of relapsed or refractory mantle cell lymphoma (MCL) in patients with prior therapies. Among the clinical studies submitted in support of this indication, Study M34103-053 is used as the basis of statistical evaluation because it is the only study by the sponsor that has enrolled sufficient number of patients from the target population for this indication.

Study M34103-053 is an ongoing single-arm, multi-center, open-label study of VELCADE in subjects with relapsed or refractory MCL. The study is designed to determine the efficacy of VELCADE in MCL as assessed by time to progression (TTP) as the primary endpoint, and by response rate, complete response rate, and duration of response as the secondary endpoints. VELCADE 1.3 mg/m² was administered on Days 1, 4, 8, and 11 of a 21-day cycle for a maximum of 17 cycles (~ 1 year of therapy). In this submission, a total of 155 patients from 35 study centers received at least one dose of VELCADE. One hundred and one (151) patients were from US, and the rest of 4 patients were from UK and Germany.

The evaluation of efficacy is based on data available up to December 1 of 2005 from Study M34103-053. The data cut-off date of December 1, 2005 was chosen so that all enrolled participants had at least 6 months of follow-up. At the time of study cut-off, all treated patients had received at least 8 cycles of VELCADE.

Results from Study M34103-053 indicate previously treated relapsed or refractory MCL patients had a 31% response to VELCADE, and the response was durable with a median duration of response of 285 days in complete and partial responders.

Statistical Issues:

- 1) Study M34103-053 was originally designed to demonstrate superior treatment advantage regarding TTP, response rates and survival in comparison with historical controls. However, among 258 identified historical controls from 3 academic centers, only 15 patients had received 1 or 2 prior therapies, including an anthracycline or mitoxantrone and rituximab. In addition to the small number of comparative controls, lack of uniform criteria to assess response and disease progression between the centers also makes statistical comparisons of efficacy endpoints between the study patients with historical controls impossible. Also the Agency had not agreed to TTP as the primary endpoint in this single arm study.
- 2) The efficacy analyses are focused on non-comparative assessments of response rate, duration of response, time-to-progression (TTP), progress free survival (PFS), and survival. The primary basis of the efficacy evaluation is the response rate and duration of response.
- 3) The sponsor calculated response rate and duration of response in patients who had measurable disease at screening and at least one post-baseline tumor assessment (defined as the RP-Final Population by the sponsor). The RP-Final Population consists of 141 out

of the 155 treated patients because 14 study participants did not have any post-baseline tumor assessments. The response rate and duration of response is also evaluated by the reviewer using all patients who had received at least one dose of VELCADE (the All Treated Population) treating these 14 subjects as non-responders.

- 4) Considering that investigators may not have followed the International Workshop Response Criteria (IWRC) rigidly and that the response and progression assessment may be biased in an open-label trial, the sponsor generated a computer algorithm to apply response criteria using independent radiological reviews and data captured in CRF. There were discrepancies between sponsor-derived and investigator-determined response assessments, the sponsor-derived responses are used as the basis for efficacy conclusions since using independent radiological reviews was recommended by the Agency.
- 5) The sponsor-determined response and duration of response were used as the basis for efficacy evaluations with the exception of patient 010-001, for whom the investigator-determined response and duration of response were used in the absence of neck scans.
- 6) Deaths prior to detectable progression could present informative censoring for time to progression calculation. Also any time to event endpoints are not interpretable in single arm studies.
- 7) The results indicate heavily treated relapsed or refractory MCL patients had a good response to VELCADE, and the response was durable. In addition, VELCADE demonstrated similar activity in patients with refractory disease, and in patient subgroups irrespective of time since diagnosis of MCL (<3 years versus ≥3 years) and number (1 versus 2 or more) and type (high-intensity versus not high-intensity) of prior chemotherapy.

Findings on Primary Outcomes – Response and Duration of Response:

Sponsor's Results

The sponsor has reported results of response rate and duration of response in the Response Population-Final (RP-Final) population, which consisted of patients with measurable disease at screening and had at least one post-baseline tumor assessment.

In this population of MCL patients receiving single-agent VELCADE as second- or third-line therapy, the sponsor has reported based on RP-Final population that the disease response rate (CR + CRu + PR) was 33% (95% confidence interval (CI): 26% - 42%) based on the sponsor-derived algorithm and was 40% (95% CI: 32% - 49%) based on investigator assessment. A total of 11 patients (8%) experienced CR or CRu based on both the sponsor-derived algorithm and the investigator assessment. PR was the best response to treatment for 36 (26%) and 46 (33%) patients as determined by the sponsor-derived algorithm and the investigator assessment, respectively.

Responses to VELCADE in this study were durable. Median duration of response for patients with CR + CRu + PR was 9.2 months (281 days; 95% CI: 148 – 409 days) based on the sponsor-derived algorithm with independent radiology review, and 8.9 months (270 days; 95% CI: 189 – 360 days) based on the investigator assessment. Median duration of response was substantially longer for patients with CR or CRu, 13.5 months (409 days) based on the sponsor-derived algorithm and 15.5 months (470 days) based on the investigator assessment.

Reviewer's Results

Duration of response for PR responders in RP-Final population

This reviewer calculated the median duration of response in PR responders because this information is also valuable in addition to median duration of response in CR+CRu+PR and CR+CRu responders as presented by the sponsor. The median duration of response in PR responders was 186 days (95% CI: 129 – 285 days) for sponsor-derived response, and was 217 days (95% CI: 143 – 279 days) for investigator-determined response, respectively.

Response rate for all treated patients

This reviewer calculated response rate for all study participants, who received at least one dose of VELCADE using sponsor-derived response for all treated patients except using investigator-determined response for subject 010-001, who did not have neck scans available for assessment by WCC but did have neck assessments by the investigator. The results were similar to those seen in RP-Final population with the overall response rate (CR+CRu+PR) of 31% (95% CI: 24% – 39%).

With subject 010-001 being considered as CR responder, the duration of response increased slightly from 281 days as reported by the sponsor to 285 days (95% CI: 164 – 421 days).

2. INTRODUCTION

2.1 Overview

Mantel Cell Lymphoma (MCL) is an aggressive, uncommon form of non-Hodgkin's lymphoma (NHL) that was first recognized as a unique clinicopathologic entity in the 1990's. It is estimated that 56,000 new cases of NHL are diagnosed annually in the US with a similar number estimated for the Europe. MCL accounts for approximately 6% of all NHL diagnoses, or about 3,000 to 4,000 new cases per year in the US.

MCL is predominantly found in males over 60 years of age. At initial diagnosis, most patients present with advanced stage disease (Stage III or IV). Extranodal involvement is frequent occurring in the gastrointestinal tract, bone marrow, liver, lungs, and soft tissues. It is an incurable disease that exhibits a rapid course of disease progression. The median survival of patients with the disease is about 3-4 years in contrast to other types of B-cell lymphoma such as follicular lymphoma where the median survival is 8-10 years. The prevalence of MCL in the US has not been reported; however, the calculated prevalence is approximately 9,500 cases, assuming an incidence of 3,000 to 4,000 cases per year and a median survival of 3 years.

MCL is incurable with standard chemotherapeutic approaches. Current initial therapy is similar to that for other aggressive lymphomas and included R-CHOP and Hyper-CVAD, often in combination with rituximab. Following chemotherapy, almost all patients experience relapse of their disease, and the median time to progression of the disease following the first line therapy rarely exceeds 1 year.

2.1.1 Background

VELCADE (bortezomib) for injection is a small molecule proteasome inhibitor that is being co-developed by Millennium Pharmaceuticals, Inc., and Johnson & Johnson Pharmaceutical Research and Development to treat both hematologic malignancies and solid tumors. In US, VELCADE was approved in May of 2003 for the treatment of patients with multiple myeloma who have received at least one prior therapy.

The sponsor developed the clinical program to investigate VELCADE as a treatment for MCL because of the drug's mechanism of action. It has been shown that bortezomib may inhibit MCL tumor cell growth through 2 control mechanisms: cell cycle arrest and induction of cell death, both of which involve inhibition of NF- κ B activation. Inhibition of the proteasome by VELCADE may result in increased intracellular levels of p27 and p53, which is associated with improved prognosis in MCL.

2.1.2 Clinical Studies

The sponsor submitted reports on the following clinical studies for VELCADE in patients with MCL:

1. Millennium-sponsored study M34103-053: An ongoing single-arm, multi-center, open-label study of VELCADE in subjects with relapsed or refractory MCL. The study is designed to determine the efficacy of VELCADE in MCL as assessed by time to progression (TTP) as the primary endpoint, and by response rate, complete response rate, and duration of response as the secondary endpoints. VELCADE 1.3 mg/m² was administered on Days 1, 4, 8, and 11 of a 21-day cycle for a maximum of 17 cycles (~ 1 year of therapy). In this submission, a total of 155 patients from 35 study centers received at least one dose of VELCADE. One hundred and one (151) patients were from US, and the rest of 4 patients were from UK and Germany.
2. NCIC-CTG-sponsored study NCIC-150: A completed single-arm, multi-center, open-label study of VELCADE in patients with untreated or relapsed MCL following up to 2 prior therapies. The study was conducted to determine response rate following treatment with VELCADE as a monotherapy. VELCADE 1.3 mg/m² was administered on Days 1, 4, 8, and 11 of a 21-day cycle. A total of 30 patients were enrolled. Thirteen (44%) of the enrolled patients did not have prior therapies.
3. Investigator-Initiated Study i34101-002: A completed single-arm, single center, open-label study of VELCADE for patients with relapsed or refractory B-Cell Lymphomas previously treated with chemotherapy. The treatment efficacy was assessed by response rate. VELCADE 1.5 mg/m² was administered on Days 1, 4, 8, and 11 of a 21-day cycle. A total of 60 patients, 33 of them with MCL, were treated with VELCADE.
4. Investigator-Initiated Study MSKCC 01-049: An ongoing single-arm, multi-center, open-label trial of VELCADE in patients with low grade lymphoproliferative disorders. VELCADE 1.3 mg/m² was administered on Days 1, 4, 8, and 11 of a 21-day cycle. A total of 74 patients, 42 of them with MCL, were treated with VELCADE.
5. Investigator-Initiated Study i34101-008: An ongoing single-arm, multi-center, open-label trial of VELCADE in patients with Hodgkin's Disease and Non-Hodgkin's Lymphoma. VELCADE 1.3 mg/m² was administered on Days 1, 4, 8, and 11 of a 21-day cycle. A total of 51 patients, 24 of them with MCL, were treated with VELCADE.

The sponsor submitted data sets on Studies M34103-053 and NCIC-150, in which all participants had MCL. Since Study NCIC-150 does not have sufficient number of relapsed patients for statistical evaluation, Study M34103-053 is used as the basis for the statistical review and evaluation.

2.1.3 Major Statistical Issues

Major statistical issues for Study M34103-053:

- 1) Study M34103-053 was originally designed to demonstrate superior treatment advantage regarding TTP, response rates and survival in comparison with historical controls. However, among 258 identified historical controls from 3 academic centers, only 15 patients had received 1 or 2 prior therapies, including an anthracycline or mitoxantrone and rituximab. In addition to the small number of comparative controls, lack of uniform criteria to assess response and disease progression between the centers also makes statistical comparisons of efficacy endpoints between the study patients with historical controls impossible. Also the Agency had not agreed to TTP as the primary endpoint in this single arm study.
- 2) The efficacy analyses are focused on non-comparative assessments of response rate, duration of response, time-to-progression (TTP), progress free survival (PFS), and survival. The primary basis of the efficacy evaluation is the response rate and duration of response.
- 3) The sponsor calculated response rate and duration of response in patients who had measurable disease at screening and at least one post-baseline tumor assessment (defined as the RP-Final Population by the sponsor). The RP-Final Population consists of 141 out of the 155 treated patients because 14 study participants did not have any post-baseline tumor assessments. The response rate and duration of response is also evaluated by the reviewer in ATP treating these 14 subjects as non-responders.
- 4) Considering that investigators may not have followed the IWRC rigidly and that the response and progression assessment may be biased in an open-label trial, the sponsor generated a computer algorithm to apply response criteria using independent radiological reviews and data captured in CRF. There were discrepancies between sponsor-derived and investigator-determined response assessments, the sponsor-derived responses are used as the basis for efficacy conclusions since using independent radiological reviews was recommended by the Agency.
- 5) The sponsor-determined response and duration of response were used as the basis for efficacy evaluations with the exception of patient 010-001, for whom the investigator-determined response and duration of response were used in the absence of neck scans.
- 6) Deaths prior to detectable progression could present informative censoring for time to progression calculation. Also any time to event endpoints are not interpretable in single arm studies.
- 7) The results indicate heavily treated relapsed or refractory MCL patients had a good response to VELCADE, and the response was durable. In addition, VELCADE demonstrated similar activity in patients with refractory disease, and in patient subgroups by time since diagnosis of MCL (<3 years versus >=3 years) and number (1 versus 2 or more) and type (high-intensity versus not high-intensity) of prior chemotherapy.

3.1.1.1 Study Design

Study M34103-053 was a prospective, multi-center, single-arm study designed to evaluate the efficacy and safety of VELCADE in patients with documented relapsed or refractory MCL. VELCADE 1.3 mg/m² was administered on Days 1, 4, 8, and 11 of a 21-day cycle for a maximum of 17 cycles (~ 1 year of therapy).

The study comprised of 4 study periods: Screening, Treatment, Short-term Follow-up, and Long-term Follow-up. Screening assessments were conducted within 14 days of the first dose administration, including medical history; Karnofsky performance status (KPS); vital signs; computed tomography (CT) of the chest, abdomen, and pelvis; evaluation of other sites of disease by radiological imaging, physical examination, or other procedures as appropriate; bone marrow aspirate and biopsy; hematology and clinical chemistry analyses; and quality of life (QOL) survey EORTC QLQ-C30. During the Treatment period, all patients were to visit study center on each day of VELCADE treatment; during the rest period of Cycles 2, 4, 6, 10, and 14; and at the End of Treatment visit. Assessments conducted during the treatment period included disease response assessments, symptom-directed physical examinations, KPS, vital signs, hematology, clinical chemistry, and QOL. An End of Treatment visit was conducted in all patients at either 28 days after the last dose of VELCADE or either if the patient required alternate antineoplastic therapy.

Following the End of Treatment visit, short-term Follow-up visits were to occur every 6 weeks until Week 18 and every 12 weeks thereafter until progressive disease (PD) or receipt of alternate antineoplastic therapy for patients who had not progressed. All patients were to have Long-term Follow-up every 3 months following disease progression or start of alternate antineoplastic therapy to assess survival.

3.1.1.2 Study Objectives

The primary objective of Study M34103-053 was to determine if VELCADE increases median time to progression (TTP) compared to historical controls in patients with MCL who have documented relapsed or progression following 1 or 2 prior lines of antineoplastic therapy.

Secondary objectives were the following:

- To evaluate the rates of complete response (CR), CR unconfirmed (CRu), and overall response (CR + CRu + partial response (PR)).
- To determine if VELCADE increases median survival compared to historical controls
- To evaluate duration of response

Reviewer's Comment:

The efficacy analyses are focused on non-comparative assessments of response rate, duration of response, time-to-progression (TTP), progression free survival (PFS), and survival. Since the treatment effect cannot be demonstrated by showing prolonged TTP in study subjects in comparison with appropriate concurrent controls, the primary objective of the efficacy analyses will be to evaluate the response rate and duration of response as a prediction of clinical benefit in subjects treated with VELCADE.

3.1.1.3 Sample Size Justification

The sponsor determined a sample size of 152 was required for this study based on the following assumptions:

- Historical control cases who were similar to the population enrolled in the study with respect to important predictors of outcome in MCL and had available information on time to progression and overall survival can be identified
- Median time to progression will be 14 months in study participants, and will be 9 months in controls
- The study will have a patient accrual period of 14.5 months (10 patients/month)
- Study error rates are set as Type I error rate $\alpha=0.05$, and Type II error rate $\beta=0.2$
- There will be a 5% of losses to follow up
- The analysis will be performed 15.5 months after the last patient was accrued with 96 events of progressive disease for a total of 192 events (96 events each from study patients and from the controls)

Reviewer's Comments:

- Among 258 identified historical controls from 3 academic centers, only 15 patients had comparable disease characteristics to study participants. The historical controls will not be considered as appropriate comparators to study participants. Time to progression will not be considered as the primary basis of evaluation.
- The final data cut-off date of December 1, 2005 was chosen so that all enrolled participants had at least 6 months of follow-up.

3.1.1.4 Analysis Populations

All Treated Population (ATP) is defined as the patients who had received at least one dose of VELCADE. A total of 155 patients were included in the All Treated Population.

Response Population-Final (RP-Final) is defined as the study participants who had a measurable disease and had at least one post-baseline tumor assessment (including measurable or assessable lesions). The Response Population-Final included 141 patients.

Per Protocol Population (PPP) includes patients in the ATP who were confirmed to have MCL by independent pathology review and had prior therapy including rituximab, anthracycline / mitoxantrone, and an alkylating agent (i.e., previously treated with 3 agents). The PPP comprised 126 of the 155 treated patients. Seventeen of the 29 patients excluded from the PPP did not have MCL confirmed on independent pathology review, and the other 12 patients excluded from the PPP were not previously treated with all 3 required agents.

Table 1 Analysis Populations

Patient population	n (%)
ATP	155 (100)
RP-Final	141 (91)
PPP	126 (81)

3.1.1.5 Efficacy Endpoints

Response Rate

First and Best response rates are calculated in the RP-Final population as the proportion of subjects who experienced complete response (CR) or complete response unconfirmed (CRu) or partial response (PR) as their first or best response on VELCADE respectively.

Complete Response (CR) required all of the following:

- Complete disappearance of all detectable clinical and radiographic evidence of disease, disappearance of all disease-related symptoms, and normalization of biochemical abnormalities definitely ascribable to lymphoma.
- All lymph node masses must have regressed to normal size. Lymph node masses that were >1.5 cm in longest transverse dimension must have regressed to ≤1.5 cm. Each lymph node mass that was 1.1 to 1.5 cm in longest transverse dimension and thought to be involved with lymphoma must have regressed to ≤1 cm in longest transverse dimension, or by more than 75% of the product of the longest perpendicular dimensions compared to the pretreatment baseline.
- If the spleen was considered to be enlarged due to involvement with lymphoma prior to therapy, it must have regressed in size, and must not have been palpable on physical examination.
- If the bone marrow was involved by lymphoma, indeterminate or not adequately assessed during screening, an adequate aspirate and biopsy of the same site must have been clear of lymphoma.

2.2 Data Sources

Data used for this review are located on network with path "\\CDERSUB1\N21602\S_010\2006-06-08\CRT\Datasets\M34103-053. Data submission occurred on June 8 of 2006.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The evaluation of efficacy will be based on data available up to December 1 of 2005 from Study M34103-053. Study M34103-053 enrolled 162 patients; a total of 155 patients received at least one dose of VELCADE. The efficacy analyses are focused on non-comparative assessments of response rate, duration of response, time-to-progression (TTP), progress free survival (PFS), and survival.

Reviewer's Comment:

Study M34103-053 was originally designed to demonstrate superior treatment advantage regarding TTP, response rates and survival in comparison with historical controls. However, among 258 identified historical controls from 3 academic centers, only 15 patients had received 1 or 2 prior therapies, including an anthracycline or mitroxitron and rituximab. In addition the small number of comparative controls, lack of uniform criteria to assess response and disease progression between the centers also makes statistical comparisons of efficacy endpoints between the study patients with historical controls impossible.

3.1.1 Study M34103-053

Study M34103-053 is a single-arm, multi-center, open-label study of VELCADE in subjects with relapsed or refractory MCL. The study was designed to determine the efficacy of VELCADE in MCL as assessed by time to progression (TTP) as the primary endpoint, and by response rate, complete response rate, and duration of response as the secondary endpoints in comparison with comparable historical cohorts. VELCADE 1.3 mg/m² was administered on Days 1, 4, 8, and 11 of a 21-day cycle for a maximum of 17 cycles (~ 1 year of therapy). First patient was enrolled on June 25 of 2003, and the last patient was enrolled on June 6 of 2005. At the time of data cut-off (December 1 of 2005) for this submission as the last patient had at least 6 months of follow-up data, a total of 155 patients from 35 study centers had received at least one dose of VELCADE. One hundred and one (151) patients were from US, and the rest of 4 patients were from UK and Germany.

CR unconfirmed (CRu) required the following:

- Criteria 1 and 3 for CR were satisfied; however:
- Any residual lymph node mass >1.5 cm in longest transverse dimension must have regressed by more than 75% of the product of the longest perpendicular dimensions compared to the pretreatment baseline.
- The bone marrow aspirate may have been indeterminate (contain increased number of size of lymphoid aggregates without cytologic or architectural atypia).

Partial Response (PR) required all of the following:

- $\geq 50\%$ decrease in the sum of the products of the longest perpendicular dimensions (SPD) of the previously identified dominant lymph node masses (up to 6)
- $\geq 50\%$ decrease in the SPD of nondominant measurable sites of disease
- No increase in the size of other sites of lymphoma that meets the criteria for progressive or relapsed disease
- No new sites of lymphoma

Since Study M34103-063 is an open-label trial, the sponsor was asked to have independent radiological review of patient scans. Based on independent radiology review by _____ and data captured from Clinical Report Form (CRF) on patient's LDH value, disease symptoms, and bone marrow aspirate and biopsy results, the sponsor developed a SAS program to determine the patient's first and best response on VELCADE. The sponsor-derived response will be referred as the MPI-derived response from here on. Response assessed by investigators at study sites as reported on CRF will be referred as the investigator-determined response for comparison with the MPI-derived response.

b(4)

Duration of response

Duration of first/best response was calculated in patients who were in the RP-Final population and had an overall CR or CRu or PR (responders) as number of days from the date of first/best response to the date of progressive disease or relapse for patients who experienced CR or CRu (PD) or censoring. Patients who died or were lost to follow-up before documentation of PD, or who discontinued VELCADE and started alternate antineoplastic therapy without documentation of PD within 2 weeks of the start of alternate antineoplastic therapy were censored at the last documented stable disease (SD) or better response prior to antineoplastic therapy for duration of response analyses.

Stable Disease (SD) required the following:

- Disease response was less than that required for PR, but the criteria for relapse or progressive disease were not met.

Progressive Disease or Relapsed Disease was indicated by any of the following:

- Appearance of any sites of lymphoma
- At least 50% increase in the product of the longest perpendicular dimensions of any previously identified lymph node mass. In addition, current measurements of lesion has to be > 1.0 cm in each dimension, and either dimension has to have an absolute increase ≥ 0.5 cm.
- At least 50% increase in the longest dimension of any previously identified lymph node mass >1 cm in longest transverse dimension. In addition, current measurements of lesion has to be > 1.0 cm in each dimension, and the longest dimension has to have an absolute increase ≥ 0.5 cm.
- At least 50% increase in the size of any other previously involved site of lymphoma.

Per MPI-derived response, the date of PD is the earliest date for the component that caused progression (measurable lesions, assessable lesions, or bone marrow progression). Per investigator-determined response, the date of progression is the earliest progression date as recorded on CRF.

Time to Progression

Time to progression (TTP) was calculated in all treated population as the duration in days from the date of first dose of VELCADE to the date of PD (or relapse for patients who experienced CR or CRu). The date of PD was determined by the sponsor-derived computer algorithm as the date of the first indication of progression (no more than 2 weeks after start of alternate antineoplastic therapy). Date of PD for the investigator determined TTP was based on the date provided in the CRF.

Patients who died, or were lost to follow-up before documentation of PD, or who discontinued VELCADE and started alternate antineoplastic therapy without documentation of PD within 2 weeks of the start of alternate antineoplastic therapy were censored at the last documented SD or better response prior to antineoplastic therapy for TTP analyses. Patients who did not have any post-baseline response assessments were censored at the date of first dose for TTP analyses.

Progression Free Survival

Progression free survival (PFS) was calculated in all treated population as the time in days from the first day of dose to disease progression or death from any cause. Censoring for PFS analyses were similar to that for TTP analyses, except that death before documentation of PD was considered an event on the date of death.

Survival

Survival was calculated in the all treated population as the duration from the date of first dose of VELCADE to date of death; patients not known to have died were censored at the time they were last known to be alive; irrespective of alternate therapy.

Reviewer's Comments:

- 1) The RP-Final consists of 141 out of the 155 ATP because 14 study participants did not have any post-baseline tumor assessments. Response rate and duration of response were proposed to be evaluated in the RP-Final population. The response rate and duration of response should be evaluated in ATP treating these 14 subjects as non-responders.
- 2) The difference between the MPI-derived and investigator-determined responses comes from independent radiological reviews. Since independent reviews were recommended by the Agency for open-label trials, the MPI-derived response will be used as the basis of primary analysis.
- 3) Any time to event endpoints are not interpretable in a single arm, non-comparative study.

3.1.1.6 Statistical Methods

Best response rate (CR, CRu, or PR as the best response on VELCADE) was tabulated with the associated 2-sided 95% exact confidence interval (CI) for the RP-Final population. The first response rate (CR, CRu, or PR as the first response on VELCADE) was calculated in the same way.

Kaplan-Meier methods were used to estimate the distribution of TTP, duration of response, PFS, and survival. Results are presented as number of events, number censored, median, 25th and 75th percentiles, and minimum and maximum.

ATP is the basis for TTP, PFS, and survival analyses. Results on TTP, PFS, and survival were also produced for PPP as supportive analyses. Best and first response rates were calculated in the RP-Final population, and duration of response was analyzed in RP-Final population for patients who achieved CR, CRu, or PR.

Efficacy analyses were also conducted on patient subgroups: patients refractory to prior therapy; patients who had been diagnosed with MCL <3 years versus ≥3 years prior to study entry; patients who had received 1 prior line of therapy versus those who had received 2 or 3 prior lines of therapy; and patients who had received prior high-intensity therapy versus those who had not received this type of therapy. In addition, TTP, PFS, time to alternate therapy and survival were analyzed by response category.

Reviewer's Comment:

The response rate and duration of response should be evaluated in ATP treating these 14 subjects as non-responders. Response rate and duration of response may also be evaluated in PPP as supportive.

3.1.1.7 Efficacy Results and Conclusions

3.1.1.7.1 Disposition of Patients

Enrollment in Study M34103-053 is complete with 162 patients screened. A total of 155 patients received at least one dose of VELCADE at 35 study centers in the US, United Kingdom, and Germany.

The data cut-off date of 1 Dec 2005 was chosen so that all treated patients have at least 6 months of follow up from the date of first dose of VELCADE. Patient disposition with regard to study completion and treatment completion at the time of data cut-off is tabulated in Table 2.

At the time of data cut-off, a total of 100 (65%) of the 155 patients continued to be on the study. The majority of these 100 patients (72 patients) were in long-term follow-up for assessment of survival; 16 were in short-term follow-up and 12 patients were still receiving treatment with VELCADE. These latter patients had all received at least 8 cycles of VELCADE at the time of data cut-off (range: 8-17 cycles). Fifty-five (55) of the 155 patients had discontinued from the study, including 52 patients who had died, 2 who were lost to follow up, and 1 patient who withdrew consent to continuing his participation in the study.

Treatment had been completed in a total of 13 (8%) of the 155 patients at the time of the data cut-off, i.e., the patients had received at least 17 cycles of therapy (7 patients) or had received 4 cycles beyond initial documentation of CR or CRu (6 patients). A total of 130 (84%) of the 155 patients had stopped treatment, primarily due to lack of efficacy (72 patients, 46%) or occurrence of adverse events (41 patients, 26%); these patients entered the follow-up phase of the study.

Table 2 Disposition of Patients

Disposition	n	(%)
Patient Screened	162	
Patient Dosed	155	100
Study Completion		
Patients continuing on treatment	12	8
Patients on short term follow-up	16	10
Patients on long-term follow-up	72	46
Off study (including follow-up)	55	35
Patient withdrew consent to participate	1	<1
Loss to follow-up	2	2
Death	52	34
Treatment Completion		
Patients completing treatment ^a	13	8
Patients continuing on treatment as of data cut-off	12	8
Patients stopping treatment due to lack of efficacy	72	46
Patient stopping treatment due to death	0	0
Patients not completing treatment, primary reason:	58	37
Occurrence of an adverse event	41	26
Patient withdrew consent for treatment	7	5
Other	10	6

^aPatients completing either 17 treatment cycles (1 year) or completing 4 treatment cycles beyond initial documentation of CR or CRu

Across the 35 study centers, 11 centers treated a total of 1 or 2 patients each, 13 centers treated between 3 and 5 patients each, and 11 centers treated between 6 and 14 patients each.

3.1.1.7.2 Demographics and Other Baseline Characteristics

Table 3 summarizes the demographic and baseline characteristics for patients in the ATP population. The majority of patients treated in this study were male (125 of 155; 81%) with a median age of 65 years and a range of 42 to 89 years. Most patients (142, 92%) were non-Hispanic white. KPS was <90% in 44 (29%) of 153 patients with data available. Results in Table 3 illustrate the poor prognostic features of the patients enrolled in this clinical study and their disease burden, including short duration since initial diagnosis, advanced stage of disease, elevated IPI scores, and LDH, and the high proportion of patients with extranodal sites of disease, including bone marrow involvement.

As required by the protocol, the majority of patients had received 1 or 2 prior lines of therapy (149 of 155, 96%); a total of 6 patients had received 3 prior lines of therapy at the time of study entry. The population of patients enrolled in this study had already received the standard therapies for the treatment of MCL. In the ATP, 91% of patients (141 of 155) had previously received an alkylating agent, an anthracycline (or mitoxantrone), and rituximab, either in

combination or as separate agents. The median TTP on last prior therapy for patients in the ATP treated in this study was 366 days (12 months).

Table 3 Demographics and Baseline Characteristics (ATP Population)

Demographics and Baseline Characteristics		n = 155
Age (years)		
Mean (std dev)		64.9 (9.32)
Median		65.0
Minimum, Maximum		42, 89
Sex [n(%)]		
Male		125 (81)
Female		30 (19)
Race [n(%)]		
White		142 (92)
Black		6 (4)
Hispanic		4 (3)
Asian or Pacific Islander		3 (2)
KPS [n(%)]		
< 50		0
50 – 60		7 (5)
70 – 80		37 (24)
90 – 100		109 (71)
Missing		2
Prognostic Factors		
Time since initial diagnosis to first dose (years)		
Mean (std dev)		2.7 (1.88)
Median		2.3
Minimum, Maximum		0.2, 11.2
Diagnosed < 3 years prior to first dose [n(%)]		103 (66)
Diagnosed ≥ 3 years prior to first dose [n(%)]		52 (34)
MCL stage at screening [n(%)]		
Stage I		5 (3)
Stage II		7 (5)
Stage III		24 (15)
Stage IV		119 (77)
IPI [n(%)]		
0-1		34(23)
2		48 (33)
3		48 (33)
4-5		17 (12)
Missing		8
LDH [n(%)]		
Normal		95 (64)
High (above upper limit of normal)		54 (36)
Missing		6

Demographics and Baseline Characteristics	n = 155
Number of involved extranodal sites [n(%)]	
0	38 (25)
1	64 (41)
2	32 (21)
3 or more	21 (14)
Bone marrow evaluation	
Positive results	84 (55)
Negative/Indeterminate Results	70 (45)
Missing	1
Prior Therapy for MCL	
Number of prior lines of therapy	
1	84 (54)
2	65 (42)
3 or more	6 (4)
Received prior regimen containing	
Anthracycline/Mitoxantrone	152 (98)
Alkylating Agents	150 (97)
Rituximab	149 (96)
Received at Least 2 of the Above 3	155 (100)
Received All of the Above 3	141 (91)
Received Prior High-Intensity Therapy ^a	58 (37)
Received SCT or hyper-CVAD with/without rituximab	50 (32)
Received Prior High-Intensity Therapy as Last Prior Regimen ^a	47 (30)
Received SCT or hyper-CVAD with/without rituximab as Last Prior Regimen	40 (26)
Number of Patients with Prior Radiation Therapy	29 (19)
Median TTP on last prior therapy (days)	366

a High intensity prior regimen defined as Hyper-CVAD, R-hyper-CVAD, ICE/ESHAP/DHAP with or without rituximab, and SCT

3.1.1.7.3 Efficacy Results

3.1.1.7.3.1 Response Rate

Best response to treatment for the RP-Final patients is presented in Table 4 by sponsor-derived algorithm, which was based on independent radiology review, and by the investigator-determined assessment as recorded on CRF.

In this population of MCL patients receiving single-agent VELCADE as second- or third-line therapy, the disease response rate (CR + CRu + PR) was 33% based on the sponsor-derived algorithm and was 40% based on investigator assessment. A total of 11 patients (8%) experienced CR or CRu based on both the sponsor-derived algorithm and the investigator assessment. PR was the best response to treatment for 36 (26%) and 46 (33%) patients as determined by the sponsor-derived algorithm and the investigator assessment, respectively. In

addition, 33% of patients had SD as the best response to treatment with both methods of assessment and ~25% had PD.

Table 4 Summary of Best Response to Treatment (RP-Final Population)

Response	Sponsor-Derived ^a N = 141		Investigator-Determined N = 141	
	n (%)	(95 % CI)	n (%)	(95% CI)
CR+CRu+PR	47 (33)	(26, 42)	57 (40)	(32, 49)
CR+CRu	11 (8)	(4, 14)	11 (8)	(4, 14)
CR	9 (6)	(3, 12)	8 (6)	(2, 11)
CRu	2 (1)	(0, 5)	3 (2)	(0, 6)
PR	36 (26)	(19, 34)	46 (33)	(25, 41)
SD	47 (33)	(26, 42)	46 (33)	(25, 41)
PD ^b	35 (25)	(18, 33)	37 (26)	(19, 34)
No post-baseline Assessment	12 (9)	(4, 14)	1 (<1)	(0, 4)

a. Based on sponsor-derived algorithm

b. Patients whose first post-baseline assessment was PD (response assessments after first PD are not included in the analysis)

Analyses were also conducted to assess first response to treatment. Based on the sponsor-derived algorithm, first response to treatment was CR + CRu + PR in 47 (33%) of the 155 patients, with CR or CRu in 5 patients (4%) and PR in 42 patients (30%). Based on the investigator assessment, first response to treatment was CR + CRu + PR in 57 (40%) of the 155 patients, with CR or CRu in 5 patients (4%) and PR in 52 patients (37%).

Reviewer's Comments:

The reviewer identified two issues related to the calculation of response:

- 1) The sponsor's study report indicates there were 12 subjects in the RP-Final population without any post-baseline assessment. However, by RP-Final definition, anyone in this population would have at least one post-baseline assessment.
- 2) As shown in Appendix, there appears to be discrepancies in best response determination between the sponsor-derived and investigator-determined methods.

The Agency received sponsor's response regarding the above mentioned issues on September 28, 2006. In summary, the sponsor clarified that:

- 1) At the data cutoff for the M34103-053 study report, there were 12 patients in the RP-Final who did not have any post-baseline response assessments by the sponsor-derived

algorithm; however, they did have post-baseline tumor measurements done at the investigational sites. Thus, the 12 patients were included in the denominator for calculations of response rate using both the sponsor algorithm and the investigator assessments.

- 2) There are two primary reasons for discrepancies between the assessment sources: a) the sponsor-derived assessments are based on independent radiology review by _____ while the investigator-determined assessments are based on radiology interpretations performed at the investigative site; b) the sponsor-derived assessment is a strict interpretation of the IWRC. Investigator-determined assessments may not always follow the IWRC as rigidly.

b(4)

Reviewer's Notes:

- Millennium response appeared to be reasonable.
- One of the 12 subjects, subject 010-001, did not have neck CTs available for assessment by _____ but did have neck assessments by the investigator. Since the protocol/algorithm allowed a clinical assessment of the neck region in the absence of scans, the investigator-determined CR response and duration of response for subject 010-001 will be used along with sponsor-derived response for calculating the Agency-accepted response rate and duration of response.

b(4)

Reviewer's Results:

Summary of MPI-derived, investigator-determined and FDA-adjudicated best response on VELCADE in ATP and PPP populations are presented in Tables 5 and 6, respectively. The results are similar to those seen in RP-Final population with the overall response rate (CR+CRu+PR) decreases from 33% in RP-Final to 31% in ATP (FDA-accepted response) since the denominator for the response rate calculation has increased.

Table 5 Summary of Best Response in ATP Population (Reviewer's Results)

Response	Sponsor-Derived ^a N = 155		Investigator-Determined N = 155		FDA-Adjudicated ^c N = 155	
	n (%)	(95 % CI)	n (%)	(95% CI)	n (%)	(95% CI)
CR+CRu+PR	47 (30)	(23, 38)	59 (38)	(30, 46)	48 (31)	(24, 39)
CR+CRu	11 (7)	(4, 12)	11 (7)	(4, 12)	12 (8)	(4, 13)
CR	9 (6)	(3, 11)	8 (5)	(7, 17)	10 (6)	(3, 12)
CRu	2 (1)	(0.2, 5)	3 (2)	(0.4, 6)	2 (1)	(0, 4)
PR	36 (23)	(17, 31)	48 (31)	(24, 39)	36 (23)	(17, 31)
SD	51 (33)	(26, 41)	48 (31)	(24, 39)	51	(26, 41)
PD ^b	35 (23)	(16, 30)	37 (24)	(17, 31)	35	(16, 30)
No post-baseline Assessment	22 (14)	(9,21)	11 (7)	(4, 12)	21	(9, 20)

- a Based on sponsor-derived algorithm
- b Patients whose first post-baseline assessment was PD (response assessments after first PD are not included in the analysis)
- c Used sponsor-derived response for all treated population except patient 010-001, for whom the investigator's response assessment was used

Table 6 Summary of Best Response in PPP Population (Reviewer's Results)

Response	Sponsor-Derived ^a N = 126		Investigator-Determined N = 126		FDA-Adjudicated ^{cd} N = 126	
	n (%)	(95 % CI)	n (%)	(95% CI)	n (%)	(95% CI)
CR+CRu+PR	42 (33)	(25, 42)	51 (40)	(32, 50)	42	(25, 42)
CR+CRu	11 (9)	(4, 15)	10 (8)	(4, 14)	11	(4, 15)
CR	9 (7)	(3, 13)	7 (6)	(2, 11)	9	(3, 13)
CRu	2 (2)	(0.2, 6)	3 (2)	(0.5, 7)	2	(0.2, 6)
PR	31 (25)	(17, 33)	41 (33)	(24, 41)	31	(17, 33)
SD	43 (34)	(26, 43)	40 (32)	(24, 41)	43	(26, 43)
PD ^b	28 (22)	(15, 30)	28 (22)	(15, 30)	28	(15, 30)
No post-baseline Assessment	13 (10)	(6, 17)	7 (6)	(2, 11)	13	(6, 17)

- a Based on sponsor-derived algorithm
- b Patients whose first post-baseline assessment was PD (response assessments after first PD are not included in the analysis)
- c Used sponsor-derived response for all treated population except patient 010-001, for whom the investigator's response assessment was used
- d FDA-Adjudicated results in PPP are the same as those of sponsor-derived because patient 010-001 was not in PPP due to inclusion/exclusion criteria violation

3.1.1.7.3.2 Duration of Response

Duration of response was calculated from the date of initial documentation of first response to the date of PD. The date of PD was determined based on independent radiology review for sponsor-derived response, and was based on PD date as provided by the investigators for investigator-determined response.

Table 7 presents results of the Kaplan-Meier analysis of duration of response for those patients in the RP-Final who achieved a CR, CRu, or PR. The Kaplan-Meier curve of duration of response is provided in Figure 1. Responses to VELCADE in this study were durable. Median duration of response for patients with CR + CRu + PR was 9.2 months (281 days) based on the sponsor-derived algorithm with independent radiology review, and 8.9 months (270 days) based on the investigator assessment. Median duration of response was substantially longer for patients with CR or CRu, 13.5 months (409 days) based on the sponsor-derived algorithm and 15.5 months (470 days) based on the investigator assessment. The Kaplan-Meier curve for duration of response indicates similar distribution for duration of response between the sponsor-derived algorithm and the investigator assessments.

Table 7 Duration of Response in Days (RP-Final, Responders Only) *

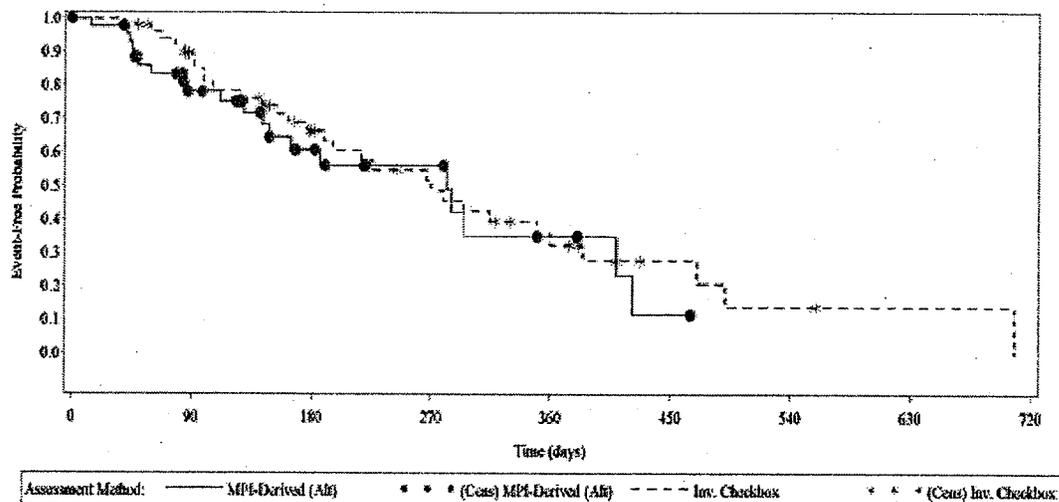
Kaplan-Meier Results:	Sponsor-Derived ^a		Investigator-Determined	
	CR + CRu + PR N=47	CR + CRu N=11	CR + CRu + PR N=57	CR + CRu N=11
Number of Events [n (%)]	20 (43)	3 (27)	30 (53)	6 (55)
Number Censored [n (%)]	27 (57)	8 (73)	27 (47)	5 (45)
25 th Percentile (95% CI)	129 (59, 186)	409 (45, NE)	143 (92, 217)	350 (189, 470)
Median (95% CI)	281 (148, 409)	409 (409, NE)	270 (189, 360)	470 (350, 708)
75 th Percentile (95% CI)	409 (285, NE)	NE (409, NE)	470 (314, 708)	708 (360, 708)
Minimum, Maximum	0+, 465+	45, 465+	0+, 708	140+, 708

Note: censored values indicated by '+'

a Based on the final sponsor-derived algorithm

* Source: Sponsor study report Table 11-2

Figure 1 Kaplan-Meier Curve of Duration of Response (RP-Final Population, Responders Only) *



* Source: Sponsor study report Figure 11-1

Reviewer's Results:

The reviewer calculated the median duration of response in PR responders because this information is also valuable in addition to median duration of response in CR+CRu+PR and CR+CRu responders as presented by the sponsor. The median duration of response in PR responders was 186 days (95% CI: 129 – 285 days) for MPI-derived response, and was 217 days (95% CI: 143 – 279 days) for investigator-determined response, respectively.

Results on duration of response are presented in Tables 8 and 9 for ATP and PPP populations, respectively. These results are almost identical to the ones seen in the RP-Final population.

Table 8 Duration of Response in Days, ATP Population (Reviewer's Results)

Kaplan-Meier Results	MPL-Derived			Investigator-Determined			FDA-Adjudicated ^c		
	CR+CRu+PR N = 47	CR+CRu N = 11	PR N = 36	CR+CRu+PR N = 59	CR+CRu N = 11	PR N = 48	CR+CRu+PR N = 48	CR+CRu N = 12	PR N = 36
Number of events [n (%)]	20 (43)	3 (27)	17 (47)	30 (51)	6 (55)	24 (50)	21 (44)	4 (33)	17 (47)
Number censored [n (%)]	27 (57)	8 (73)	19 (53)	29 (49)	5 (45)	24 (50)	27 (56)	8 (67)	19 (53)
25 th percentile (95% CI)	129 (59, 186)	409 (45, NE)	85 (50, 164)	143 (9, 217)	350 (189, 470)	99 (91, 176)	129 (59, 186)	409 (143, 470)	85 (50, 164)
Median (95% CI)	281 (148, 409)	409 (409, NE)	186 (129, 285)	270 (189, 360)	470 (350, 708)	217 (143, 279)	285 (164, 421)	470 (409, 470)	186 (129, 285)
75 th percentile (95% CI)	409 (285, NE)	NE (409, NE)	285 (281, 421)	470 (314, 708)	708 (360, 708)	384 (226, 491)	421 (285, 470)	470 (409, 470)	285 (281, 421)
Min, Max	0+, 465+	0+, 465+	0+, 421	0+, 708	0+, 708	0+, 559+	0+, 470	0+, 470	0+, 421

Note: NE = Not Estimable

c Used sponsor-derived response for all treated population except patient 010-001, for whom the investigator's response assessment was used

Table 9 Duration of Response in Days, PPP Population (Reviewer's Results)

Kaplan-Meier Results	MPI-Derived			Investigator-Determined		
	CR+CRu+PR N = 42	CR+CRu N = 11	PR N = 31	CR+CRu+PR N = 51	CR+CRu N = 10	PR N = 41
Number of events [n (%)]	19 (45)	3 (27)	16 (52)	27 (53)	5 (50)	22 (54)
Number censored [n (%)]	23 (55)	8 (73)	15 (48)	24 (47)	5 (50)	19 (46)
25 th percentile (95% CI)	129 (59, 186)	409 (45, NE)	85 (46, 186)	143 (92, 217)	350 (189, 708)	106 (84, 196)
Median (95% CI)	281 (148, 409)	409 (409, NE)	186 (129, 285)	270 (196, 360)	708 (314, 708)	217 (143, 279)
75 th percentile (95% CI)	409 (285, NE)	NE (409, NE)	285 (281, 421)	491 (314, 708)	708 (360, 708)	384 (266, 491)
Min, Max	0+, 465+	0+, 465+	0+, 421	0+, 708	0+, 708	0+, 559+

Note: NE = Not Estimable

3.1.1.7.3.3 Time to Progression (TTP)

TTP was defined as the duration in days from the date of first dose of VELCADE to the date of progressive disease (PD) and was analyzed based on PD date determined using the final sponsor-derived algorithm from the independent radiology review and based on PD date as provided by the investigators.

Table 10 present results on TTP for the ATP population for both the sponsor-derived and investigator-determined response assessments. The Kaplan-Meier curve of TTP is displayed in Figure 2. In the ATP, median TTP was 6.2 months (189 days) using both the sponsor-derived algorithm and the investigator-determined dates of progression. The primary reasons for censoring in TTP calculation were receipt of alternate therapy prior to progression and the study cut-off date. The Kaplan-Meier curves of TTP for the sponsor-derived and investigator-determined response assessments were similar.

Table 10 Time to Progression in Days (ATP Population) *

Kaplan-Meier Results:	Sponsor-Derived^a N=155	Investigator-Determined N=155
Number of Events [n (%)]	75 (48)	96 (62)
Number Censored [n (%)]	80 (52)	59 (38)
25 th Percentile (95% CI)	43 (38, 83)	48 (38, 93)
Median (95% CI)	189 (123, 211)	189 (132, 210)
75 th Percentile (95% CI)	379 (223, 463)	385 (240, 479)
Minimum, Maximum	0+, 503+	0+, 750
Reason for Censoring [n (%)]	(N=80 censored)	(N=59 censored)
Alternate Therapy	39 (49)	23 (39)
Death	8 (10)	8 (14)
Study Cut-off ^b	15 (19)	22 (37)
Not Evaluated	2 (3)	1 (2)
PD by investigator (no more scans performed)	3 (4)	0
Lost to Follow-up/Data Not Available	13 (16)	5 (8)

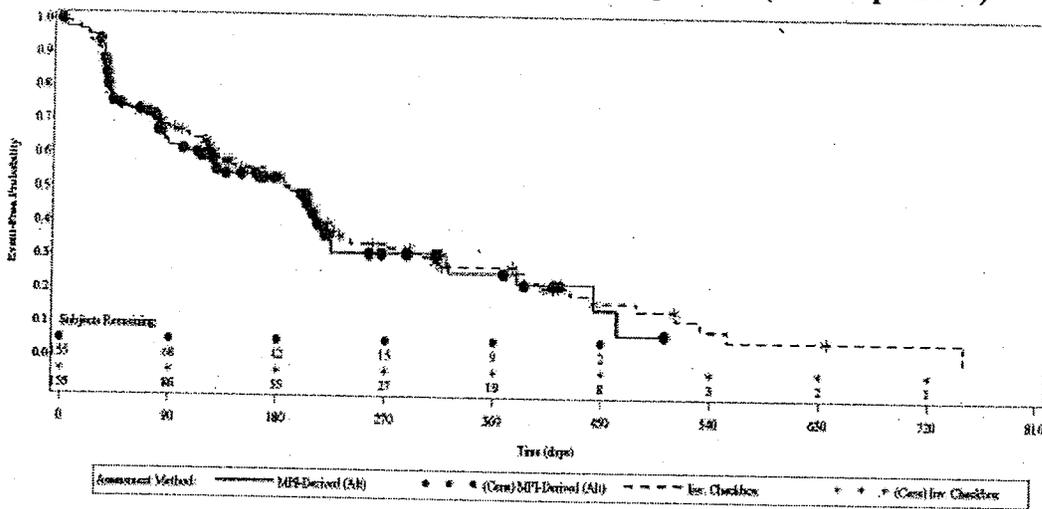
Note: censored values indicated by '+'

a Based on the final sponsor-derived algorithm

b Last assessment conducted within 90 days of data cut-off

* Source: Sponsor study report Table 11-3

Figure 2 Kaplan-Meier Curve for Time to Progression (ATP Population) *



* Source: Sponsor study report Figure 11-2

As a supportive analysis, TTP was also analyzed in the PPP, i.e., patients with independent pathology confirmation of mantle cell lymphoma who had previously received an anthracycline/mitoxantrone, an alkylating agent, and rituximab (i.e., had received all 3 types of chemotherapeutics prior to study entry). The TTP results in these 126 patients were similar to those reported for the ATP and also were similar between the sponsor-derived and investigator-determined analyses. Median TTP for the PPP was 6.5 months (199 days) based on the sponsor-derived algorithm and 6.7 months (203 days) based on investigator-determined results and the Kaplan-Meier curves based on the 2 methods were similar (Figure 3).

Table 11 Time to Progression in Days (PPP Population) *

Kaplan-Meier Results:	Sponsor-Derived^a N=126	Investigator-Determined N=126
Number of Events [n (%)]	64 (51)	79 (63)
Number Censored [n (%)]	62 (49)	47 (37)
25 th Percentile (95% CI)	70 (38, 88)	70 (39, 116)
Median (95% CI)	199 (126, 219)	203 (143, 231)
75 th Percentile (95% CI)	379 (224, 463)	385 (272, 479)
Minimum, Maximum	0+, 503+	0+, 750
Reason for Censoring: [n (%)]	(N=62 censored)	(N=47 censored)
Alternate Therapy	30 (48)	19 (40)
Death	6 (10)	6 (13)
Study Cut-off ^b	13 (21)	17 (36)
Not Evaluated	0	0
PD by investigator (no more scans performed)	3 (5)	0
Lost to Follow-up	10 (16)	5 (11)

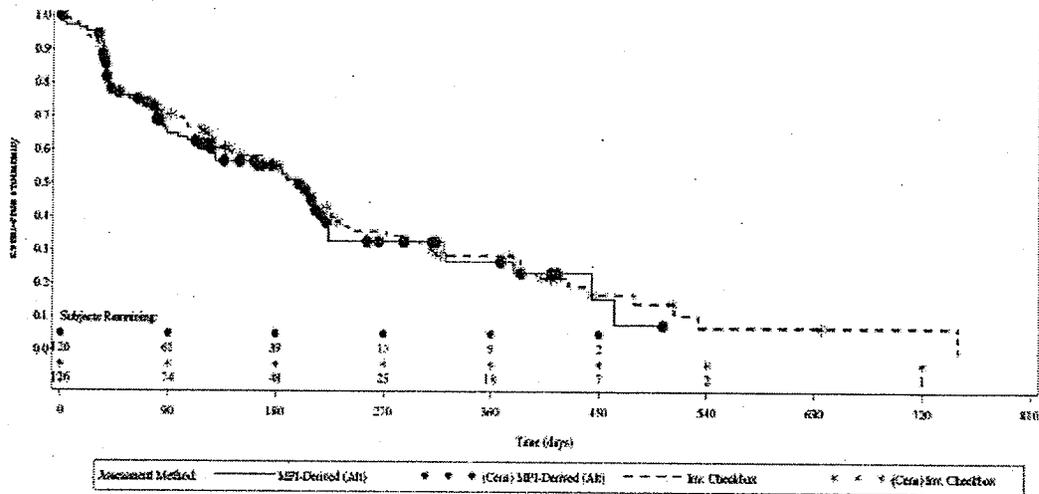
Note: censored values indicated by '+'

a Based on the final sponsor-derived algorithm

b Last assessment conducted within 90 days of data cut-off

* Source: Sponsor study report Table 11-4

Figure 3 Kaplan-Meier Curve of Time to Progression (PPP Population) *



Source: Sponsor study report Figure 11-3

Reviewer's Comment:

Deaths prior to detectable progression could present informative censoring for TTP calculation. However, with only 8 out of 155 subjects censored due to deaths, the bias in TTP calculation due to informative censoring is likely to be minimal.

3.1.1.7.3.4 Progression Free Survival (PFS)

PFS was defined similar to TTP, with the exception that both death due to any cause and PD were included as events. Table 12 summarizes the Kaplan-Meier analyses for PFS. Median PFS was 6.1 months (184 days) based on the sponsor-derived algorithm and 5.9 months (179 days) based on the investigator assessment. The number of patients with events (ie, with PD or death) also was similar between the 2 analysis methods: 101 patients and 108 patients had progression or had died as of the time of the data cut-off for this report based on the sponsor-derived algorithm and the investigator assessment, respectively.

Table 12 Progression Free Survival in Days (ATP Population) *

Kaplan-Meier Results:	Sponsor-Derived^a N=155	Investigator-Determined N=155
Number of Events [n (%)]	101 (65)	108 (70)
Number Censored [n (%)]	54 (35)	47 (30)
25 th Percentile (95% CI)	39 (37, 76)	41 (36, 76)
Median (95% CI)	184 (115, 209)	179 (123, 210)
75 th Percentile (95% CI)	322 (223, 444)	379 (233, 444)
Minimum, Maximum	0+, 646	0+, 750

Note: censored values indicated by '+'

^a Based on the final sponsor-derived algorithm

* Source: Sponsor study report Table 11-5

As a supportive analysis, PFS was also analyzed in PPP population. Similar results were noted in PPP with the median PFS to be 6.2 months (189 days) based on the sponsor-derived algorithm and 6.1 months (185 days) based on the investigator assessment.

3.1.1.7.3.5 Survival

Survival was defined as the duration from the date of first dose of VELCADE to date of death; patients not known to have died were censored at the time they were last known to be alive, irrespective of alternate therapy. With a median duration of follow-up of more than 13 months, median survival had not been reached in either the PPP or the ATP. At the time of data cut-off, 103 (66%) of 155 patients were alive, including 86 (68%) of 126 patients in the PPP.

The probability of survival at 6 months was 82% and at 12 months was 69% in the ATP.

Table 13 Overall Survival in Days (ATP and PPP Populations) *

	ATP N=155	PPP N=126
Kaplan-Meier Results:		
Median Duration of Follow-up for Survivors	407	435
Number of Events [n (%)]	52 (34)	40 (32)
Number Censored [n (%)]	103 (66)	86 (68)
25 th Percentile (95% CI)	278 (194, 438)	292 (194, 527)
Median (95% CI)	NE (601, NE)	NE (601, NE)
75 th Percentile (95% CI)	NE	NE
Minimum, Maximum	10, 774+	14, 774+
Kaplan-Meier Estimates^a		
6 Months	81.7% (N=119)	82.4% (N=99)
12 Months	69.3% (N=69)	71.5% (N=60)
Reason for Censoring [n (%)]	(N=103 censored)	(N=86 censored)
Study Cut-off ^b	97 (94)	83 (97)
Lost to Follow-up	6 (6)	3 (3)

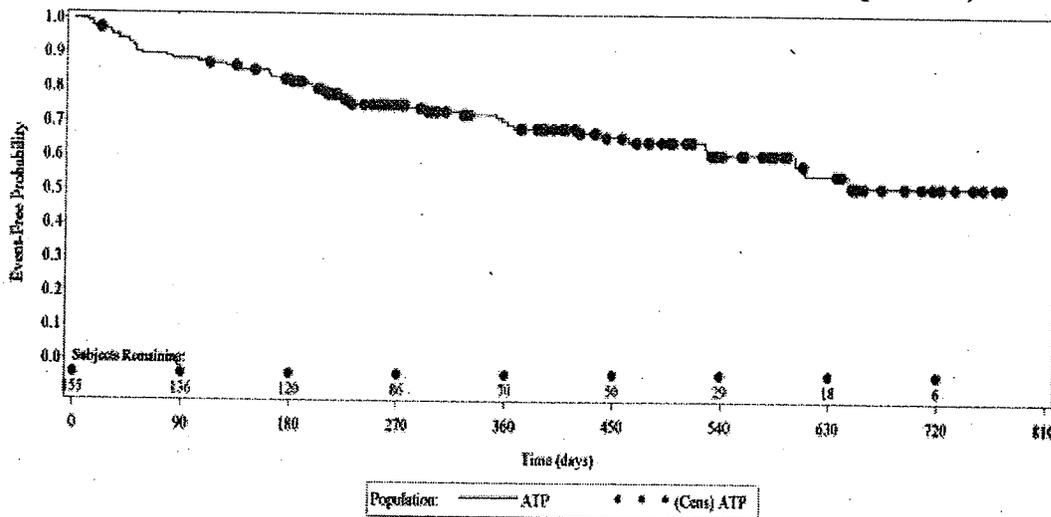
Note: censored values indicated by '+'; NE = not estimable

a Percent of event-free patients (number of patients at risk)

b Last known alive date within 90 days of data cut-off

* Source: Sponsor study report Table 11-6

Figure 4 Kaplan-Meier Curve of Overall Survival (ATP Population) *



* Source: Sponsor study report Figure 11-4

3.1.1.7.3.6 Exploratory Analyses

The sponsor has conducted exploratory analyses including evaluation of time to event parameters such as TTP, PFS, time to alternate therapy (TTA), and survival by best overall response; and additional patient subgroup analyses.

The key results from evaluation of time to event parameters are presented in Table 14. Median time to progression, progression free survival, and time to alternative therapy were increased with improved response. Overall survival was immature at the data cut-off for evaluating relationship between survival and response. Patients who had complete response had the longest TTP, PFS, and time from start of VELACDE to alternate therapy. The sponsor also reported the probability of survival at 12 months based on Kaplan-Meier estimates increased with improved response, and was 46%, 83%, 92%, and 100% for patients who achieved PD, SD, PR, and CR or CRu, respectively, as best response on treatment.

Table 14 Time to Event Parameters (Days) Based on the Sponsor-Derived Algorithm by Best Response (RP-Final Population) *

Response Category Kaplan-Meier Results:	TTP	PFS	TTA	Survival
CR + CRu + PR (N=47)				
Median (95% CI)	322 (223, 463)	322 (223, 463)	387 (280, NE)	NE (601, NE)
Event-free pts at 6 mos ^a	78.7% (n=26)	79.2% (n=28)	91.3% (n=41)	100.0% (n=44)
CR + CRu (N=11)				
Median (95% CI)	444 (223, NE)	444 (223, NE)	590 (535, NE)	NE (601, NE)
Event-free pts at 6 mos ^a	90.9% (n=9)	90.9% (n=9)	100.0% (n=11)	100.0% (n=11)
PR (N=36)				
Median (95% CI)	224 (199, 379)	224 (204, 379)	288 (252, NE)	NE
Event-free pts at 6 mos ^a	74.2% (n=17)	75.1% (n=19)	88.6% (n=30)	100.0% (n=33)
SD (N=47)				
Median (95% CI)	206 (184, 211)	206 (185, 219)	207 (135, 320)	NE (646, NE)
Event-free pts at 6 mos ^a	67.3% (n=13)	72.7% (n=19)	55.3% (n=26)	95.7% (n=44)
PD (N=35)				
Median (95% CI)	37 (35, 38)	37 (35, 38)	70 (58, 87)	361 (163, NE)
Event-free pts at 6 mos ^a	-- (0)	-- (0)	21.1% (n=5)	65.7% (n=21)

^a Kaplan-Meier estimates of percent of event-free patients (number of patients at risk).

* Source: Sponsor study report Table 11-8

The sponsor provided efficacy results for patient subgroups, including results in patients with refractory disease, results based on time since diagnosis of MCL to entry into the study (<3 years

versus ≥ 3 years), results based on number (1 versus 2 or more) and type (high-intensity versus not high-intensity) of prior chemotherapy, and whether or not the patient had received prior hyper-CVAD or stem cell transplant.

The key results from analyses on patient subgroups are presented in Table 15 for refractory patients; Table 16 for results by time since diagnosis of MCL; Table 17 for results by number of lines of prior therapy; Table 18 for results by type of prior therapy; and Table 19 for results by whether the patient had received prior hyper-CVAD or stem cell transplant.

Table 15 Summary of Best Response to Treatment (Refractory Patients in RP-Final) *

Response	Sponsor-Derived ^a N=51		Investigator-Determined N=51	
	n (%)	(95% CI)	n (%)	(95% CI)
CR + CR _n + PR	16 (31)	(19, 46)	16 (31)	(19, 46)
CR + CR _u	3 (6)	(1, 16)	2 (4)	(0, 13)
CR	1 (2)	(0, 10)	1 (2)	(0, 10)
CR _u	2 (4)	(0, 13)	1 (2)	(0, 10)
PR	13 (25)	(14, 40)	14 (27)	(16, 42)
SD	14 (27)	(16, 42)	18 (35)	(22, 50)
PD ^b	17 (33)	(21, 48)	17 (33)	(21, 48)
No Post-baseline Assessment	4 (8)	(2, 19)	0	

a Based on the final sponsor-derived algorithm

b Patients whose first post-baseline assessment was PD (i.e., response assessments after first PD are not included in the analysis)

* Source: Sponsor study report Table 11-9

Table 16 Summary of Best Response to Treatment and Duration of Response Based on Time since Diagnosis of MCL (RP-Final Population) *

Analysis:	<3 Years Since Diagnosis (N=93)		≥3 Years Since Diagnosis (N=48)	
	n (%)	(95% CI)	n (%)	(95% CI)
Response Rate:				
Sponsor-Derived^a				
CR + CRu + PR	23 (25)	(16, 35)	24 (50)	(35, 65)
CR + CRu	6 (6)	(2, 14)	5 (10)	(3, 23)
Investigator-Determined				
CR + CRu + PR	32 (34)	(25, 45)	25 (52)	(37, 67)
CR + CRu	7 (8)	(3, 15)	4 (8)	(2, 20)
Duration of Response:				
	No. of Events (%)	Median (95% CI)	No. of Events (%)	Median (95% CI)
Sponsor-Derived^a				
CR + CRu + PR	12 (52)	285 (148, 409)	8 (33)	281 (143, NE)
CR + CRu	2 (33)	409 (409, NE)	1 (20)	NE (143, NE)
Investigator-Determined				
CR + CRu + PR	17 (53)	266 (143, 470)	13 (52)	279 (176, 384)
CR + CRu	4 (57)	470 (360, 708)	2 (50)	350 (314, NE)

a Based on the final sponsor-derived algorithm ; * Source: Sponsor study report Table 11-12
Note: Events = Responders

Table 17 Summary of Best Response to Treatment and Duration of Response Based on Number of Lines of Prior Therapy (RP-Final Population) *

Analysis:	1 Prior Line (N=77)		>1 Prior Line (N=64)	
	n (%)	(95% CI)	n (%)	(95% CI)
Response Rate:				
Sponsor-Derived^a				
CR + CRu + PR	23 (30)	(20, 41)	24 (38)	(26, 50)
CR + CRu	5 (6)	(2, 15)	6 (9)	(4, 19)
Investigator-Determined				
CR + CRu + PR	25 (32)	(22, 44)	32 (50)	(37, 63)
CR + CRu	5 (6)	(2, 15)	6 (9)	(4, 19)
Duration of Response:				
	No. of Events (%)	Median (95% CI)	No. of Events (%)	Median (95% CI)
Sponsor-Derived^a				
CR + CRu + PR	11 (48)	285 (164, 409)	9 (38)	186 (129, NE)
CR + CRu	1 (20)	409 (NE, NE)	2 (33)	NE (143, NE)
Investigator-Determined				
CR + CRu + PR	13 (52)	350 (154, 708)	17 (53)	226 (176, 314)
CR + CRu	3 (60)	534 (350, 708)	3 (50)	470 (314, 470)

a Based on the final sponsor-derived algorithm ; * Source: Sponsor study report Table 11-14; Events = Responders

Table 18 Summary of Best Response to Treatment and Duration of Response Based on Type of Prior Therapy (RP-Final Population) *

Analysis:	Prior High-Intensity Therapy (N=52)		No Prior High-Intensity Therapy (N=89)	
	n (%)	(95% CI)	n (%)	(95% CI)
Response Rate:				
Sponsor-Derived^a				
CR + CRu + PR	14 (27)	(16, 41)	33 (37)	(27, 48)
CR + CRu	4 (8)	(2, 19)	7 (8)	(3, 16)
Investigator-Determined				
CR + CRu + PR	20 (38)	(25, 53)	37 (42)	(31, 53)
CR + CRu	4 (8)	(2, 19)	7 (8)	(3, 16)
Duration of Response:	No. of Events (%)	Median (95% CI)	No. of Events (%)	Median (95% CI)
Sponsor-Derived^a				
CR + CRu + PR	5 (36)	281 (164, NE)	15 (45)	285 (129, 409)
CR + CRu	0	NE	3 (43)	409 (143, NE)
Investigator-Determined				
CR + CRu + PR	10 (50)	266 (106, 491)	20 (54)	279 (196, 384)
CR + CRu	1 (25)	NE (350, NE)	5 (71)	470 (314, 708)

a Based on the final sponsor-derived algorithm ; * Source: Sponsor study report Table 11-16; Events = Responders

Table 19 Summary of Best Response to Treatment and Duration of Response Based on Receipt of Hyper-CVAD/Stem Cell Transplant (RP-Final Population) *

Analysis:	Received Prior Hyper-CVAD/SCT (N=45)		Did not Receive Prior Hyper-CVAD/SCT (N=96)	
	n (%)	(95% CI)	n (%)	(95% CI)
Response Rate:				
Sponsor-Derived^a				
CR + CRu + PR	12 (27)	(15, 42)	35 (36)	(27, 47)
CR + CRu	4 (9)	(2, 21)	7 (7)	(3, 14)
Investigator-Determined				
CR + CRu + PR	18 (40)	(26, 56)	39 (41)	(31, 51)
CR + CRu	4 (9)	(2, 21)	7 (7)	(3, 14)
Duration of Response:	No. of Events (%)	Median (95% CI)	No. of Events (%)	Median (95% CI)
Sponsor-Derived^a				
CR + CRu + PR	4 (33)	281 (164, NE)	16 (46)	285 (129, 409)
CR + CRu	0	NE	3 (43)	409 (143, NE)
Investigator-Determined				
CR + CRu + PR	9 (50)	266 (106, 491)	21 (54)	279 (196, 384)
CR + CRu	1 (25)	NE (350, NE)	5 (71)	470 (314, 708)

a Based on the final sponsor-derived algorithm; * Source: Sponsor study report Table 11-18; Events = Responders

3.1.1.7.4 Conclusions for Efficacy

In this reviewer's opinion, the study results from the submitted Phase II, single-arm, multi-center trial supports the claim of efficacy based on response rate and duration of response as the primary outcomes for the treatment of relapsed or refractory mantle cell lymphoma in patients with prior therapies. The results indicate heavily treated relapsed or refractory MCL patients had a good response to VELCADE, and the response was durable. In addition, VELCADE demonstrated similar activity in patients with refractory disease, and in patient subgroups by time since diagnosis of MCL (<3 years versus ≥3 years) and number (1 versus 2 or more) and type (high-intensity versus not high-intensity) of prior chemotherapy.

3.2 Evaluation of Safety

Safety evaluations included physical examinations, monitoring for adverse events (AE), clinical laboratory tests, vital signs measurements, and evaluation of concomitant medications, procedures, and supportive therapies.

Safety was assessed for the ATP and RP-Final populations.

3.2.1 Statistical Methods for Safety Evaluations

The incidence of treatment-emergent adverse events (AEs) and the incidence of treatment-emergent AEs related to VELCADE were summarized for the following categories: all AEs, Grade 3, Grade 3 or higher, Grade 4, Grade 5, serious adverse events and AEs resulting in VELCADE discontinuation.

Descriptive statistics for actual values and changes from baseline to each on-study time point were tabulated for laboratory data, vital signs, and KPS. Shift analyses from baseline to worst on study value, based on the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) were produced for clinical laboratory data.

3.2.2 Safety Results and Conclusions

Please refer to Clinical Evaluations of this application for safety results and conclusions.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The sponsor didn't produce efficacy results for Study M34103-053 by gender, race and age because the majority of study participants are male, age 60+, Caucasians. Females counted for 30 or 19% of the 155 treated patients. The median age of treated patients was 65 years. Among the treated 155 patients, 92% were non-Hispanic white.

To evaluate the potential difference among gender, race and age in primary outcomes, the reviewer calculated the response rate and duration of response by gender (males, females), and by age (< 65 yrs, >= 65 yrs old at baseline). No separate analyses were performed by race due to the small number of participants other than non-Hispanic whites.

Summary of best response and duration of response by gender is presented in Table 20. It appears that the response rate was lower in females compared to males. There was a discrepancy in duration of response between sponsor-derived and investigator-determined response, especially in females.

Table 20 Best Response and Duration of Response by Gender, ATP Population (Reviewer's Results)

Analysis	Males (n= 125)		Females (n = 30)	
	n (%)	(95% CI)	n (%)	(95% CI)
Response Rate:				
Sponsor-Derived				
CR+CRu+PR	35 (28)	(20, 37)	12 (40)	(23, 59)
CR+CRu	7 (6)	(2, 11)	4 (13)	(4, 31)
PR	28 (22)	(15, 31)	8 (27)	(12, 46)
Investigator-Determined				
CR+CRu+PR	46 (37)	(28, 46)	13 (43)	(25, 63)
CR+CRu	8 (6)	(3, 12)	3 (10)	(2, 27)
PR	38 (30)	(22, 39)	10 (33)	(17, 53)
Duration of Response:	No. of Events (%)	Median (95% CI)	No. of Events (%)	Median (95% CI)
Sponsor-Derived				
CR+CRu+PR	14	281 (164, 421)	6	409 (45, NE)
CR+CRu	1	NE (143, NE)	2	409 (45, NE)
PR	13	281 (129, 295)	4	148 (41, NE)
Investigator-Determined				
CR+CRu+PR	25	270 (162, 350)	5	360 (196, NE)
CR+CRu	4	470 (350, 708)	2	360 (189, NE)
PR	21	176 (126, 279)	3	226 (196, NE)

Summary of best response and duration of response by age is presented in Table 21. The response rate was similar between patients younger than 65 and patients 65 years or older. However, a more durable response was observed in patients who were 65 years or younger.

Table 21 Best Response and Duration of Response by Age, ATP Population (Reviewer's Results)

Analysis	Age < 65 Years (n = 75)		Age ≥ 65 Years (n = 80)	
	n (%)	(95% CI)	n (%)	(95% CI)
Response Rate:				
Sponsor-Derived				
CR+CRu+PR	21 (28)	(18, 40)	26 (33)	(22, 44)
CR+CRu	4 (5)	(1, 13)	7 (9)	(4, 17)
PR	17 (23)	(14, 34)	19 (24)	(15, 35)
Investigator-Determined				
CR+CRu+PR	27 (36)	(25, 48)	32 (40)	(29, 52)
CR+CRu	6 (8)	(3, 17)	5 (6)	(2, 14)
PR	21 (28)	(18, 40)	27 (34)	(24, 45)
Duration of Response:	No. of Events (%)	Median (95% CI)	No. of Events (%)	Median (95% CI)
Sponsor-Derived				
CR+CRu+PR	9	295 (196, 708)	11	281 (84, NE)
CR+CRu	1	NE (143, NE)	2	409 (409, NE)
PR	8	285 (164, 421)	9	85 (59, 281)
Investigator-Determined				
CR+CRu+PR	11	285 (164, 421)	19	217 (154, 384)
CR+CRu	3	529 (314, 708)	3	470 (189, 470)
PR	8	266 (143, 295)	16	176 (106, 384)

4.2 Other Special/Subgroup Populations

Please refer to section 3.1.1.7.3.6 for additional examinations of subgroups.

5. SUMMARY AND CONCLUSIONS

This is a supplemental NDA submission seeking indication for relapsed or refractory mantle cell lymphoma (MCL) in patients with prior therapies. Among the clinical studies submitted in support of this indication, Study M34103-053 is used as the basis of statistical evaluation because it is the only study by the sponsor that enrolled sufficient number of patients from the target population for this indication.

Study M34103-053 is an ongoing single-arm, multi-center, open-label study of VELCADE in subjects with relapsed or refractory MCL. The study was designed to determine the efficacy of VELCADE in MCL as assessed by time to progression (TTP) as the primary endpoint, and by response rate, complete response rate, and duration of response as the secondary endpoints. VELCADE 1.3 mg/m² was administered on Days 1, 4, 8, and 11 of a 21-day cycle for a maximum of 17 cycles (~ 1 year of therapy). In this submission, a total of 155 patients from 35 study centers received at least one dose of VELCADE. One hundred and one (151) patients were from US, and the rest of 4 patients were from UK and Germany.

The evaluation of efficacy is based on data available up to December 1 of 2005 from Study M34103-053. The data cut-off date of December 1, 2005 was chosen so that all enrolled participants had at least 6 months of follow-up. At the time of study cut-off, all treated patients had received at least 8 cycles of VELCADE.

Results from the Study M34103-053 support the claim of efficacy based on response rate and duration of response as the primary outcomes for the treatment of relapsed or refractory mantle cell lymphoma in patients with prior therapies. In patients who had measurable disease at screening and had at least one post-baseline tumor assessment, the proportion of subjects had CR+CRu+PR on VELCADE was 33% with median duration of response of 281 days. Using all treated patients, the response rate of CR+CRu+PR was 30%. In all VELCADE treated patients, the median time to progression was 189 days, and the median progression free survival was 184 days. At the time of data cut-off, median survival had not been reached with 52 (34%) deaths observed.

5.1 Statistical Issues and Collective Evidence

- 1) Study M34103-053 was originally designed to demonstrate superior treatment advantage regarding TTP, response rates and survival in comparison with historical controls. However, among 258 identified historical controls from 3 academic centers, only 15 patients had received 1 or 2 prior therapies, including an anthracycline or mitoxantrone and rituximab. In addition to the small number of comparative controls, lack of uniform criteria to assess response and disease progression between the centers also makes statistical comparisons of efficacy endpoints between the study patients with historical controls impossible. Also the Agency had not agreed to TTP as the primary endpoint in this single arm study.
- 2) The efficacy analyses are focused on non-comparative assessments of response rate, duration of response, time-to-progression (TTP), progress free survival (PFS), and survival. The primary basis of the efficacy evaluation is the response rate and duration of response.
- 3) The sponsor calculated response rate and duration of response in patients who had measurable disease at screening and at least one post-baseline tumor assessment (defined

as the RP-Final Population by the sponsor). The RP-Final Population consists of 141 out of the 155 treated patients because 14 study participants did not have any post-baseline tumor assessments. The response rate and duration of response is also evaluated by the reviewer in ATP treating these 14 subjects as non-responders.

- 4) Considering that investigators may not have followed the IWRC rigidly and that the response and progression assessment may be biased in an open-label trial, the sponsor generated a computer algorithm to apply response criteria using independent radiological reviews and data captured in CRF. There were discrepancies between sponsor-derived and investigator-determined response assessments, the sponsor-derived responses are used as the basis for efficacy conclusions since using independent radiological reviews was recommended by the Agency.
- 5) The sponsor-determined response and duration of response were used as the basis for efficacy evaluations with the exception of patient 010-001, for whom the investigator-determined response and duration of response were used in the absence of neck scans.
- 6) Deaths prior to detectable progression could present informative censoring for time to progression calculation. Also any time to event endpoints are not interpretable in single arm studies.
- 7) Results from the Study M34103-053 support the claim of efficacy based on response rate and duration of response as the primary outcomes for the treatment of relapsed or refractory mantle cell lymphoma in patients with prior therapies. In all treated patients, the proportion of subjects had CR+CRu+PR on VELCADE was 31% with median duration of response of 285 days. The median time to progression was 189 days, and the median progression free survival was 184 days in all VELCADE treated patients. At the time of data cut-off, median survival had not been reached with 52 (34%) deaths observed.
- 8) Examinations of patient subgroups indicate VELCADE was effective in refractory patients in terms of response and durability of response, and the efficacy profile remained similar regardless of time since diagnosis of MCL, number of lines and type of prior therapy, and whether the patient had received hyper-CVAD or stem cell transplant.

5.2 Conclusions and Recommendations

In this reviewer's opinion, results from the submitted Phase II, single-arm, multi-center trial supports the claim of efficacy based on response rate and duration of response as the primary outcomes for the treatment of relapsed or refractory mantle cell lymphoma in patients with prior therapies. The results indicate heavily treated relapsed or refractory MCL patients had a good response to VELCADE, and the response was durable. Whether lacking appropriate controls for comparison, inclusion of partial response for overall response rate, choice of endpoints, and the size and durability of response are adequate for approval will be a clinical decision.

APPENDIX

Table 22 Best Response in RP-Final (n = 141)

Obs	CNOPATNO	Sponsor	Investigator
1	001-001		PD
2	001-002	SD	PR
3	001-003	SD	PR
4	001-004	CR	CR
5	001-005	SD	SD
6	001-006	SD	SD
7	001-007	SD	PR
8	001-008	SD	SD
9	001-009	SD	PD
10	001-010	SD	PD
11	002-001	PR	PD
12	002-002	CR	PR
13	002-003	PD	PD
14	003-001	PD	PD
15	004-001	SD	PR
16	004-002	PR	PR
17	004-003		PD
18	004-004	SD	SD
19	004-005	PD	SD
20	004-006	SD	PD
21	006-002	CR	CR
22	006-003	CR	CRu
23	006-004	SD	PR
24	006-005		
25	006-006	PR	PR
26	007-001	SD	SD
27	007-003	PR	PR

Obs	CNOPATNO	Sponsor	Investigator
28	007-004	PR	PR
29	007-005	SD	SD
30	007-006		PD
31	007-008	PD	SD
32	008-001	CR	CR
33	009-001	PR	PR
34	009-002	SD	SD
35	010-001		CR
36	010-002	PR	PR
37	010-003	CR	CR
38	010-005	PR	PR
39	010-006	PD	PD
40	010-007	PR	SD
41	010-008	SD	PR
42	010-009	PD	PD
43	011-001	CRu	CRu
44	011-002		PD
45	011-003	PD	SD
46	011-004	PR	PR
47	011-005	SD	SD
48	011-006	PD	PD
49	011-008	SD	SD
50	012-001	SD	SD
51	012-003	PR	SD
52	012-004	PD	PR
53	012-005	PR	PR
54	013-001	PD	PD
55	013-002		PD
56	013-003	PD	PD
57	013-004	SD	SD

Obs	CNQPATNO	Sponsor	Investigator
58	013-005	PD	SD
59	013-006	SD	SD
60	014-002	PD	PR
61	014-003	PD	SD
62	014-004	PR	CR
63	014-005	CRu	CR
64	015-001	PR	PR
65	015-002	SD	SD
66	015-003	PR	PR
67	015-004	CR	PR
68	017-001	PR	PR
69	018-001	PR	CRu
70	018-002		PD
71	018-003	PD	PD
72	018-004	PD	SD
73	018-005	PD	PD
74	019-001	PR	PR
75	019-002	SD	SD
76	019-003	SD	SD
77	020-001	SD	PD
78	020-002	SD	SD
79	020-003	PD	PR
80	020-005	SD	SD
81	021-001	SD	SD
82	021-002	SD	SD
83	022-001	PR	PR
84	022-002	SD	SD
85	023-001	PD	PD
86	024-001	PR	PR
87	024-002	SD	PR

Obs	CNOPATNO	Sponsor	Investigator
88	024-004	PR	PR
89	027-001	SD	PR
90	027-002		PD
91	027-003		PD
92	027-004	PD	PD
93	027-005	SD	SD
94	027-006	PR	PR
95	027-008		SD
96	027-009	PD	PD
97	028-002	PD	SD
98	028-003	PR	PR
99	028-005	SD	PD
100	028-007	SD	SD
101	029-001	PD	PD
102	029-002	SD	SD
103	029-003	PD	PD
104	029-004	SD	PR
105	031-001	PD	SD
106	031-003	SD	PD
107	031-004	SD	SD
108	031-005	SD	SD
109	031-006	PR	PR
110	034-001	PR	PR
111	034-002	PD	PD
112	034-003	PD	PD
113	034-005	PR	PR
114	034-006	PD	SD
115	034-007	PD	PD
116	034-008	SD	SD
117	034-009	SD	PR

Obs	CNOSPATNO	Sporno	Intestato
118	034-011	PD	SD
119	034-012	PR	PR
120	034-013	PR	PR
121	035-001		PD
122	038-001	PR	SD
123	038-002	SD	SD
124	038-003	SD	SD
125	039-001	PD	PD
126	041-001	PR	PR
127	041-002	PD	PD
128	041-003	PR	PR
129	041-004	SD	SD
130	042-001	SD	SD
131	042-002	PD	PD
132	042-003	CR	PR
133	042-004	PR	SD
134	043-001	PD	PD
135	043-002	PR	PR
136	048-001	SD	PR
137	049-001	PR	PR
138	049-002	PR	PR
139	049-003	PD	SD
140	049-004	PR	PR
141	049-005	CR	CR

Table 23

Cross Tabulation of Best Response by Sponsor-Derived and Investigator-Determined Methods

Best Response Sponsor-Derived	Best Response Investigator-Determined						Total
	CR	CRu	PD	PR	SD		
Frequency	1	1	0	9	0	1	12
Percent	0.71	0.71	0.00	6.38	0.00	0.71	8.51
Row Per	8.33	8.33	0.00	75.00	0.00	8.33	
Col Per	100.00	12.50	0.00	24.32	0.00	2.17	
CR	0	5	1	0	3	0	9
	0.00	3.55	0.71	0.00	2.13	0.00	6.38
	0.00	55.56	11.11	0.00	33.33	0.00	
	0.00	62.50	33.33	0.00	6.52	0.00	
CRu	0	1	1	0	0	0	2
	0.00	0.71	0.71	0.00	0.00	0.00	1.42
	0.00	50.00	50.00	0.00	0.00	0.00	
	0.00	12.50	33.33	0.00	0.00	0.00	
PD	0	0	0	21	3	11	35
	0.00	0.00	0.00	14.89	2.13	7.80	24.82
	0.00	0.00	0.00	60.00	8.57	31.43	
	0.00	0.00	0.00	56.76	6.52	23.91	
PR	0	1	1	1	29	4	36
	0.00	0.71	0.71	0.71	20.57	2.84	25.53
	0.00	2.78	2.78	2.78	80.56	11.11	
	0.00	12.50	33.33	2.70	63.04	8.70	
SD	0	0	0	6	11	30	47
	0.00	0.00	0.00	4.26	7.80	21.28	33.33
	0.00	0.00	0.00	12.77	23.40	63.83	
	0.00	0.00	0.00	16.22	23.91	65.22	
Total	1	8	3	37	46	46	141
	0.71	5.67	2.13	26.24	32.62	32.62	100.00

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Chia-Wen Ko, Ph.D.
Date:

Concurring Reviewers: Rajeshwari Sridhara, Ph.D.
Team Leader

Aloka Chakravarty, Ph.D.
Director, Division of Biometrics V

cc:

HFD-150/Mrs. Tammie Brent-Steele
HFD-150/Dr. Robert Kane
HFD-150/Dr. Ann Farrell
HFD-711/Dr. Chia-Wen Ko
HFD-711/Dr. Rajeshwari Sridhara
HFD-711/Dr. Aloka Chakravarty
HFD-700/Dr. Robert O'Neill
HFD-700/Ms. Lillian Patrician

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Chia-wen Ko
11/29/2006 12:55:48 PM
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Rajeshwari Sridhara
11/29/2006 03:06:37 PM
BIOMETRICS

Aloka Chakravarty
11/30/2006 09:17:39 AM
BIOMETRICS

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-602 / S-010

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 21-602/S-010 _____ **b(4)**
BRAND NAME: VELCADE
GENERIC NAME: Bortezomib (PS-341)
**DOSAGE FORM/
STRENGTH:** 3.5 mg Bortezomib in Vials
for Intravenous Injection
INDICATIONS: Mantle Cell Lymphoma and Multiple Myeloma
SUBMISSION DATES: 08-Jun-2006 and 28-Dec-2005
SUBMISSION TYPES: NDA Supplement and Amendment
APPLICANT: Millennium Pharmaceuticals, Inc.
ODDP: Office of Oncology Drug Products
OCP DIVISION: Division of Clinical Pharmacology 5
OCP REVIEWER: Sophia Abraham, Ph.D.
OCP TEAM LEADER: Brian Booth, Ph.D.

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1. EXECUTIVE SUMMARY

Millennium Pharmaceuticals seeks approval of a supplemental New Drug Application (sNDA) for the use of VELCADE (bortezomib) for Injection in the treatment of patients with relapsed or refractory mantle cell lymphoma (MCL) who received at least one prior therapy (S-010). Mantle cell lymphoma (MCL) is an aggressive uncommon form of non-Hodgkin's lymphoma that historically has been resistant to current standard chemotherapies. The median survival time of patients with MCL is 2.5-4 years.

VELCADE (bortezomib) for Injection was approved on 12-May-2003 as a single agent for the treatment of patients with multiple myeloma. The approved dose is 1.3 mg/m² administered as a bolus intravenous injection twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period.

To support the safety and effectiveness of VELCADE in the new indication (Viz., in patients with relapsed or refractory MCL who had received at least 1 prior therapy), the Applicant submitted a Phase 2, multi-center, single-arm, open-label, non-comparative study in 155 patients with relapsed or refractory MCL (Study M34103-053) under sNDA 21-602 (S-010). VELCADE was administered at the current approved dose and schedule of 1.3 mg/m² administered twice per week for 2 weeks followed by a 10-day rest period. Study M34103-053 is currently ongoing; data submitted to this sNDA are through a cut-off date of 01-Dec-2005. The primary clinical endpoint used in this study was disease response rate. The safety profile of VELCADE in patients with relapsed MCL was comparable to that previously described in patients with relapsed multiple myeloma.

The approvable letter of 12-May-2003 contained some Phase 4 Commitments that have to be addressed. In this submission, the Applicant has addressed the Phase 4 Commitment # 6 of the approvable letter of 12-May-2003 by submitting a final study report for Study M34103-058 as an amendment to NDA 21-602 (S-000/F4). In Study M34103-058, the pharmacokinetics (PK) and the pharmacodynamics (PD) of bortezomib were assessed on Days 1 and 11 of each of Cycles 1 and 3 in 24 patients with multiple myeloma at doses of 1.0 mg/m² (n=12) and 1.3 mg/m² (n=12). The results of this study showed that bortezomib accumulates upon twice weekly administration. The exposure of bortezomib (mean AUC) was 3.7-fold higher after the 1.0 mg/m² dose and 4.2-fold higher after the 1.3 mg/m² dose on Day 11 than on Day 1 of Cycle. Accumulation is less during Cycle 3 (2- to 3- fold). The maximum proteasome inhibition was comparable between the 1.0 mg/m² and 1.3 mg/m² doses across days and cycles, ranging from 70-84%. In general, the incidence of adverse events (AEs) was higher in the 1.3 mg/m² dose group compared to the 1.0 mg/m² dose group.

1.1 RECOMMENDATION

The Applicant has fulfilled the Phase 4 Commitment # 6 according to the approval letter of 12-May-2003 for VELCADE for Injection. The Applicant should incorporate the Clinical Pharmacology Labeling Recommendations as outlined under Section 3 of this review.

Please forward the above Overall Recommendation and Clinical Pharmacology Labeling Recommendations (Section 3 of this review) to the Applicant.

1.2 PHASE 4 COMMITMENTS

[None]

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMA-CEUTICS FINDINGS

VELCADE (bortezomib) was granted an accelerated approval on 12-May-2003 as a single agent for the treatment of patients with multiple myeloma. The approvable letter of 12-May-2003 contained some Phase 4 Commitments that have to be addressed by the Applicant. The Applicant submitted a final study report for Study M34103-058, entitled "*Repeat-Dose Pharmacokinetics and Pharmacodynamics of Bortezomib in Patients with Relapsed Multiple Myeloma*" to address the following Phase 4 Commitment:

Commitment #6: "Conduct a study to characterize the pharmacokinetics (PK) of bortezomib as a single agent at 1.3 mg/m² and 1.0 mg/m² twice weekly in at least 12 multiple myeloma patients at each dose level. Patients should have normal to mildly decrease creatinine clearance value (≥ 50 mL/min). The pharmacokinetics should be characterized both at Cycle 1 and at a subsequent cycle to address the time-dependent changes in the PK of bortezomib as a single agent".

Study M34103-058 was a prospective, multi-center, open-label, randomized study in 42 patients with multiple myeloma. Patients were randomized (1:1) to receive either 1.0 mg/m² or 1.3 mg/m² doses of bortezomib intravenously twice weekly on Days 1, 4, 8, and 11 of each treatment cycle, followed by a 10-day rest period (21-day cycle). The pharmacokinetics of bortezomib and the 20S proteasome inhibition were evaluated in 12 patients following the 1.0 mg/m² (n=12) and 1.3 mg/m² (n=12) doses on Day 1 and Day 11 during Cycle 1 and Cycle 3. The results of the study demonstrated that bortezomib plasma levels declined biexponentially with a mean elimination half-life ($t_{1/2}$) of 30 hours after the 1.0 mg/m² dose and 11.5 hours after the 1.3 mg/m² dose on Day 1 of Cycle 1. Bortezomib accumulates upon chronic administration. The mean AUC of bortezomib was 3.7- to 4-fold higher on Day 11 than on Day 1 of Cycle 1 ($p < 0.05$). During Cycle 3, the mean AUC was 2- to 3-fold higher on Day 11 than on Day 1 ($p < 0.05$). Bortezomib exhibits time-dependent kinetics. The mean AUC of bortezomib was 2- to 3-fold higher on Day 1/Cycle 3 than on Day 1/Cycle 1 ($p < 0.05$). Time-dependence was less pronounced on Day 11; the mean AUC was 1.3- to 1.7-fold higher during Cycle 3 than Cycle 1 ($p > 0.05$). Analyses of data from 39 patients in this study showed that both dose-normalized AUC and C_{max} tend to increase as age increased. Patients of ≥ 65 years of age (n=13) had 33-35% higher mean dose-normalized AUC and C_{max} than those between the age of 36-64 years (n=26). The current labeling has some recommendations of the use of VELCADE in elderly patients under the Precautions section. Gender has no effect on both mean dose-normalized AUC and C_{max} . The effect of race could be assessed as most of the patients were Caucasians. Following twice weekly bortezomib administration, the mean maximum proteasome inhibition was comparable between the 1.0 and 1.3 mg/m² doses across study days and cycles. The mean observed maximum inhibition of 20S proteasome activity (relative to baseline) ranged from 70-83.5% and from 73-83% for the 1.0 mg/m² and 1.3 mg/m² doses, respectively. In general, the incidence of adverse events (AEs) was higher in the 1.3 mg/m² dose group compared to the 1.0 mg/m² dose group.

2 QUESTION BASED REVIEW

Please refer to the original NDA 21-602 (Submission Date: 21-Jan-2003) for the following issues (Questions 2.1.1 to 2.1.3):

2.1 *General Attributes of the Drug*

- 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology review?
- 2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?
- 2.1.3 What are the proposed dosage(s) and route(s) of administration?

2.2 *General Clinical Pharmacology*

- 2.2.1 **What are the design features of the clinical studies used to support dosing or claims?**

In support of the new indication for VELCADE in the (Viz., in the treatment of patients with relapsed or refractory MCL who had received at least 1 prior therapy), the Applicant submitted a Phase 2 study, entitled "*A Phase 2 Study of VELCADE in Subjects with Relapsed or Refractory Mantle Cell Lymphoma*" (Study M34103-053). The primary objective of this study was to determine whether VELCADE increases median time to progression (TTP) compared to historical controls in patients with MCL. Study M34103-053 was an open-label, multi-center, single-arm, Phase 2 study in 155 patients with relapsed or refractory MCL. Most of the patients enrolled in this study were males (N=125; 81%) with a median age of 65 years (ranged from 42 to 89 years). Most patients were Caucasians (N=142, 92%). Patients received VELCADE 1.3 mg/m² as a bolus intravenous (IV) infusion twice weekly on Days 1, 4, 8, and 11 of a 21-day treatment cycle for up to 17 treatment cycles. The primary endpoint was disease response rate. Study M34103-053 is currently ongoing. At the cut-off date of 01- Dec-2005, the response rate was 33% in the final evaluable population [47/141 patients achieved complete response (CR), complete response unconfirmed (CRu), or partial response (PR)].

The most commonly reported adverse events (AEs) in this study were asthenic conditions (72%), peripheral neuropathy (55%), constipation (50%), diarrhea (47%), nausea (44%), and appetite decreased (39%). These AEs were comparable to those previously reported in clinical studies of VELCADE in patients with multiple myeloma. No PK information was obtained in this study.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Response rate was selected as the primary endpoint in the Phase 2 Study M34103-053 in MCL patients. In lymphoma, response rate is generally considered to be an important predictor of clinically relevant antitumor activity. The response rate was assessed using the International Workshop Response Criteria (IWRC) as follows:

Table 1. Response Criteria Based on IWRC

Response Category:	Criteria Required:
CR required ALL criteria:	a.) Complete disappearance of all detectable clinical and radiographic evidence of disease, disappearance of all disease-related symptoms, and normalization of biochemical abnormalities definitely ascribable to lymphoma (eg, LDH). b.) All lymph node masses must have regressed to normal size. Lymph node masses that were >1.5 cm in longest transverse dimension must have regressed to ≤1.5 cm. Each lymph node mass that was 1.1 to 1.5 cm in longest transverse dimension and thought to be involved with lymphoma must have regressed to ≤1 cm in longest transverse dimension, or by more than 75% of the product of the longest perpendicular dimensions compared to the pretreatment baseline. c.) If the spleen was considered to be enlarged due to involvement with lymphoma prior to therapy, it must have regressed in size, and must not have been palpable on physical examination. d.) If the bone marrow was involved by lymphoma, indeterminate or not adequately assessed during screening, an adequate aspirate and biopsy of the same site must have been clear of lymphoma.
CRu required:	Criteria (a) and (c) for CR were satisfied; however: Any residual lymph node mass >1.5 cm in longest transverse dimension must have regressed by more than 75% of the product of the longest perpendicular dimensions compared to the pretreatment baseline and The bone marrow aspirate may have been indeterminate (contain increased number or size of lymphoid aggregates without cytologic or architectural atypia).
PR required ALL criteria:	a.) ≥50% decrease in the sum of the products of the longest perpendicular dimensions (SPD) of the previously identified dominant lymph node masses (up to 6) b.) ≥50% decrease in the SPD of nondominant measurable sites of disease c.) No increase in the size of other sites of lymphoma that meets the criteria for progressive or relapsed disease d.) No new sites of lymphoma.
SD required:	Disease response was less than that required for PR, but the criteria for relapse or progressive disease were not met.
PD/relapse required any:	a.) Appearance of any sites of lymphoma b.) ≥50% increase in the product of the longest perpendicular dimensions of any previously identified lymph node mass c.) ≥50% increase in the longest dimension of any previously identified lymph node mass >1 cm in longest transverse dimension d.) ≥50% increase in the size of any other previously involved site of lymphoma Note: In all cases the smallest prior measurement was to be used as the baseline for comparison when evaluating for progressive or relapsed disease.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

No pharmacokinetic information was obtained in Study M34103-053 in patients with mantle cell lymphoma. In Study M34103-058, plasma samples were analyzed for bortezomib to determine the pharmacokinetic parameters and exposure response relationships.

Please refer to the original NDA 21-602 (Submission Date: 21-Jan-2003) for the following issues (Questions 2.2.4.1 to 2.2.4.4):

2.2.4 Exposure-Response

- 2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?
- 2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?
- 2.2.4.3 Does this drug prolong the QT or QTc interval?
- 2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?
- 2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters?

Study M34103-058 was a prospective, multi-center, open-label, randomized, single- and multiple-dose study in a total of 42 patients with multiple myeloma. Patients were randomized (1:1) to receive either 1.0 mg/m² (Arm A) or 1.3 mg/m² (Arm B) dose of bortezomib. Bortezomib doses were administered intravenously twice weekly (on Days 1, 4, 8, and 11) of each treatment cycle, followed by a 10-day rest period (21-day cycle). Out of the 42 patients, twenty-four (12 in the 1.0 mg/m² dose group and 12 in the 1.3 mg/m² dose group) completed dosing through Cycles 1-3 without a dosing modification, and had adequate sampling to assess the pharmaco-kinetics (PK) and pharmacodynamics (PD) of bortezomib. Blood samples were collected up to 48 hours after administration on Days 1 and 11 of Cycles 1 and 3 to characterize the single- and multiple-dose plasma PK of bortezomib. Plasma concentrations of bortezomib were measured using a validated liquid chromatography coupled with tandem mass spectrometry (LC/MS/MS) method. The PK parameters were to be calculated by non-compartmental analysis of the plasma concentration time data (Tables 2 and 3). The 20S proteasome enzyme activity (based on chymotryptic:trypsin ratio [ChT:T]) was

measured in whole blood during Cycles 1 and 3 at the same times of the PK sampling. The pharmacodynamic (PD) effect of bortezomib was measured by change in 20S proteasome enzyme activity (based on percent inhibition of ChT:T versus baseline). The observed maximum inhibition, time to maximum inhibition (T_{max}), and area under the % inhibition/time curve from time 0 to 48 hours (AUC_{0-48}), predicted concentration of drug in plasma that produces 50% of the maximum effect (EC_{50}), and model-predicted peak inhibition were determined from the relationship between the percent 20S proteasome inhibition (relative to baseline) and log plasma concentrations of bortezomib (Figures 8 and 9).

Pharmacokinetic Results:

Table 2. Mean±SD (CV%) PK parameters of PS-341 following the 1.0 mg/m² dose in 12 patients with multiple myeloma [6 males and 6 females]

Parameter	Cycle 1		Cycle 3	
	Day 1	Day 11	Day 1	Day 11
*CLcr (mL/min)	59 (37.9-121)			
C_{max} (ng/ml)	56.7±36 (64%)	106±47 (44%)	66±43 (64%)	84±69 (82%)
T_{max} (h)	0.13±0.12 (99%)	0.07±0.03 (47%)	0.12±0.12 (100%)	0.16±0.17 (106%)
AUC (ng.h/ml)	57±45 (79%)	212±155 (73%)	116±58.8 (50%)	359±195 (54%)
$t_{1/2}$ (h)	30.7±44.7 (145%)	78.9±50.9 (64%)	39.8±14.4 (36%)	193±169 (87%)
CL (L/h/m ²)	57.1±25.3 (44%)	12.9±8.9 (69%)	17.9±9.4 (52%)	8.3±6.9 (83%)
V_{ss} (L/m ²)	795±1061 (133%)	799±388 (48%)	923±468 (51%)	1783±1560 (87%)

*Median (range) creatinine clearance

Table 3. Mean±SD (CV%) PK parameters of PS-341 following the 1.3 mg/m² dose in 12 patients with multiple myeloma [6 males and 6 females]

Parameter	Cycle 1		Cycle 3	
	Day 1	Day 11	Day 1	Day 11
*CLcr (mL/min)	75 (43.8-118)			
C_{max} (ng/ml)	112±122 (109%)	88±47 (53%)	120±71 (58%)	115±98 (85%)
T_{max} (h)	0.11±0.06 (58%)	0.20±0.28 (142%)	0.10±0.05 (49%)	0.10±0.05 (49%)
AUC (ng.h/ml)	44±17.4 (39%)	188±92.8 (49%)	133±51 (38%)	254±98 (38%)
$t_{1/2}$ (h)	11.5±12.7 (110%)	75.5±49.9 (66%)	49.1±34.6 (70%)	108±64.7 (59%)
CL (L/h/m ²)	58.2±41.8 (71%)	14.9±9.4 (63%)	17.1±7.6 (45%)	8.8±3.6 (41%)
V_{ss} (L/m ²)	285±266 (93%)	1070±712 (66%)	925±684 (74%)	1231±843 (68%)

*Median (range) creatinine clearance

Following twice weekly administration, bortezomib plasma levels declined biexponentially with a mean elimination half-life ($t_{1/2}$) of 30 hours after the 1.0 mg/m² dose and 11.5 hours after the 1.3 mg/m² dose on Day 1 of Cycle 1.

Bortezomib accumulates upon chronic administration. The mean AUC of bortezomib was 3.7- to 4-fold higher on Day 11 than on Day 1 of Cycle 1 ($p < 0.05$). During Cycle 3, the mean AUC was 2- to 3-fold higher on Day 11 than on Day 1 ($p < 0.05$).

Bortezomib exhibits time-dependent kinetics. The mean AUC of bortezomib was 2- to 3-fold higher on Day 1/Cycle 3 than on Day 1/Cycle 1 ($p < 0.05$). Time-dependence was less pronounced on Day 11; the mean AUC was 1.35- to 1.7-fold higher during Cycle 3 than Cycle 1 ($p > 0.05$).

Fig. 1. Mean bortezomib plasma concentration/time profiles after 1.0 mg/m² dose (n=12)

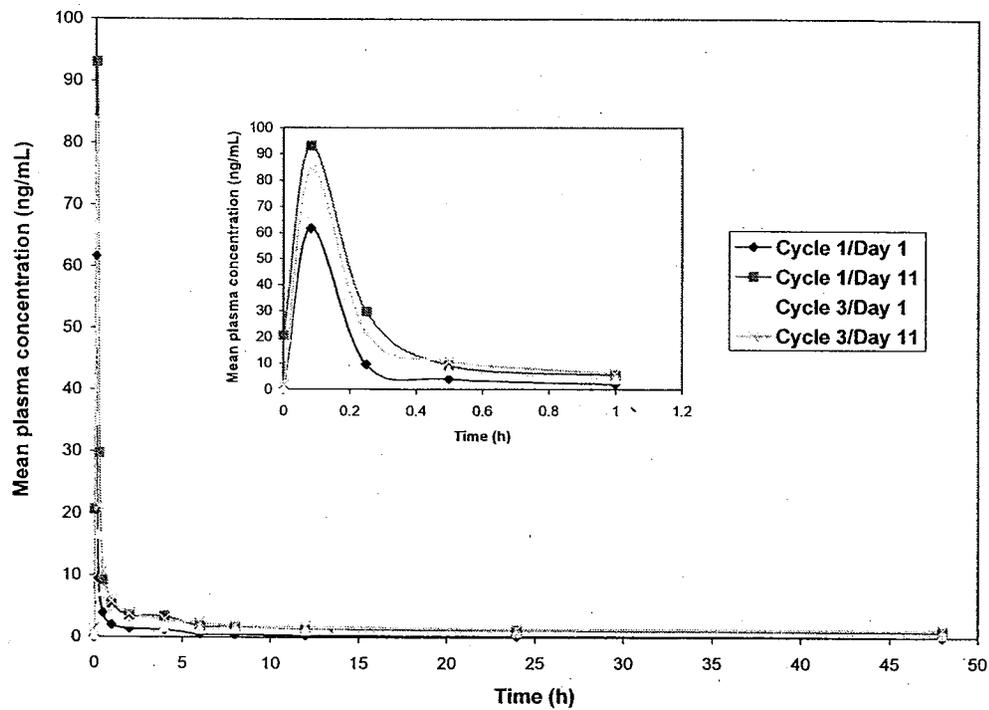
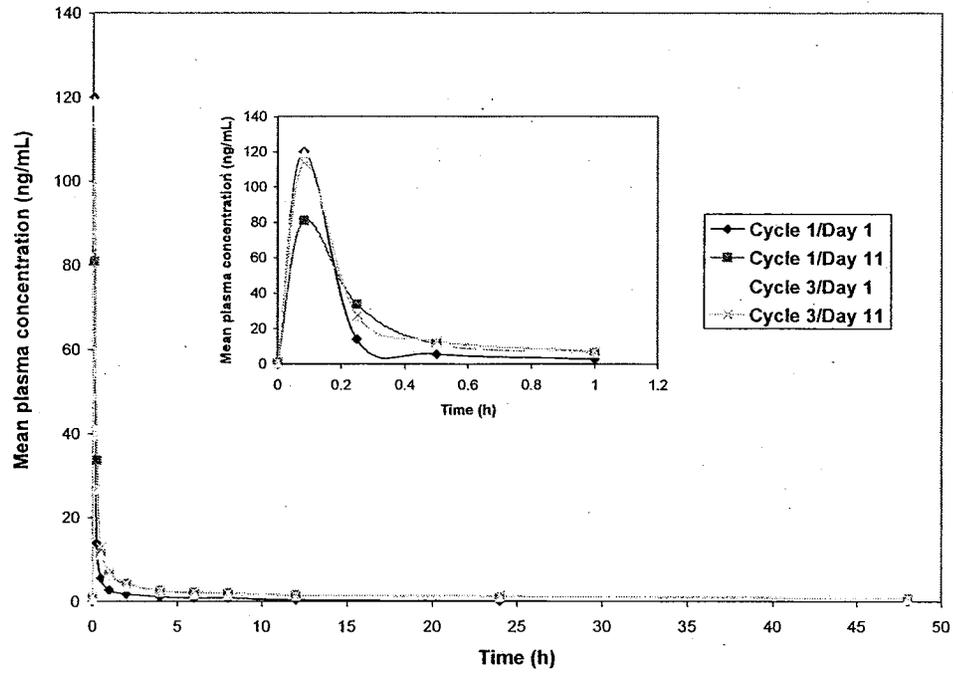
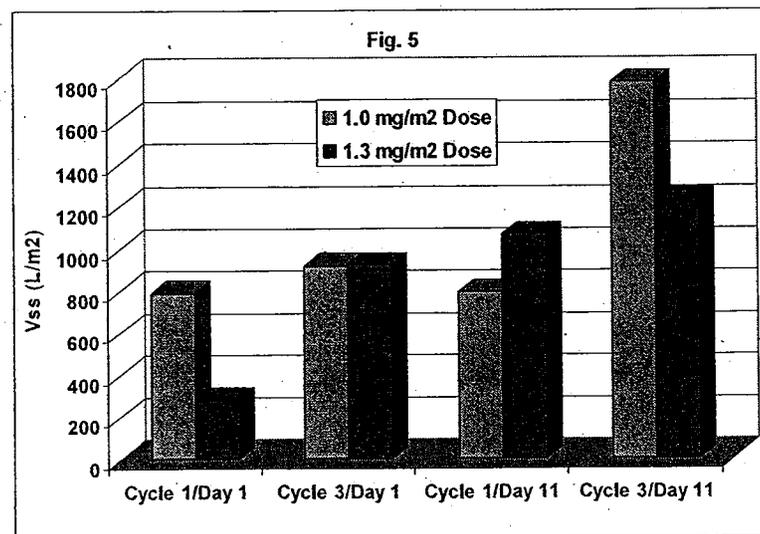
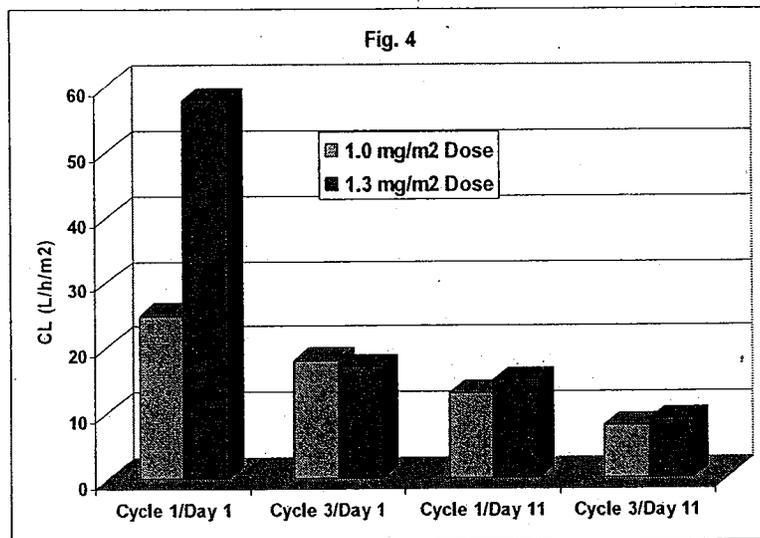
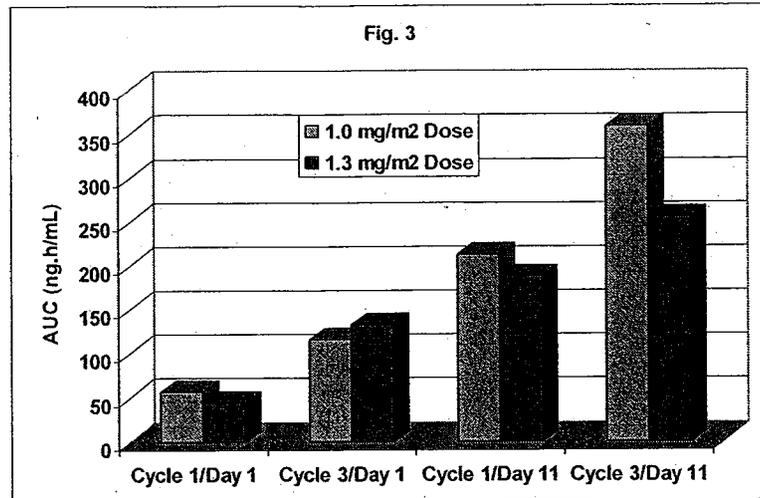


Fig. 2. Mean bortezomib plasma concentration/time profiles after 1.3 mg/m² dose (n=12)





Pharmacodynamic Results:

Table 4. Mean±SD percent inhibition of proteasome activity in whole blood (from baseline) in cancer patients

Parameter	Cycle 1		Cycle 3	
	Day 1	Day 11	Day 1	Day 11
1.0 mg/m ² dose (n=12)				
T _{max} (h)	0.14±0.10	0.083±0.06	0.32±0.38	0.42±0.60
Observed Maximum Inhibition (%)	69.7±10.9	83.4±7.0	78.3±7.1	83.5±7.0
AUC ₀₋₄₈ (%.h)	1648±473	2566±489	2536±647	2795±717
1.3 mg/m ² dose (n=12)				
T _{max} (h)	0.14±0.08	0.96±1.7	0.46±1.2	0.35±0.36
Observed Peak inhibition (%)	73.04±10.8	78.6±6.5	78.2±9.3	82.9±9.5
AUC ₀₋₄₈ (%.h)	1425±717	2278±748	1824±1047	2386±577

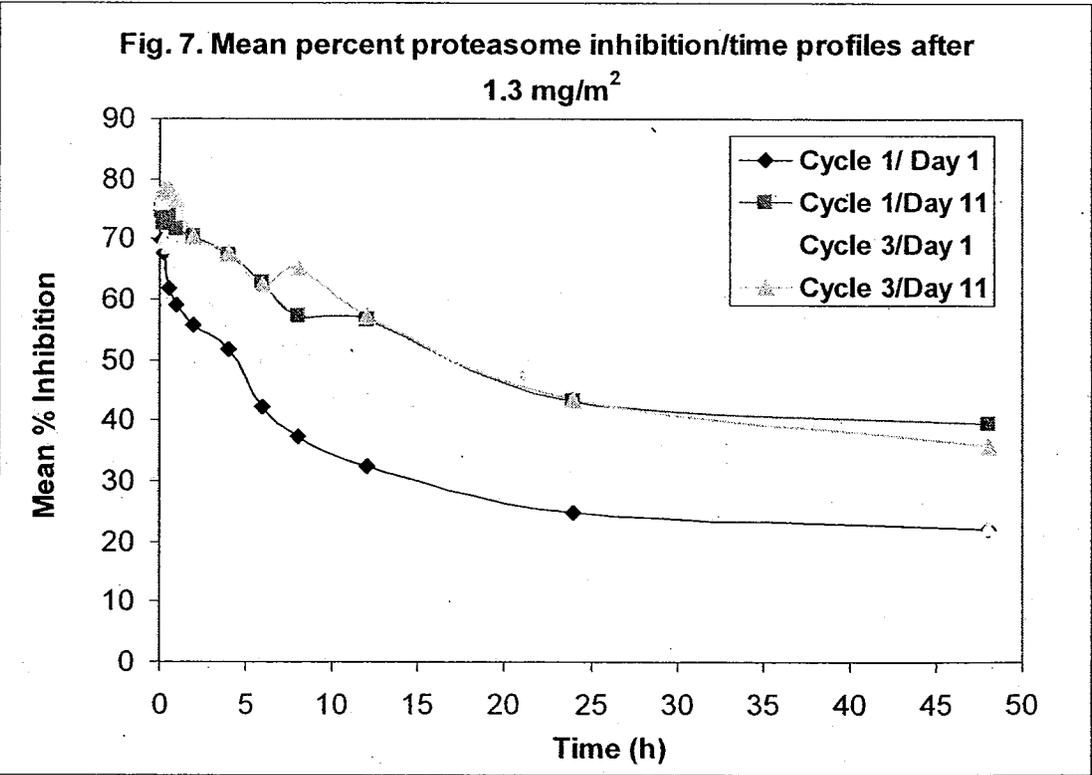
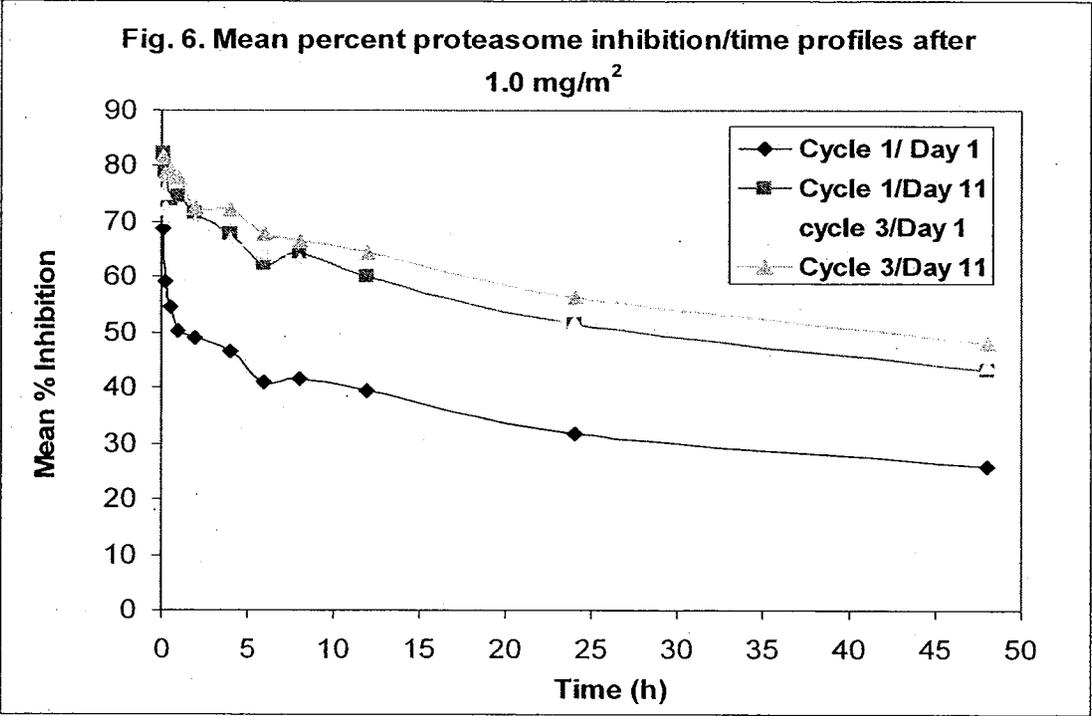
Table 5. Model-predicted PD parameters of proteasome inhibition

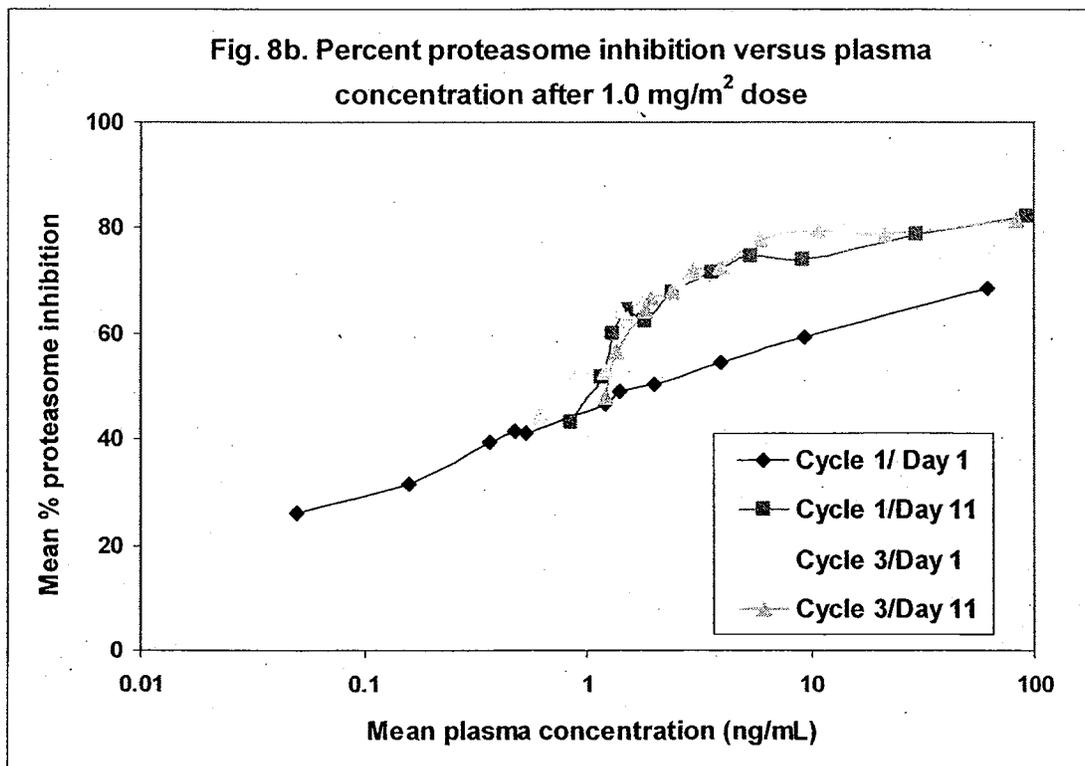
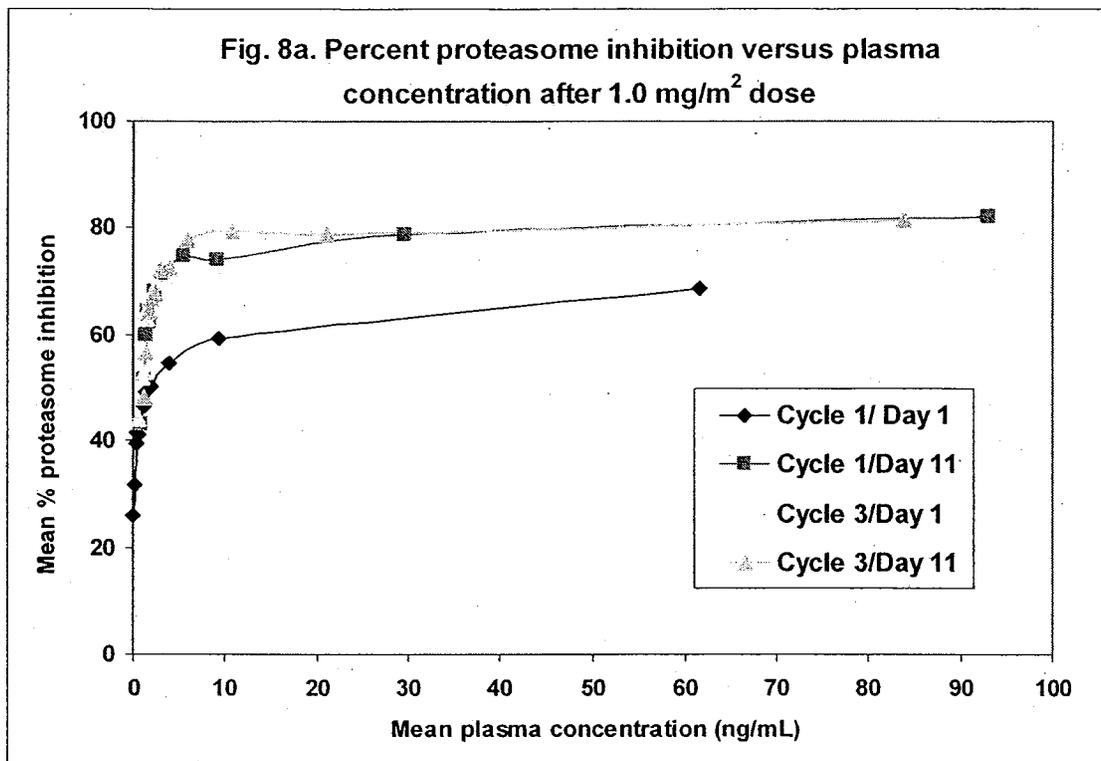
Mean (SE) Percent Inhibition of Chymotryptic:Tryptic Activity Ratio (ChT:T)				
	Day 1/Cycle 1	Day 11/Cycle 1	Day 1/Cycle 3	Day 11 / Cycle 3
Model predicted Peak inhibition (%)	66.3 (1.5)	80.9 (1.4)	77.2 (2.2)	84.1 (2.1)
EC ₅₀ (ng/mL)	0.43 (0.05)	0.65 (0.05)	0.66 (0.08)	0.81 (0.08)

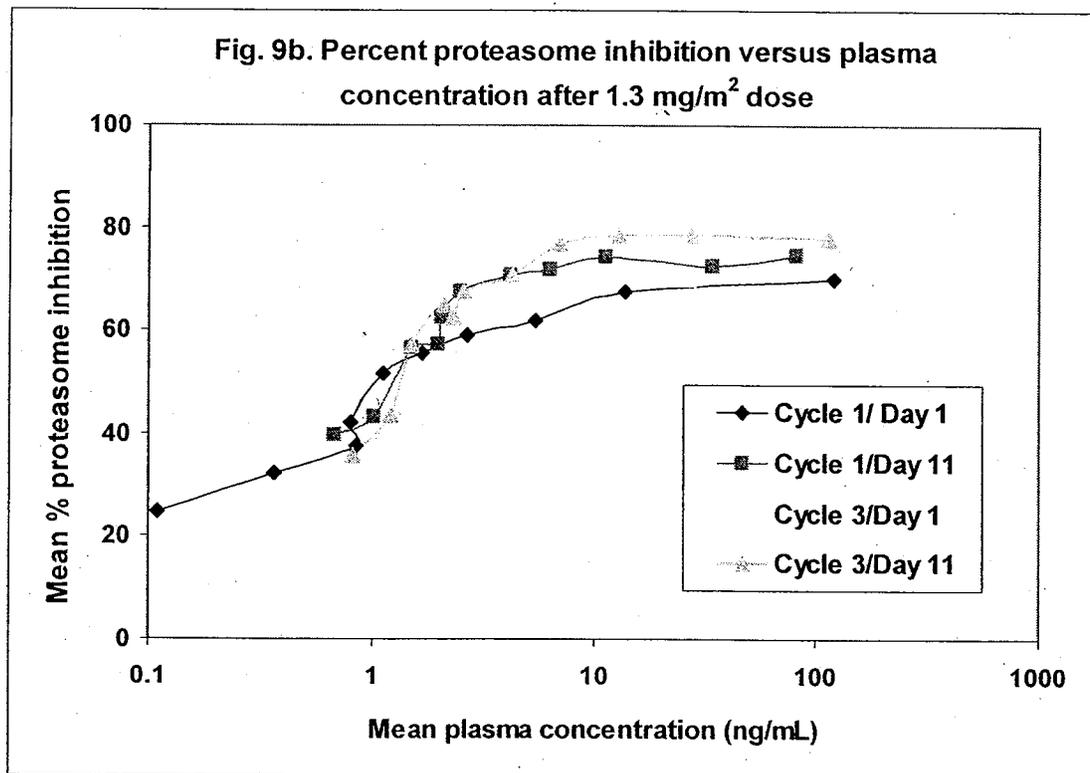
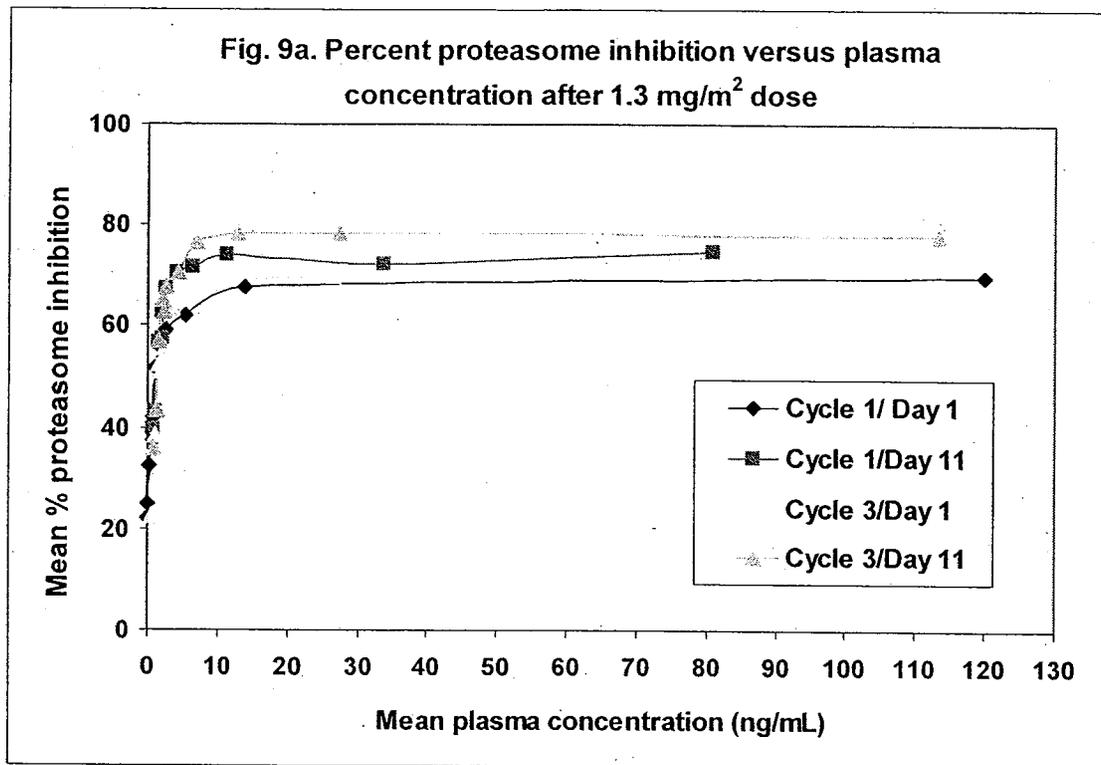
Following twice weekly bortezomib administration, the mean percent proteasome inhibition was comparable between the 1.0 and 1.3 mg/m² doses across study days and cycles. The mean observed maximum percent inhibition of proteasome activity (relative to baseline) ranged from 70-84% and from 73-83% for the 1.0 mg/m² and 1.3 mg/m² doses, respectively.

The relationship between the percent proteasome inhibition and bortezomib plasma concentrations could be described by E_{max} model with maximum inhibition and *EC₅₀ values consistent across study days with the exception of Day 1 of Cycle 1. The model-predicted maximum inhibition was lower on Day 1 of Cycle 1 (66.3%) then was comparable thereafter, ranging from 77-84%. EC₅₀ ranged from 0.43-0.81 ng/mL; which is much lower than maximum plasma concentrations (C_{max}) for the drug.

*[EC₅₀ = plasma concentration of bortezomib that resulted in 50% reduction in proteasome activity]



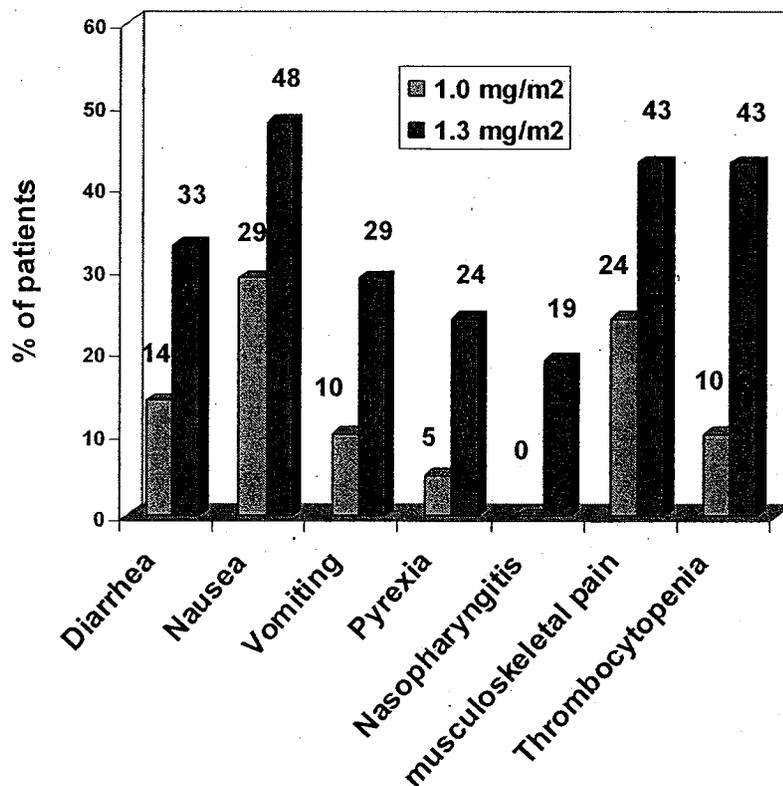




Safety Results:

In general, the incidence of adverse events (AEs) was higher (2- to 5-fold) in the 1.3 mg/m² dose group than in the 1.0 mg/m² dose group. The most commonly reported AEs were shown in the Fig. below.

Fig. 15. Incidence of adverse events versus dose



In conclusion, bortezomib accumulates upon twice weekly administration; the mean AUC of bortezomib was 3.7- to 4.2-fold higher on Day 11 than on Day 1 during Cycle 1 ($p < 0.05$). Bortezomib exhibits time-dependent kinetics; the mean AUC of bortezomib was 2- to 3-fold higher on Day 1/Cycle 3 than on Day 1/Cycle 1 ($p < 0.05$). The maximum proteasome inhibition was comparable between the 1.0 mg/m² and 1.3 mg/m² doses across days and cycles, ranging from 70-84%. The incidence of adverse events was 2- to 5-fold higher following the 1.3 mg/m² dose than the 1.0 mg/m² dose.

Please refer to the original NDA 21-602 (Submission Date: 21-Jan-2003) for the following issues (Questions 2.2.5.2 to 2.2.5.10):

- 2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?
- 2.2.5.3 What are the characteristics of drug absorption?
- 2.2.5.4 What are the characteristics of drug distribution?

- 2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?
- 2.2.5.6 What are the characteristics of drug metabolism?
- 2.2.5.7 What are the characteristics of drug excretion?
- 2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?
- 2.2.5.9 How do the PK parameters change with time following chronic dosing?
- 2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups?

The effect of age, gender, creatinine clearance (CLcr), and hepatic function (measured by elevation of liver enzymes) on bortezomib exposure (dose-normalized AUC and C_{max}) was evaluated in Study M34103-058 (by the Reviewer) on **Day 1** of Cycle 1 after the two doses (1.0 mg/m² and 1.3 mg/m²) in 42 patients. Patients had a median age of 61.5 years (range=36-83 years). There were 23 males and 19 females; 29 Caucasians, 7 Blacks, 3 Hispanics, and 3 Others. The effect of race could not be evaluated as most of patients enrolled in the study were Whites. Patients had a median creatinine clearance (CLcr) of 69.8 mL/min (1.3-165 mL/min). Three patients had no PK data available and were excluded from the analyses; thus, the total number of patients analyzed was 39. Most creatinine clearance (CLcr) values were within the normal-to-mild range of renal impairment according to the FDA published guidance on renal impairment studies (<http://www.fda.gov/cder/guidance/3625fnl.pdf>) (CLcr > 80 and CLcr=50-80 mL/min, n=15 and 19, respectively). Four patients had creatinine clearance values within the moderate range (CLcr=30-49 mL/min). Only one patient had severe renal impairment (CLcr < 30 mL/min).

2.3.2.1 Age

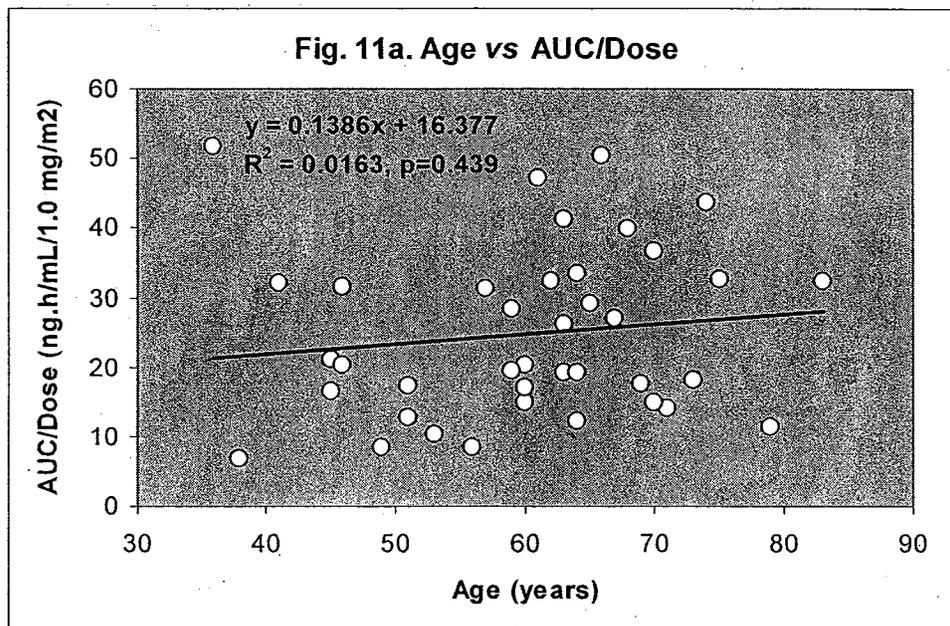
Both dose-normalized AUC and C_{max} tend to increase as age increased. Patients of ≥ 65 years of age (n=13) had 33% higher mean dose-normalized AUC and 35% higher mean dose-normalized C_{max} than those between the age of 36-64 years (n=26). The current labeling has some recommendations of the use of VELCADE in elderly patients under the Precautions section.

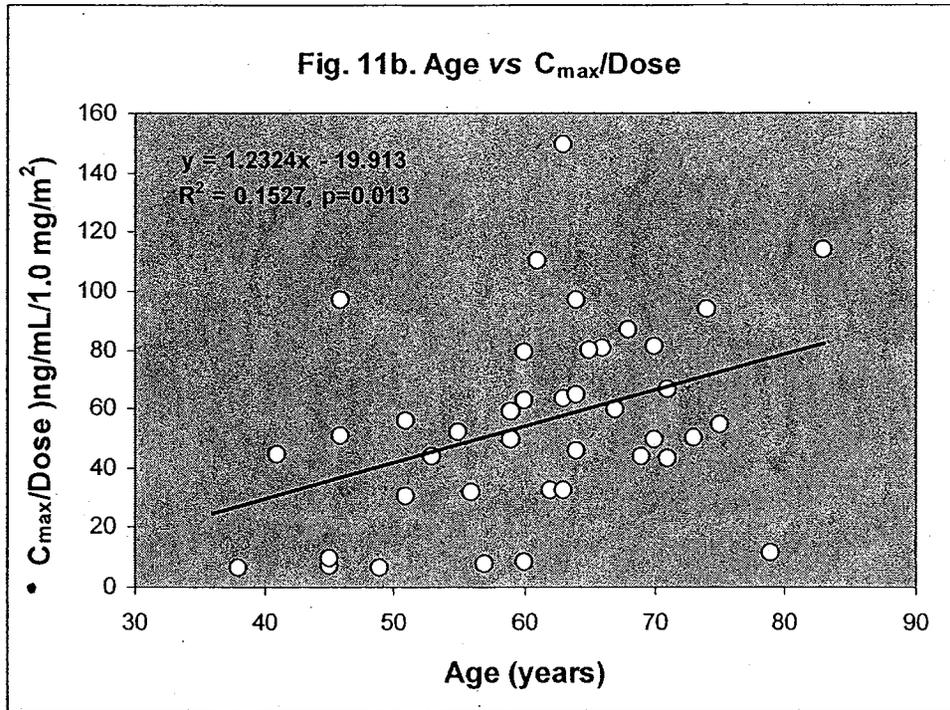
Table 6. Effect of Age

Mean±SD (CV%)	*Age Groups	
	58 (36-64) years	≥ 65 years
N	26	13
AUC/Dose (ng.h/ml/1.0 mg/m ²)	22.2±11.8 (53%)	29.6±11.7 (39%)
#p-value	--	0.041
C _{max} /Dose (ng/mL/1.0 mg/m ²)	49.6±36.3 (73%)	66.9±26.3 (39%)
#p-value	--	0.091

*Median (Range)

#(Student's t-Test with 2 samples of equal variance)





2.3.2.2 Pediatric patients

VELCADE has not been evaluated in pediatric patients.

2.3.2.3 Gender

Gender has no effect on the exposure to bortezomib (dose-normalized AUC and C_{max}) on Day 1 of Cycle 1.

Table 7. Effect of Gender

Mean±SD (CV%)		
	Males	Females
N	22	17
AUC/Dose (ng.h/ml/1.0 mg/m ²)	23.8±12.4 (52%)	25.5±12.2 (51%)
*p-value	0.343	
C_{max}/Dose (ng/mL/1.0 mg/m ²)	55.5±36.5 (65%)	54.6±29.5 (54%)
*p-value	0.467	

*(Student's t-Test with 2 samples of equal variance)

Fig. 12a. Gender vs AUC/Dose

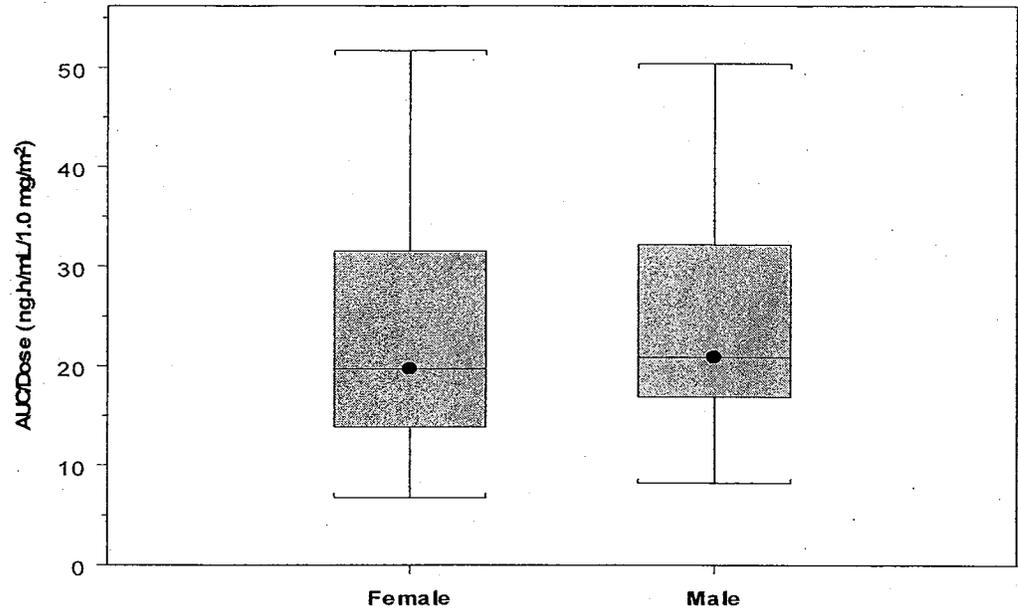
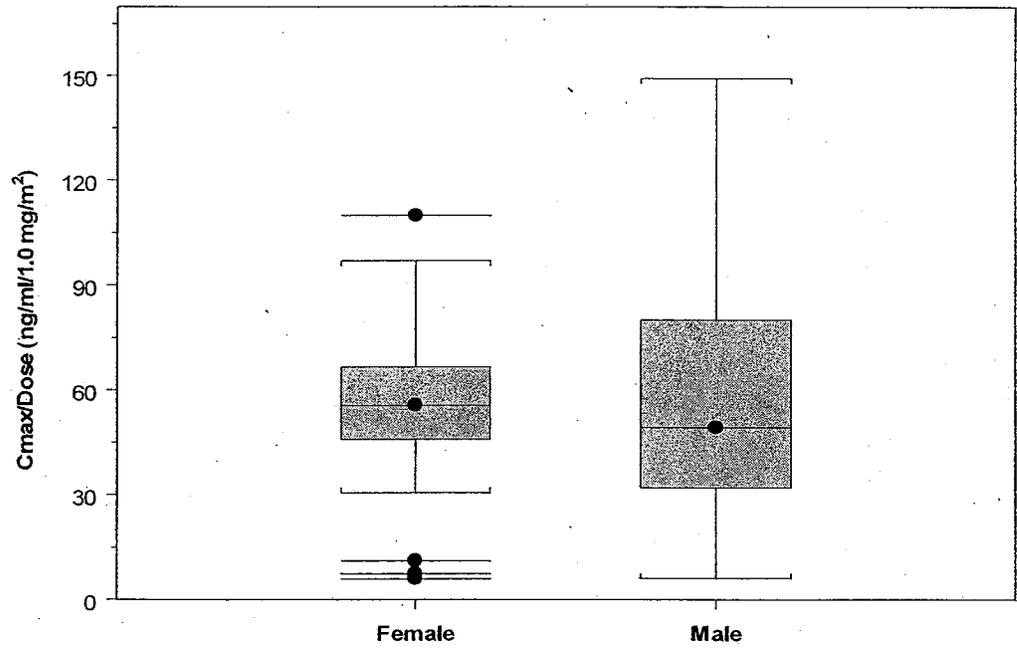


Fig. 12b. Gender vs C_{max} /Dose



2.3.2.4 Race

The effect of race on the PK of bortezomib could not be evaluated as most of the patients enrolled in the study were Caucasians.

2.3.2.5 Renal impairment

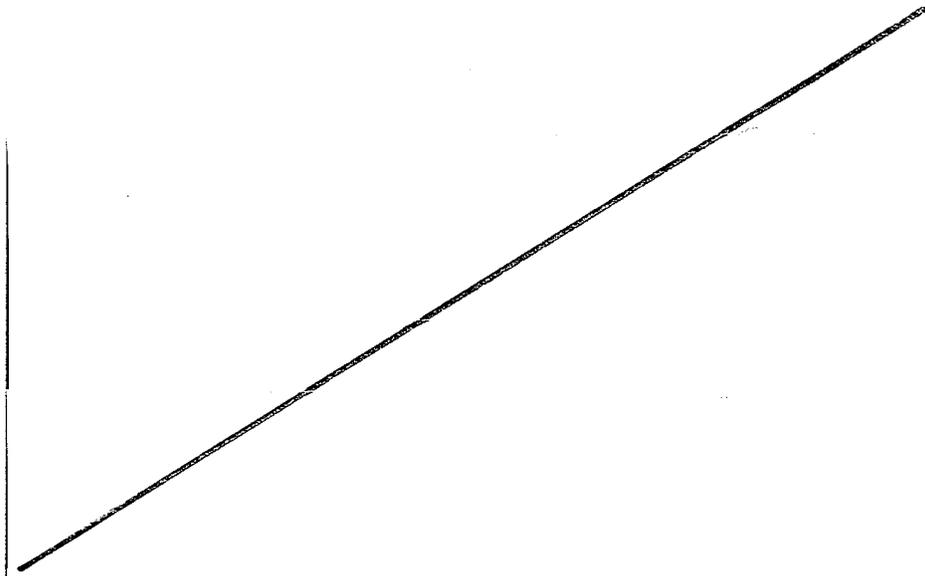
Patients with mild renal impairment had comparable mean dose-normalized AUC and C_{max} values to patients with normal renal function after bortezomib administration on Day 1 of Cycle 1. Patients with moderate renal impairment had about 40% higher mean $C_{max}/Dose$ than patients with normal renal function after bortezomib administration on Day 1 of Cycle 1 ($p > 0.05$).

Table 8. Mean \pm SD (CV%)

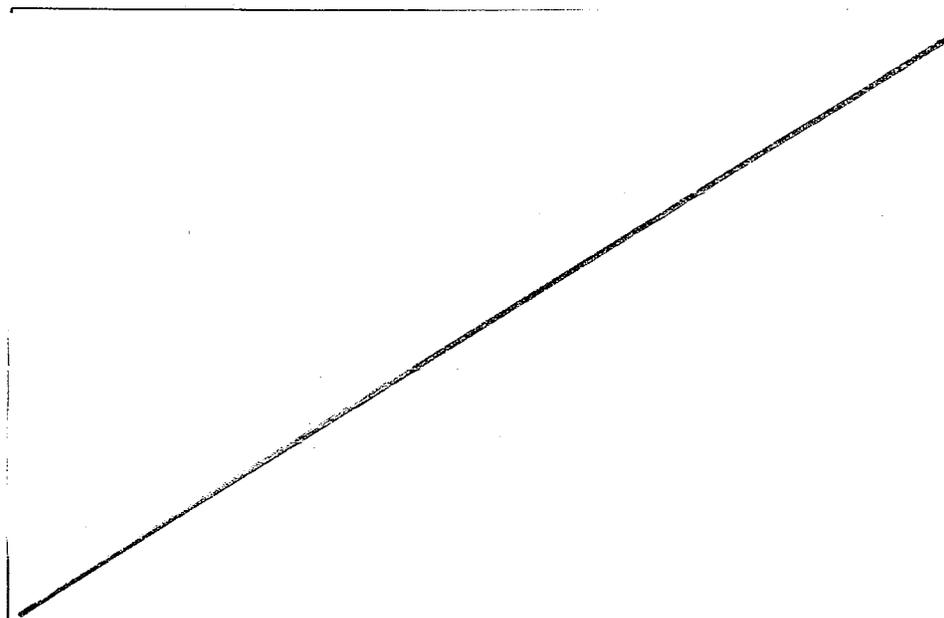
Renal group	Median (Range) CLcr (mL/min)	N	AUC/Dose (ng.h/mL/1.0 mg/m ²)	p-value	$C_{max}/Dose$ (ng/mL/1.0 mg/m ²)	p-value
Normal	99.6 (80.2-164.7)	15	26.2 \pm 14.1 (54%)	--	51.9 \pm 32.5 (62%)	--
Mild	64.7 (50.9-78.1)	19	24.2 \pm 10.8 (45%)	0.328	53.6 \pm 33.3 (62%)	0.445
Moderate	42.4 (40.2-43.8)	4	22.2 \pm 11.2 (50%)	0.308	72.2 \pm 45.1 (62%)	0.163
Severe	1.3	1	NA	--	52.15	--

NA=Not Available

No obvious relationship was observed between each of AUC/dose and $C_{max}/dose$ and CLcr ($p=0.717$ and 0.238 , respectively). Most patients enrolled in the study had CLcr values within the normal to the mild range of renal impairment (see Table 5).



b(4)



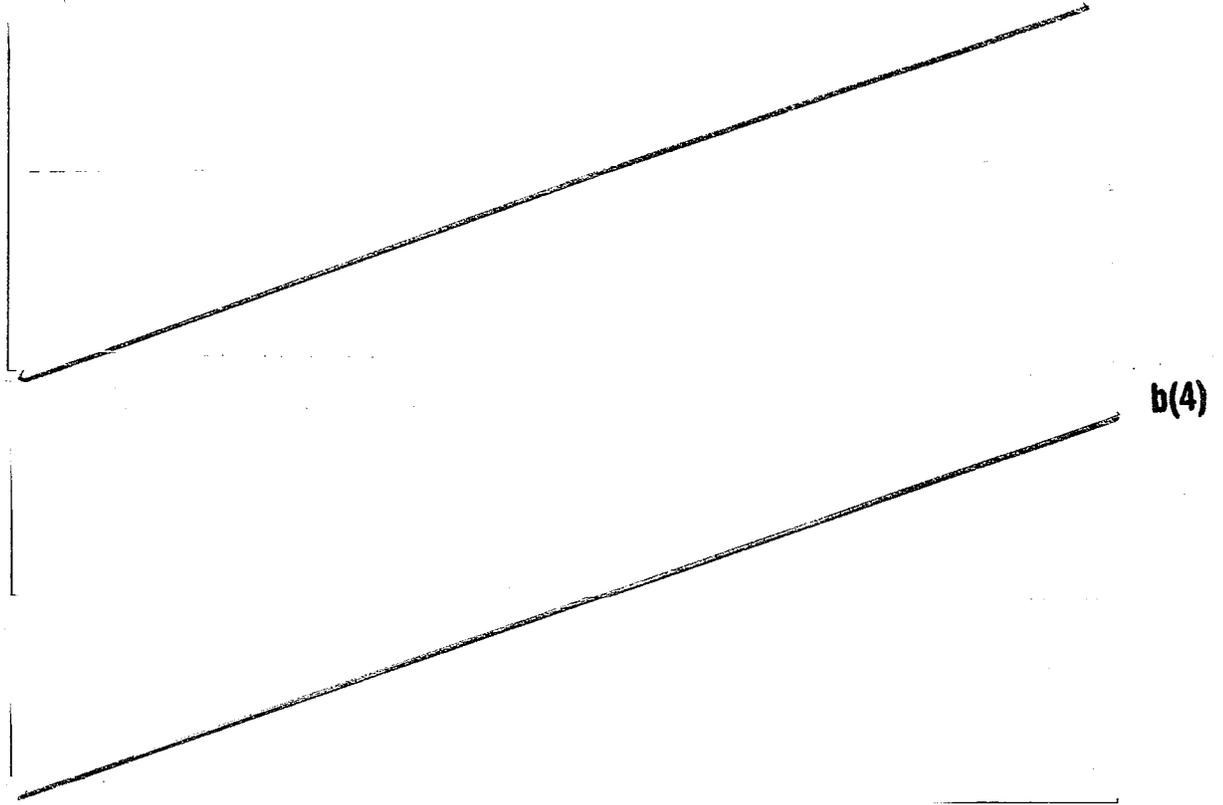
b(4)

Patients with severe renal impairment ($CL_{cr} < 30$ mL/min) were not studied. The results of this analysis will not be included in the labeling at the present time as the Applicant has submitted a formal PK study in patients with various degrees of renal impairment to fulfill the Phase 4 Commitment # 8; this study is under review.

2.3.2.6 Hepatic impairment

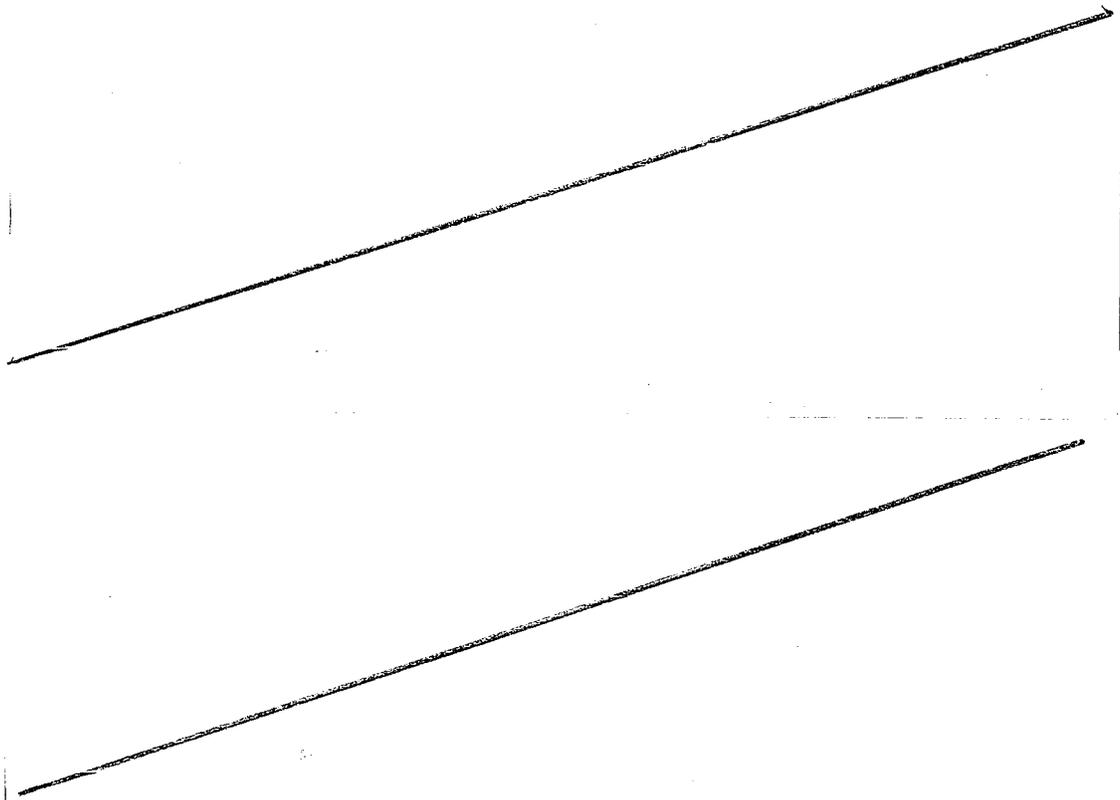
The liver enzymes measured in the study were alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin. The median (range) values for these enzymes were 18 (6-88) U/L, 23 (11-88) U/L, 63 (7-282) U/L, and 8 (4-15) mg/dL, respectively. The median value for these enzymes was within the normal range except for total bilirubin which was 8-fold higher than the upper limit of normal (ULN) (i.e., severe liver impairment). Linear regression analyses showed no obvious correlations between bortezomib AUC/Dose or C_{max} /Dose and each of ALT, AST, alkaline phosphatase, and total bilirubin levels ($p > 0.05$). These data are not sufficient to support any dosing recommendations for the use of VELCADE in patients with hepatic impairment. The Applicant has still to address the Phase 4 Commitment #7 of the approval letter of 12-May-2003 by conducting a formal PK study in patients with hepatic impairment.

Fig. 14



Normal Limits
ALT = 11-47 U/L
AST = 7-53 U/L
Alkaline Phosphatase = 20-130 U/L
Total Bilirubin = 0.1-1.0 mg/dL

Fig. 15.



b(4)

b(4)

Normal Limits

ALT = 11-47 U/L

AST = 7-53 U/L

Alkaline Phosphatase = 20-130 U/L

Total Bilirubin = 0.1-1.0 mg/dL

Please refer to the original NDA 21-602 (Submission Date: 21-Jan-2003) for the following issues (Questions 2.3.2.7 to 2.4.3):

- 2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?
- 2.3.2.8 What pregnancy and lactation use information is there in the application?

2.4 Extrinsic Factors

- 2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

2.4.2 Drug-drug interactions

- 2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?
- 2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?
- 2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?
- 2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?
- 2.4.2.5 Are there other metabolic/transporter pathways that may be important?
- 2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?
- 2.4.2.7 What other co-medications are likely to be administered to the target patient population?
- 2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?
- 2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?
- 2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

2.5 General Biopharmaceutics

[NOT APPLICABLE]

- 2.5.1 Based on the Biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?
- 2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?
- 2.5.3 What data support or do not support a waiver of in vivo BE data?
- 2.5.4 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?
- 2.5.5 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?
- 2.5.6 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?
- 2.5.7 When would a fed BE study be appropriate and was one conducted?
- 2.5.8 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?
- 2.5.9 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

2.5.10 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

2.5.11 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

2.5.12 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

2.5 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Bortezomib was the only active moiety measured in plasma samples.

2.6.2 Which metabolites have been selected for analysis and why?

No metabolites were measured in plasma samples.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total (unbound+bound) drug was measure in plasma samples.

2.6.4 What bioanalytical methods are used to assess concentrations?

Bortezomib concentrations in plasma samples were analyzed using a liquid chromatography/tandem mass spectrometry (LC/MS/MS) method. Plasma samples were deproteinized with acetonitrile and the supernatant was analyzed by turbo ion spray LC/MS/MS in the positive ion mode.

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

Standard curves were linear over the concentration range of 0.5-100 ng/ml

2.6.4.2 What is the lower limit of quantification (LLOQ)?

The LLOQ was 0.5 ng/ml.

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

The intra-assay and inter-assay precision ranged from 1.3-3.3% at all tested Quality Control (QC) Sample concentrations.

The intra-assay and inter-assay accuracy ranged from 2.5-7.2% at all QC concentration at the tested QC Sample concentrations.

3. Detailed Clinical Pharmacology Labeling Recommendations

The sponsor should incorporate the following labeling recommendations in their current package insert for VELCADE (revised based on the results obtained from Study M34103-058):

Clinical Pharmacology

Pharmacokinetics

Following twice weekly intravenous administration of 1.0 mg/m² and 1.3 mg/m² doses to 24 patients with multiple myeloma (n=12 per each dose level), the mean maximum plasma concentrations of bortezomib (C_{max}) after the first dose (Day 1) were 57 and 112 ng/mL, respectively. In subsequent doses, the mean maximum plasma concentrations ranged from 67 to 106 ng/mL for the 1.0 mg/m² dose and 89 to 120 ng/mL for the 1.3 mg/m² dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 30 to 193 hours after the 1.0 mg/m² dose and 11.5 to 108 hours after the 1.3 mg/m² dose. The mean total body clearance was 102 and 112 L/h following the first dose for doses of 1.0 mg/m² and 1.3 mg/m², respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1.0 and 1.3 mg/m², respectively.

Distribution

The mean distribution volume of bortezomib ranged from 285 to 1783 L/m² following single- or repeat-dose administration of 1.0mg/m² or 1.3mg/m² to patients with multiple myeloma. This suggests bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100 to 1000 ng/mL.

Metabolism

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

Elimination

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

Special Populations

Age: Analyses of data after the first dose of Cycle 1 (Day 1) in 39 multiple myeloma patients who had received intravenous doses of 1.0 mg/m² and 1.3 mg/m² showed that both dose-normalized AUC and C_{max} tend to increase as age increased. Patients of ≥ 65 years of age (n=13) had 33-35% higher mean dose-normalized AUC and C_{max} than those less than 65 years of age (n=26) (see PRECAUTIONS).

Gender: Mean dose-normalized AUC and C_{max} values were comparable between male (n=22) and female (n=17) patients after the first dose of Cycle 1 for the 1.0 and 1.3 mg/m² doses.

Race: The effect of race on exposure of bortezomib could not be assessed as most of the patients were Caucasians.

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

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

Pediatric: There are no pharmacokinetic data in pediatric patients.

Drug Interactions

No formal drug interaction studies have been conducted with bortezomib.

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

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

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

Pharmacodynamics

Following twice weekly administration of 1.0 mg/m² and 1.3 mg/m² bortezomib doses (n=12 per each dose level), the maximum inhibition of 20S proteasome activity (relative to baseline) in whole blood was observed 5 minutes after drug administration.

Comparable mean observed maximum percent inhibition of 20S proteasome activity was observed between the 1.0 mg/m² and 1.3 mg/m² doses; the mean maximum inhibition ranged from 70% to 84% and from 73% to 83% for the 1.0 mg/m² and 1.3 mg/m² dose regimens, respectively. The incidence of major adverse events such as diarrhea, nausea, vomiting, pyrexia, and thrombocytopenia was 2- to 5-fold higher in the 1.3 mg/m² dose group than that in the 1.0 mg/m² dose group.

Precautions

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

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

Geriatric Use

Exposure of Bortezomib tends to be higher in patients of ≥ 65 years of age than younger patients (see **CLINICAL PHARMACOLOGY/ Pharmacokinetics-Special Populations**). Of the 669 patients enrolled in the phase 3 multiple myeloma study, 245 (37%) were 65 years of age or older: 125 (38%) on the VELCADE arm and 120 (36%) on dexamethasone arm. Median time to progression and median duration of response for patients ≥ 65 were longer on VELCADE compared to dexamethasone [5.5 mo versus 4.3 mo, and 8.0 mo versus 4.9 mo, respectively]. On the VELCADE arm, 40% (n=46) of evaluable patients aged ≥ 65 experienced response (CR+PR) versus 18% (n=21) on the dexamethasone arm. The incidence of Grade 3 and 4 events was 64%, 78% and 75% for VELCADE patients ≤ 50 , 51-64 and ≥ 65 years old, respectively (see **CLINICAL STUDIES**).

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

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

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

I. General Information About the Submission				
		Information		Information
NDA Number	21-602	Brand Name	Velcade	
OCP Division (1-5)	DPE 5	Generic Name	Bortezomib	
Medical Division	HFD-150	Drug Class	Dipeptidyl boronic acid	
OCP Reviewer	Sophia Abraham, Ph.D.	Indication(s)	Mantle Cell Lymphoma	
OCP Team Leader	Brian Booth, Ph.D.	Dosage Form	3.5 mg single-dose vials	
		Dosing Regimen	1.3 mg/m ² twice weekly	
Date of Submission	09-Jun-2006	Route of Administration	intravenously	
Estimated Due Date of OCPB Review	01-Sep-2006	Sponsor	Millennium Pharmaceuticals	
PDUFA Due Date	09-Dec-2006	Priority Classification	P	
Division Due Date	01-Nov-2006			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies				
-				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X			
Comments sent to firm ?				
QBR questions (key issues to be considered)				

Other comments or information not included above	
Primary reviewer Signature and Date	Sophia Abraham
Secondary reviewer Signature and Date	

CC: NDA 21-602, DCP5 (Electronic Entry), DDOP (Brent-Steele), DCP 5 (Rahman, Booth, Abraham), CDR (Biopharm)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sophia Abraham
11/21/2006 11:48:08 AM
BIOPHARMACEUTICS

Brian Booth
12/6/2006 05:37:07 PM
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-602 / S-010

OTHER REVIEW(S)

17/480-485	Adverse events thought by the investigator to be drug-related and leading to discontinuation.... In total, 2% of the patients died and the cause of death was considered by the investigator to be possibly related to study drug....	Are these claims supported by substantial evidence? These can be used as basis for safety advertisements.
17/488-490	In the absence of a randomized comparator arm, it is often not possible to distinguish between adverse events that are drug-caused and those that reflect the patient's underlying disease.	Are these claims supported by substantial evidence? These can be used as basis for safety advertisements.
19/500-501	Grade 3 GI events occurred in 18% of patients; Grade 4 events were rare (1%)	The inclusion of this statement does not seem consistent with other PIs. It could be used promotionally to suggest improved safety with Velcade.
20/566-568	In the postmarketing experience, rare cases of herpes meningoencephalitis and ophthalmic herpes have been reported.	The inclusion of this statement does not seem consistent with other PIs. It could be used promotionally to suggest improved safety with Velcade.
22/627	<hr/>	This phrase was included in the previously FDA approved PI and has been removed. Does the Division agree with its removal?

b(4)

Additional Comments

In the proposed revised labeling, the claim “..the safety profile of VELCADE was similar in patients with multiple myeloma and mantle cell lymphoma.” (page 17/lines 461-62) is made. However, a section entitled, “**Description of Selected Adverse Events from the Phase 2 and 3 Multiple Myeloma and Phase 2 Mantle Cell Lymphoma Studies,**” is also included in the label which summarizes and compares the adverse events observed between MM patients and MCL patients. These claims seem to counterbalance each other. DDMAC suggests inclusion of only one of these claims in the proposed labeling to help eliminate possible confusion.

REGULATORY PROJECT MANAGER REVIEW OF LABELING

NDA 21-602/S-010

Drug: Velcade (bortezomib) for Injection 3.5 mg

Applicant: Millennium Pharmaceuticals, Inc.

Submission Date(s): June 8, 2006

Receipt Date(s): June 9, 2006

Submission	Date Submitted	Date Received
SE1 010	6/8/06	6/9/06
SLR 009 FA	7/10/06	7/11/06

BACKGROUND:

The SLR 009 was approved on May 31, 2006 with draft labeling attached. The Final Printed Labeling (FPL) was submitted on July 10, 2006. SE1 010 was submitted on June 8, 2006 as a Supplemental New Drug Application for a New Indication. The new indication is for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy. The sponsor requested regular approval and a priority review. The filing meeting occurred on Wednesday, August 2, 2006. The sNDA includes draft labeling.

DOCUMENTS REVIEWED:

The latest approved draft labeling attached to the May 31, 2006 approval letter was compared to the final printed labeling submitted on July 10, 2006. There were no new changes in the FPL. The final printed labeling was then compared to the draft labeling submitted June 8, 2006 with SE1 010.

REVIEW: The changes in the S010 draft labeling are listed below and include those areas needing additional review.

CLINICAL PHARMACOLOGY

Pharmacokinetics

From:

b(4)

b(4)

To:

Distribution:

b(4)

CLINICAL STUDIES

Addition:

A Phase 2 Single-arm Clinical Study in Relapsed Mantle Cell Lymphoma

The safety and efficacy of VELCADE in relapsed or refractory mantle cell lymphoma were evaluated in an open-label, single-arm, multicenter study of 155 patients with progressive disease who had received at least 1 prior therapy. _____

b(4)

An IV bolus injection of VELCADE 1.3 mg/m²/dose was administered twice weekly for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21) for a maximum of 17 treatment cycles. The study employed dose modifications for toxicity (see **DOSAGE AND ADMINISTRATION**).

[Redacted content]

b(4)

Responses to VELCADE are shown in Table [Redacted content]

[Redacted content]

[Redacted]

b(4)

[Redacted]

b(4)

INDICATIONS AND USAGE

From:

[Redacted]

b(4)

To:

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

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

PRECAUTIONS:

Peripheral Neuropathy:

Addition:

The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

Hypotension:

From:

[Redacted]

b(4)

To:

The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 13%.

Cardiac Disorders:

From:

b(4)

To:

In the phase 3 multiple myeloma study, the incidence of any treatment-emergent cardiac disorder was 15% and 13% in the VELCADE and dexamethasone groups, respectively.

Laboratory Test:

From:

b(4)

To:

Complete blood counts (CBC) should be frequently monitored during treatment with VELCADE.

Thrombocytopenia/Neutropenia:

Addition:

b(4)

Geriatric Use:

From:

b(4)

To:

Of the 669 patients enrolled in the phase 3 multiple myeloma study, 245 (37%) were 65 years of age or older: 125 (38%) on the VELCADE arm and 120 (36%) on dexamethasone arm.

From:

b(4)

To:

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

ADVERSE REACTIONS:

From:

b(4)

To:

Randomized Open-Label Phase 3 Multiple Myeloma Study

From:

b(4)

To:

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

From:

b(4)

To:

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

The most common adverse events from the phase 3 multiple myeloma study are shown in Table ✓

b(4)

From:

Table ✓. Most Commonly Reported Adverse Events ($\geq 10\%$ in VELCADE arm), with Grades 3 and 4 Intensity in the Phase 3 Randomized Study (N=663)

b(4)

To:

Table 8: Most Commonly Reported Adverse Events ($\geq 10\%$ in VELCADE arm), with Grades 3 and 4 Intensity in the Phase 3 Multiple Myeloma Study (N=663)

Addition:

The Phase 2 Open-Label Extension Study in Relapsed Multiple Myeloma

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

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

Safety data from phase 2 and 3 studies of VELCADE 1.3 mg/m²/dose twice weekly for 2 weeks followed by a 10-day rest period in 1163 patients with multiple myeloma (N=1008) and mantle cell lymphoma (N=155) were integrated and tabulated. In these studies, the safety profile of VELCADE was similar in patients with multiple myeloma and mantle cell lymphoma.

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

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

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

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

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

Most Commonly Reported Adverse Events in the Integrated Summary of Safety

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

b(4)

Addition:

**Table / Most Commonly Reported (≥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	≥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 ^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

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

Addition:

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

Gastrointestinal Events

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

Thrombocytopenia

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

Peripheral Neuropathy

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

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

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

Hypotension

The incidence of hypotension (postural hypotension, orthostatic hypotension and hypotension NOS) was 13%. Hypotension was Grade 1 or 2 in the majority of patients and Grade 3 in 3% and \geq Grade 4 in <1%. Three percent (3%) of patients had hypotension reported as an SAE, and 1% discontinued due to hypotension. The

incidence of hypotension was similar in patients with multiple myeloma (12%) and those with mantle cell lymphoma (15%). In addition, 2% of patients experienced hypotension and had a syncopal event. Doses of antihypertensive medications may need to be adjusted in patients receiving VELCADE (see PRECAUTIONS).

Neutropenia

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

Asthenic conditions (Fatigue, Malaise, Weakness)

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

Pyrexia

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

Reactivation of Herpes Virus Infection

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

Eye Disorders:

From:

b(4)

To:

Diplopia and blurred vision, conjunctival infection, irritation

Skin and Subcutaneous tissue disorders:

From:

b(4)

To:

Urticaria, face edema, rash (which may be pruritic), leukocytoclastic vasculitis

OVERDOSAGE:

From:

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

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

To:

In humans, fatal outcomes following the administration of more than twice the recommended therapeutic dose have been reported, which were associated with the acute onset of symptomatic hypotension and thrombocytopenia.

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

Dose Modification and Re-initiation of Therapy:

From:

b(4)

To:

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

b(4)

PATIENT INFORMATION

Addition:

Herpes zoster (Shingles):

Contact your doctor if you develop a rash.

Heart Failure and Lung Failure:

From:

To:

Heart Failure and Lung Disease:

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

CONCLUSION - RECOMMENDED REGULATORY ACTION:

With the concurrence of the noted reviewers, this supplement should be approved and FPL requested. The FA for S009 should be acknowledged and retained.

Tammie Brent, RN MSN

Concurrence:

**Dorothy Pease
Chief, Project Management Staff**

b(4)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Tammie Brent-Steele
11/2/2006 04:22:41 PM
CSO

Dotti Pease
11/3/2006 07:41:35 AM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-602 Supplement # 010 Efficacy Supplement Type SE- 1

Proprietary Name: Velcade
Established Name: Bortezomib
Strengths: 3.5mg

Applicant: Millennium Pharmaceuticals, Inc.
Agent for Applicant (if applicable): None

Date of Application: June 8, 2006
Date of Receipt: June 9, 2006
Date clock started after UN:
Date of Filing Meeting: August 2, 2006
Filing Date: August 8, 2006
Action Goal Date (optional): User Fee Goal Date: December 9, 2006

Indication(s) requested: Treatment of Patients with mantle cell lymphoma who have received at least one prior therapy

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain: Exclusivity expires 5/13/10

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES

This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fml.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

- 3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, X 3 Years
NO

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO X

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 56,515

- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) September 14, 2004 NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) January 17, 2006 NO

If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request: Submitted prior to 6/30/06

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES NO

- Risk Management Plan consulted to OSE/IO? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 2, 2006

NDA #: 21-602/010

DRUG NAMES: Velcade (bortezomib)

APPLICANT: Millennium Pharmaceuticals, Inc.

BACKGROUND:

Original Velcade NDA was approved on May 13, 2003. This sNDA is for a new indication, Mantle Cell Lymphoma in patients who have received at least 1 prior therapy.

ATTENDEES:

Robert Justice, MD, Division Director
Ann Farrell, MD, Acting Division Deputy Director
Ramzi Dagher, MD, Medical Team Leader
Robert Kane, MD, Medical Officer
Rajeshwari Sridhara, PhD., Team Leader Math Statistician
Chia-wen Ko, PhD., Math Statistician
Sophia Abraham, PhD., Clinical Pharmacology Reviewer
Richard Pazdur, MD., Office Director, OODP
Dorothy Pease, Chief Project Manager
Rafel Reives, MD, Medical Team Leader
Somesh Chattopadhyay, PhD., Math Statistician

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization

Medical Reviewer:
Medical Imaging Medical Reviewer:
Statistical:
Pharmacology:
Statistical Pharmacology:
Chemistry:
Environmental Assessment (if needed):
Clinical Pharmacology:
Microbiology, sterility:
Microbiology, clinical (for antimicrobial products only):
DSI:
OPS:
Regulatory Project Management:
Other Consults:

Reviewer

Robert Kane, MD
Scheldon Kress, MD
Chia-wen Ko, PhD.
Leigh Verbois, Ph.D.

Liang Zhou, PhD.

Sophia Abraham, PhD.

Lloyd Johnson

Tammie Brent-Steele, RN, MSN
DDMAC, DSRCS, OSE

Per reviewers, are all parts in English or English translation?
If no, explain:

YES NO

CLINICAL

FILE

REFUSE TO FILE

- Clinical site audit(s) needed? YES NO
If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY

N/A

FILE

REFUSE TO FILE

STATISTICS

N/A

FILE

REFUSE TO FILE

CLINICAL PHARMACOLOGY

FILE

REFUSE TO FILE

- Biopharm. study site audits(s) needed? NO

PHARMACOLOGY/TOX

N/A

FILE

REFUSE TO FILE

- GLP audit needed? YES NO

CHEMISTRY

FILE

REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Sterile product? YES NO
- If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

- 1. Ensure that the review and chemical classification codes, as well as any other pertinent

classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
3. Convey document filing issues/no filing issues to applicant by Day 74.
4. Timing of team meetings. Mid to end September, and then monthly. No Mid-Cycle meeting.
5. Target date for completed reviews. 11/1/06
6. Target date for first labeling review. 11/1/06
7. Consults: Patient consultant, Alexandra Levine, Alma Rodriguez, Maha Hussein-Chair, no consultant for medical imaging.

Tammie Brent-Steele RN, MSN
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and,
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES NO

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.
- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO
- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(*Pharmaceutical alternatives* are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If "Yes," to (c), proceed to question 7.

NOTE: If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is YES NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? YES NO
(This is different from the patent declaration submitted on form FDA 3542 and 3542a.)

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

Not applicable (e.g., solely based on published literature. See question # 7)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-602 Supplement # 010 Efficacy Supplement Type SE- 1

Proprietary Name: Velcade
Established Name: Bortezomib
Strengths: 3.5mg

Applicant: Millennium Pharmaceuticals, Inc.
Agent for Applicant (if applicable): None

Date of Application: June 8, 2006
Date of Receipt: June 9, 2006
Date clock started after UN:
Date of Filing Meeting: August 2, 2006
Filing Date: August 8, 2006
Action Goal Date (optional): User Fee Goal Date: December 9, 2006

Indication(s) requested: Treatment of Patients with mantle cell lymphoma who have received at least one prior therapy

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain: Exclusivity expires 5/13/10

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, X 3 Years
NO

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO X

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 56,515

- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) September 14, 2004 NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) January 17, 2006 NO

If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request: Submitted prior to 6/30/06
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 2, 2006

NDA #: 21-602/010

DRUG NAMES: Velcade (bortezomib)

APPLICANT: Millennium Pharmaceuticals, Inc.

BACKGROUND:

Original Velcade NDA was approved on May 13, 2003. This sNDA is for a new indication, Mantle Cell Lymphoma in patients who have received at least 1 prior therapy.

ATTENDEES:

Robert Justice, MD, Division Director
Ann Farrell, MD, Acting Division Deputy Director
Ramzi Dagher, MD, Medical Team Leader
Robert Kane, MD, Medical Officer
Rajeshwari Sridhara, PhD., Team Leader Math Statistician
Chia-wen Ko, PhD., Math Statistician
Sophia Abraham, PhD., Clinical Pharmacology Reviewer
Richard Pazdur, MD., Office Director, OODP
Dorothy Pease, Chief Project Manager
Rafel Reives, MD, Medical Team Leader
Somesh Chattopadhyay, PhD., Math Statistician

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization

Medical Reviewer:
Medical Imaging Medical Reviewer:
Statistical:
Pharmacology:
Statistical Pharmacology:
Chemistry:
Environmental Assessment (if needed):
Clinical Pharmacology:
Microbiology, sterility:
Microbiology, clinical (for antimicrobial products only):
DSI:
OPS:
Regulatory Project Management:
Other Consults:

Reviewer

Robert Kane, MD
Scheldon Kress, MD
Chia-wen Ko, PhD.
Leigh Verbois, Ph.D.

Liang Zhou, PhD.

Sophia Abraham, PhD.

Lloyd Johnson

Tammie Brent-Steele, RN, MSN
DDMAC, DSRCS, OSE

OSE/DDRE - Jennifer Steele

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

• Clinical site audit(s) needed? YES NO
If no, explain:

• Advisory Committee Meeting needed? YES, date if known _____ NO

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

CLINICAL PHARMACOLOGY FILE REFUSE TO FILE

• Biopharm. study site audits(s) needed? NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

• GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

• Establishment(s) ready for inspection? YES NO

• Sterile product? YES NO

If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

The application is unsuitable for filing. Explain why:

The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

No filing issues have been identified.

Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent

classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
3. Convey document filing issues/no filing issues to applicant by Day 74.
4. Timing of team meetings. Mid to end September, and then monthly. No Mid-Cycle meeting.
5. Target date for completed reviews. 11/1/06
6. Target date for first labeling review. 11/1/06
7. Consults: Patient consultant, Alexandra Levine, Alma Rodriguez, Maha Hussein-Chair, no consultant for medical imaging.

Tammie Brent-Steele RN, MSN
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and,
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)
- YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?
- YES NO

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.
- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?
- YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO
- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(*Pharmaceutical alternatives* are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If "Yes," to (c), proceed to question 7.

NOTE: If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is YES NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Tammie Brent-Steele
8/8/2006 02:45:59 PM
CSO

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-602 / S-010

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

021602

NAME OF APPLICANT / NDA HOLDER

Millennium Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

VELCADE for Injection

ACTIVE INGREDIENT(S)

bortezomib

STRENGTH(S)

3.5 mg/vial

DOSAGE FORM

Injectable, intravenous

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

5,780,454

b. Issue Date of Patent

7/14/1998

c. Expiration Date of Patent

10/28/2014

d. Name of Patent Owner

Millennium Pharmaceuticals, Inc.

Address (of Patent Owner)

40 Landsdowne St.

City/State

Cambridge, MA

ZIP Code

02139

FAX Number (if available)

Telephone Number

(617) 679-7000

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Signature of Scott A. Brown

4/28/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Scott A. Brown

Address

40 Landsdowne St.

City/State

Cambridge, MA

ZIP Code

02139

Telephone Number

(617) 551-8662

FAX Number (if available)

(617) 551-8820

E-Mail Address (if available)

scott.brown@mpi.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

021602

NAME OF APPLICANT / NDA HOLDER

Millennium Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

VELCADE for Injection

ACTIVE INGREDIENT(S)

bortezomib

STRENGTH(S)

3.5 mg/vial

DOSAGE FORM

Injectable, intravenous

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

II. GENERAL

a. United States Patent Number 6,083,903	b. Issue Date of Patent 7/4/2000	c. Expiration Date of Patent 10/28/2014
---	-------------------------------------	--

d. Name of Patent Owner Millennium Pharmaceuticals, Inc.	Address (of Patent Owner) 40 Landsdowne St.	
	City/State Cambridge, MA	
	ZIP Code 02139	FAX Number (if available)
	Telephone Number (617) 679-7000	E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)

Date Signed

Scott A. Brown

4/28/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Scott A. Brown

Address

40 Landsdowne St.

City/State

Cambridge, MA

ZIP Code

02139

Telephone Number

(617) 551-8662

FAX Number (if available)

(617) 551-8820

E-Mail Address (if available)

scott.brown@mpi.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

021602

NAME OF APPLICANT / NDA HOLDER

Millennium Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

VELCADE for Injection

ACTIVE INGREDIENT(S)

bortezomib

STRENGTH(S)

3.5 mg/vial

DOSAGE FORM

Injectable, intravenous

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

6,297,217

b. Issue Date of Patent

10/2/2001

c. Expiration Date of Patent

10/28/2014

d. Name of Patent Owner

Millennium Pharmaceuticals, Inc.

Address (of Patent Owner)

40 Landsdowne St.

City/State

Cambridge, MA

ZIP Code

02139

FAX Number (if available)

Telephone Number

(617) 679-7000

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) 1-13, 16-19 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)
Treatment of mantle cell lymphoma patients who have received at least one prior therapy.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6 Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Scott A. Brown

4/28/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Scott A. Brown

Address

40 Landsdowne St.

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Cambridge, MA

ZIP Code

02139

Telephone Number

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FAX Number (if available)

(617) 551-8820

E-Mail Address (if available)

scott.brown@mpi.com

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Rockville, MD 20857

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**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

021602

NAME OF APPLICANT / NDA HOLDER

Millennium Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

VELCADE for Injection

ACTIVE INGREDIENT(S)

bortezomib

STRENGTH(S)

3.5 mg/vial

DOSAGE FORM

Injectable, intravenous

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

GENERAL

a. United States Patent Number

6,617,317

b. Issue Date of Patent

9/9/2003

c. Expiration Date of Patent

10/28/2014

d. Name of Patent Owner

Millennium Pharmaceuticals, Inc.

Address (of Patent Owner)

40 Landsdowne St.

City/State

Cambridge, MA

ZIP Code

02139

FAX Number (if available)

Telephone Number

(617) 679-7000

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

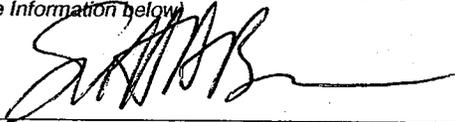
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



4/28/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Scott A. Brown

Address
40 Landsdowne St.

City/State
Cambridge, MA

ZIP Code
02139

Telephone Number
(617) 551-8662

FAX Number (if available)
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**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

021602

NAME OF APPLICANT / NDA HOLDER

Millennium Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

VELCADE for Injection

ACTIVE INGREDIENT(S)

bortezomib

STRENGTH(S)

3.5 mg/vial

DOSAGE FORM

Injectable, intravenous

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

I. GENERAL

a. United States Patent Number 6,713,446	b. Issue Date of Patent 3/30/2004	c. Expiration Date of Patent 1/25/2022
---	--------------------------------------	---

d. Name of Patent Owner Government of the United States of America, Represented by the Secretary, Department of Health and Human Services	Address (of Patent Owner) National Institutes of Health, Office of Technology Transfer, 6011 Executive Blvd., Suite 325	
	City/State Rockville, MD	
	ZIP Code 20852-3804	FAX Number (if available)
	Telephone Number (301) 435-5236	E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Signature of Scott A. Brown

4/28/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Scott A. Brown

Address

40 Landsdowne St.

City/State

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FAX Number (if available)

(617) 551-8820

E-Mail Address (if available)

scott.brown@mpi.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

021602

NAME OF APPLICANT / NDA HOLDER

Millennium Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

VELCADE for Injection

ACTIVE INGREDIENT(S)

bortezomib

STRENGTH(S)

3.5 mg/vial

DOSAGE FORM

Injectable, intravenous

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
6,747,150 B2

b. Issue Date of Patent
6/8/2004

c. Expiration Date of Patent
10/28/2014

d. Name of Patent Owner

Millennium Pharmaceuticals, Inc.

Address (of Patent Owner)
40 Landsdowne St.

City/State
Cambridge, MA

ZIP Code
02139

FAX Number (if available)

Telephone Number
(617) 679-7000

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6 Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below) Date Signed
 4/28/02

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Scott A. Brown	
Address 40 Landsdowne St.	City/State Cambridge, MA
ZIP Code 02139	Telephone Number (617) 551-8662
FAX Number (if available) (617) 551-8820	E-Mail Address (if available) scott.brown@mpi.com

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**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER
021602
NAME OF APPLICANT / NDA HOLDER
Millennium Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
VELCADE® for Injection

ACTIVE INGREDIENT(S)
Bortezomib

STRENGTH(S)
3.5 mg/vial

DOSAGE FORM
Injectable, intravenous

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL		
a. United States Patent Number 6,958,319 B2	b. Issue Date of Patent 10/25/2005	c. Expiration Date of Patent 1/25/2022
d. Name of Patent Owner Government of the United States of America, Represented by the Secretary, Department of Health and Human Services	Address (of Patent Owner) National Institutes of Health, Office of Technology Transfer, 6011 Executive Blvd., Suite 325	
	City/State Rockville, MD	
	ZIP Code 20852	FAX Number (if available)
	Telephone Number (301) 435-5236	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6 Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)	Date Signed
	4/28/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Scott A. Brown	
Address Millennium Pharmaceuticals, Inc. 40 Landsdowne St.	City/State Cambridge, Massachusetts
ZIP Code 02139	Telephone Number (617) 551-8662
FAX Number (if available) (617) 551-8820	E-Mail Address (if available) scott.brown@mpi.com

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EXCLUSIVITY SUMMARY

NDA # 21-602

SUPPL # 010

HFD # 150

Trade Name VELCADE

Generic Name Bortezomib

Applicant Name Millennium Pharmaceuticals, Inc.

Approval Date, If Known 12-8-06

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

New indication to treat Mantle Cell Lymphoma

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-602

Velcade (bortezomib) for injection (IV)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

M34103-53, A Phase 2 Study of Velcade in Patients with Relapsed or Refractory Mantle Cell Lymphoma

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

M34103-53, A Phase 2 Study of Velcade in Patients with Relapsed or Refractory Mantle Cell Lymphoma

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 56,515	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

Investigation #2		!
		!
IND #	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
! YES NO
Explain: ! Explain:

Investigation #2 !
! YES NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Tammie Brent
Title: Regulatory Project Manager
Date: 12/8/06

Name of Office/Division Director signing form: Robert Justice, MD
Title: Division Director, Division of Drug Oncology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ramzi Dagher
12/11/2006 08:17:23 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-602 Supplement Type (e.g. SE5): SE1 Supplement Number: 010

Stamp Date: June 9, 2006 Action Date: December 9, 2006

HFD 150 Trade and generic names/dosage form: Velcade (bortezomib) for Injection 3.5mg

Applicant: Millennium Pharmaceuticals, Inc. Therapeutic Class:

Indication(s) previously approved: Multiple Myeloma- Orphan (no peds page)

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Mantle Cell Lymphoma

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study

- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Tammie Brent, RN, MSN
Regulatory Project Manager

cc: NDA 21-602
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

NDA 21-602

Page 3

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-602
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Tammie Brent-Steele
12/12/2006 12:44:03 PM

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

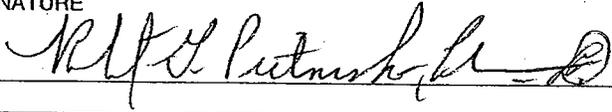
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	Please refer to Appendix A for a list of investigators with no financial agreements with the sponsor.	
	Please refer to Appendix B for a list of investigators from which ownership of equity interest has not been obtained.	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Robert G. Pietrusko, Pharm.D.	TITLE Senior Vice President, Worldwide Regulatory Affairs
FIRM / ORGANIZATION Millennium Pharmaceuticals, Inc.	
SIGNATURE 	DATE 15 May 2006

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

10 Page(s) Withheld

√ Trade Secret / Confidential (b4)

 Draft Labeling (b6)

 Draft Labeling (b5)

 Deliberative Process (b5)

**FORM FDA 3454; CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

Appendix B to Form FDA 3454

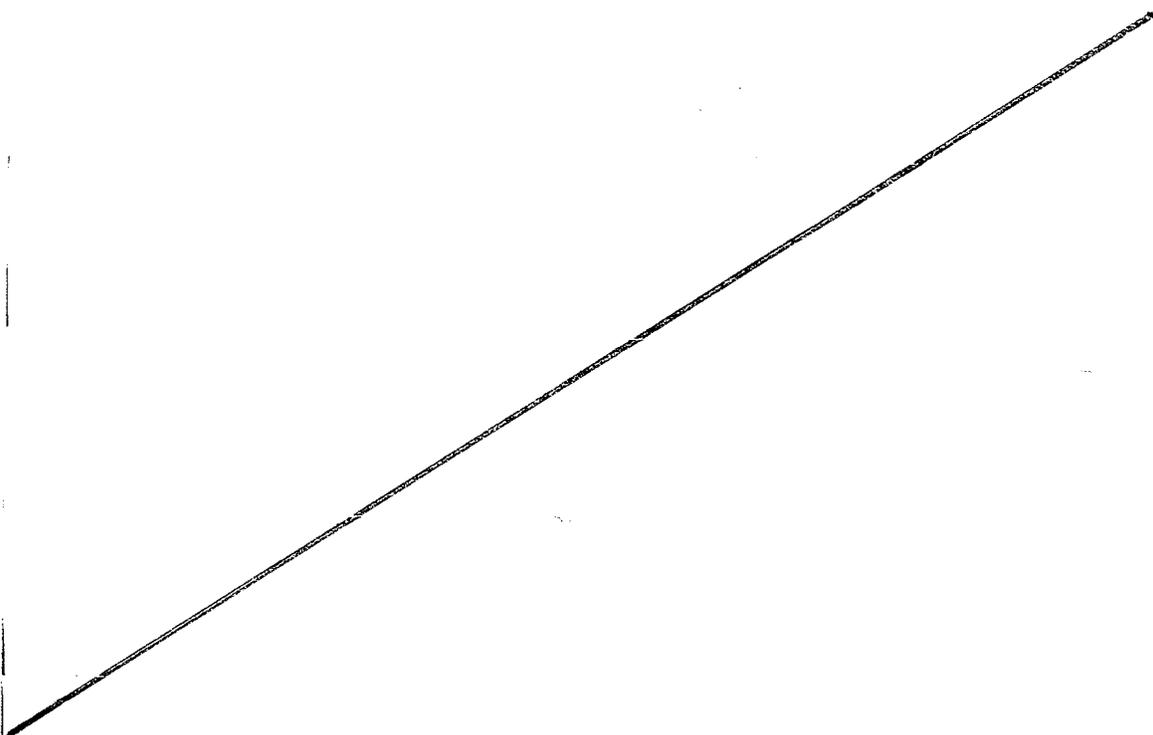
Financial Disclosure information regarding the ownership of an equity interest (greater than \$50,000 in value) in Millennium Pharmaceuticals, Inc. has not been obtained from the following investigators.

Although, financial disclosure forms are either missing or incomplete for these investigators, none of the following investigators:

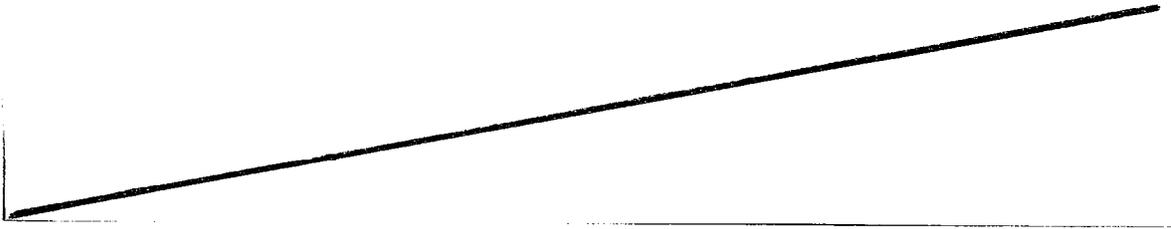
- Has entered into a financial arrangement with Millennium Pharmaceuticals, Inc. whereby the value of any compensation to the investigator could be influenced by the outcome of the study.
- Has received a Significant Payment of Other Sorts (SPOOS) in excess of \$25,000.

Despite due diligence, information for these investigators has not been received. Additional requests were issued to the sites in an effort to retrieve this information.

Millennium Pharmaceuticals, Inc. will continue to collect this information.



b(4)



b(4)

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Name of clinical investigator

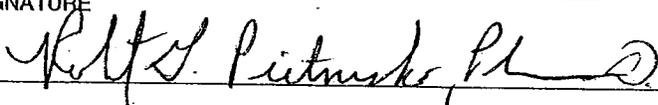
Name of clinical study

b(6)

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Robert G. Pietrusko, Pharm.D.	TITLE Senior Vice President, Worldwide Regulatory Affairs
FIRM / ORGANIZATION Millennium Pharmaceuticals, Inc.	
SIGNATURE 	DATE 15 May 2006

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

**FORM FDA 3455; DISCLOSURE: FINANCIAL INTEREST AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

Appendix A to Form FDA 3455

b(6)

Investigator for Clinical Trial: _____

_____, has disclosed an equity interest in Millennium Pharmaceuticals, Inc. The interest has been reported as compensation in the form of _____ greater than \$25,000 cumulatively.

b(6)

According to Millennium Pharmaceuticals, Inc. financial records for the reporting period, there have been no payments paid to this investigator during the conduct of the covered clinical study.

Throughout the course of the above noted clinical trial, representatives of Millennium Pharmaceuticals, Inc. performed 100% verification of all study data collected from patients enrolled at this study center.

As a result of thorough and routine site and data monitoring, Millennium Pharmaceuticals, Inc. considered the potential for bias to be minimal.

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Name of clinical investigator

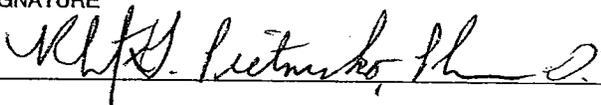
Name of clinical study

b(6)

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Robert G. Pietrusko, Pharm.D.	TITLE Senior Vice President, Worldwide Regulatory Affairs
FIRM / ORGANIZATION Millennium Pharmaceuticals, Inc.	
SIGNATURE 	DATE 15 May 2006

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Rockville, MD 20857

**FORM FDA 3455; DISCLOSURE: FINANCIAL INTEREST AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

Appendix A to Form FDA 3455

b(6)

_____ designated by _____
has disclosed an equity interest in Millennium Pharmaceuticals, Inc. The interest has been
reported as _____
_____ greater than \$25,000 cumulatively.

According to Millennium Pharmaceuticals, Inc. financial records for the reporting period,
there have been no payments paid to this investigator during the conduct of the covered
clinical study.

Throughout the course of the above mentioned clinical trial, representatives of
Millennium Pharmaceuticals, Inc. performed 100% verification of all study data collected
from patients enrolled at this study center.

As a result of thorough and routine site and data monitoring, Millennium
Pharmaceuticals, Inc. considered the potential for bias to be minimal.

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Name of clinical investigator

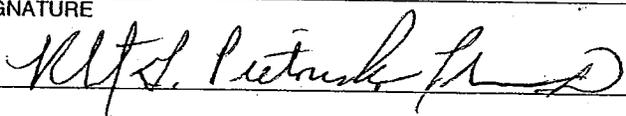
Name of clinical study

b(6)

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Robert G. Pietrusko, Pharm.D.	TITLE Senior Vice President, Worldwide Regulatory Affairs
FIRM / ORGANIZATION Millennium Pharmaceuticals, Inc.	
SIGNATURE 	DATE 15 May 2006

Paperwork Reduction Act Statement

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**FORM FDA 3455; DISCLOSURE: FINANCIAL INTEREST AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

Appendix A to Form FDA 3455

_____, designated by _____
_____, has disclosed an equity interest in Millennium
Pharmaceuticals, Inc. The interest has been reported as _____

b(6)

According to Millennium Pharmaceuticals, Inc. financial records for the reporting period, only \$1,500.00 was paid to this investigator during the conduct of the covered clinical study and therefore, will not be required to be reported per the applicable CFR regulations.

Throughout the course of the above mentioned clinical trial, representatives of Millennium Pharmaceuticals, Inc. performed 100% verification of all study data collected from patients enrolled at this study center.

As a result of thorough and routine site and data monitoring, Millennium Pharmaceuticals, Inc. considered the potential for bias to be minimal.

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Name of clinical investigator

Name of clinical study

b(6)

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Robert G. Pietrusko, Pharm.D.	TITLE Senior Vice President, Worldwide Regulatory Affairs
FIRM / ORGANIZATION Millennium Pharmaceuticals, Inc.	
SIGNATURE 	DATE 15 May 2006

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Rockville, MD 20857

**FORM FDA 3455; DISCLOSURE: FINANCIAL INTEREST AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

Appendix A to Form FDA 3455

_____, designated by _____

_____ has disclosed an equity interest in Millennium Pharmaceuticals, Inc. The interest has been reported as a financial arrangement with the sponsor _____ whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study.

According to Millennium Pharmaceuticals, Inc. financial records for the reporting period, only \$10,086.98 was paid to this investigator during the conduct of the covered clinical study and therefore, will not be required to be reported per the applicable CFR regulations.

Throughout the course of the above mentioned clinical trial, representatives of Millennium Pharmaceuticals, Inc. performed 100% verification of all study data collected from patients enrolled at this study center.

As a result of thorough and routine site and data monitoring, Millennium Pharmaceuticals, Inc. considered the potential for bias to be minimal.

b(6)

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Name of clinical investigator
Name of clinical study

b(6)

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Robert G. Pietrusko, Pharm.D.	TITLE Senior Vice President, Worldwide Regulatory Affairs
FIRM / ORGANIZATION Millennium Pharmaceuticals, Inc.	
SIGNATURE 	DATE 15 May 2006

Paperwork Reduction Act Statement

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Department of Health and Human Services
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5600 Fishers Lane, Room 14-72
Rockville, MD 20857

**FORM FDA 3455; DISCLOSURE: FINANCIAL INTEREST AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

Appendix A to Form FDA 3455

_____, designated by _____
_____, has disclosed an equity interest in Millennium Pharmaceuticals,
Inc. The interest has been reported as a significant equity interest in the sponsor of the
covered study as _____

b(6)

_____ that exceeds \$50,000.

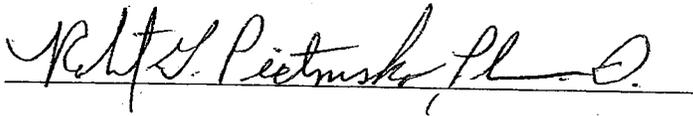
According to Millennium Pharmaceuticals, Inc. financial records for the reporting period,
there have been no payments paid to this investigator during the conduct of the covered
clinical study.

Throughout the course of the above noted clinical trial, representatives of Millennium
Pharmaceuticals, Inc. performed 100% verification of all study data collected from
patients enrolled at this study center.

As a result of thorough and routine site and data monitoring, Millennium
Pharmaceuticals, Inc. considered the potential for bias to be minimal.

1.3.3 Debarment Certification

Millennium Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity, the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



Robert G. Pietrusko, Pharm.D.
Senior Vice President
Worldwide Regulatory Affairs
Millennium Pharmaceuticals, Inc.

15 May 2006

Date

See above for NDA#

**DSI Note to Review
Division:**

Millennium Pharmaceuticals submitted a supplemental New Drug application (sNDA) for Velcade® (bortezomib), for mantle cell lymphoma in patients who have received at least 1 prior therapy. Response was evaluated according to a sponsor-derived algorithm which was developed using the International Workshop Response Criteria (IWRC). To ensure consistency in the interpretation of the CT scans across all participating study centers, the sponsor contracted _____ to perform an independent, blinded review of all CT scans. The radiology reviews were conducted by CT radiologists that received specific training on Protocol M34103-053.

b(4)

The purpose of inspecting _____ was to verify the source document radiology data residing at _____, blinding of the independent review, consistency of tumor measurements conducted by _____ radiologists, and to verify the accuracy of the response assessment data listings generated by the sponsor.

b(4)

At the conclusion of the inspection, a one item FDA 483 was issued pertaining to four instances of rounding errors on tumor measurement values recorded in the CRFs in four subjects. The tumor measurement values were to be rounded to the nearest tenths per sponsor's instruction by a specified date but the values, in these four instances, were not rounded off. The inspectional findings also identified some files that contained different tumor measurements than those listed in the data listings.

Prior to the inspection conclusion of the inspection, _____, addressed the tumor measurement discrepancies in a letter dated October 16, 2006. The sponsor was made aware of the discrepancy findings and the sponsor sent a copy of the letter to DBOP. The letter identified a total of 12 subject files with discrepancies when compared to the data listings. However, further evaluation of the identified discrepancies showed that only two subjects (Subjects 001-002 and 042-003) were impacted in terms of their tumor response assessments. The evaluation showed only a slight change in the duration of response from 9.7 months to 8.7 months. The evaluation showed no change in the median time to progression and median duration of response for subjects achieving CR or Cru.

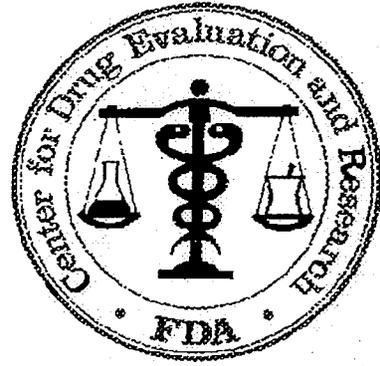
b(4)

The finding was not an issue since it did not have any significant impact on the submitted data.

A formal letter outlining the one inspectional finding was sent to _____ by DSI on May 2, 2008. A formal response was received by _____ dated April 1, 2009. It referenced the initial response of November 16, 2006 and reiterated the corrective action plan as well as the corrected data for the 3 subjects involved. It was requested that a confirmation letter be sent.

b(4)

FAX



**FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS**

Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To: Tanya Lewis, M.S.

From: Tammie Brent-Steele RN MSN

Fax: 617-551-3742

Fax: (301) 796-9845

Phone: 617-551-8951

Phone: (301) 796-1409

Pages, including cover sheet: 32

Date: 12/8/06

Re: sNDA 21-602/010 Velcade New Indication Approval Letter with Label

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Please refer to sNDA 21-602 supplement number 010 re: New Indication: Velcade (bortezomib) for Injection is indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

Please find a copy of your Approval Letter with Labeling attached.

Please contact me if you have any questions or concerns.

**Thanks,
Tammie**

Brent-Steele, Tammie

From: Brent-Steele, Tammie
Sent: Friday, December 08, 2006 3:45 PM
To: CDER-APPROVALS; CDER-ODDP-ALL
Subject: NDA 21-602/S-010 Velcade (bortezomib) Approval

Attachments: Final Approval Letter Label with signature.pdf

Today, December 8, 2006, the Division of Drug Oncology Products approved NDA 21-602/SE1-010 for Velcade (bortezomib) for Injection.

Approval information follows:

NDA: NDA 21-602/SE1-010

Drug: Velcade (bortezomib) for Injection

Applicant: Millennium Pharmaceuticals, Inc.

Indication: Velcade (bortezomib) for Injection for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

Route of administration: I.V.

Priority review

Rx

The approval letter and labeling are attached.



Final Approval
Letter Label wi...

Brent-Steele, Tammie

From: Johnson, J. Lloyd
Sent: Tuesday, November 07, 2006 9:14 AM
To: Kane, Robert; Brent-Steele, Tammie
Subject: Clinical inspection - Dr. Benjamin Djulbegovic

Good Morning Bob and Tammie,

DSI has received preliminary inspection results from FLA District Office. The inspection of Dr. Djulbegovic (Site #010, 8 total subjects), H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL has been completed for the Velcade NDA.

The inspection found several deviations including failure to list all sub-investigators on the Form FDA-1572; failure to obtain informed consent in one subject prior to initiating screening/test procedures; 2 subjects did not sign current version of the consent form; failure to list a concomitant medication (Procrit between 2/10/04 and 3/12/04) in the CRF for one subject and 2 adverse events (thrombocytopenia, feet swelling) for one subject were not listed in the CRF. There were also minor and isolated record keeping anomalies brought to the attention of the PI during the inspection closeout. Overall, the comparison of data in the case report forms with the sponsor's data listings found no observed differences. Dr. Djulbegovic promised corrective actions on the inspectional findings and will respond to the FDA 483.

The findings above are still preliminary, the inspection report upon receipt will be reviewed and final classification and regulatory compliance actions will be determined. Based on these preliminary findings, the observations should not impact the reliability and validity of the data from this study site.

We still have one remaining clinical investigator (Dr. Andre Goy, Hackensack University, NJ) inspection to be completed for this NDA.

Will be keeping you posted.

loyd

*J. Lloyd Johnson, Pharm.D.
Good Clinical Practice Branch II
Division of Scientific Investigations
MPN-1, HFD-47, Rm. 1422
CDER, USFDA
phone: 301-827-5459
fax: 301-827-5290
Lloyd.Johnson@fda.hhs.gov*



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-602

Millennium Pharmaceuticals, Inc.
Attention: Tanya Lewis, MSc
Associate Director, Regulatory Affairs
75 Sidney Street
Cambridge, MA 02139

Dear Ms. Lewis:

We acknowledge receipt of your July 10, 2006 submission containing final printed labeling in response to our May 31, 2006 letter approving your new drug application (NDA) for VELCADE.

We have reviewed the labeling that you submitted in accordance with our May 31, 2006 letter, and we find it acceptable.

If you have any questions, call Tammie Brent, Regulatory Project Manager, at 301-796-1409.

Sincerely,

{See appended electronic signature page}

Robert Justice, M.D.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Dotti Pease

11/6/2006 08:30:03 AM

Signing for Robert Justice, M.D.

Brent-Steele, Tammie

From: Abraham, Sophia
Sent: Friday, November 03, 2006 5:01 PM
To: Brent-Steele, Tammie
Subject: RE: NDA 21-602 Post Marketing #8

Yes, I need a full study report and raw data to make decisions regarding the label, submitted electronically, thanks

From: Brent-Steele, Tammie
Sent: Friday, November 03, 2006 4:54 PM
To: Abraham, Sophia
Subject: NDA 21-602 Post Marketing #8

Hi Sophia,

Tanya Lewis from Millennium called to ask me to forward a question to you regarding NDA 21-602 Post marketing commitment #8. She asked if you need the full study report to make decisions regarding the label. If not, what data would you accept in lieu of the full report? I told her I would forward her question.

Thanks very much,
Tammie

Brent-Steele, Tammie

From: CDER-EDRADMIN
Sent: Friday, October 27, 2006 4:09 PM
To: Brent-Steele, Tammie; Mejia, Bertha*; Padua, Alex*; Pease, Dorothy W; Prather, Mia; Wilder, Lisa C
Cc: Talastas, Hercules*; Emmons, Prentiss*; Langhnoja, Urvi *; Tokoli, Thomas*; CDER-EDRADMIN
Subject: EDR - NDA021602 from MILLENNIUM PHARMS drug name VELCADE (BORTEZOMIB) INJ 3.5MG

Hi !

The EDR has received an Electronic Document on CD-ROM for division HFD-150:

NDA# N21602
Incoming Document Type: N
Incoming Document Type Sequence Number: 000
Supplement Modification Type: C
Letter Date: 10/24/2006

It has section 20.

The network path location is: \\CDSESUB1\N21602\N_000\2006-10-24
It is now available on the network. You can review this submission by entering EDR in your browser.

Please address any questions concerning this electronic submission to:

EDRAdmin@cderr.fda.gov

Thanks,
EDR Staff RA

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER
21-602

APPLICANT INFORMATION

NAME OF APPLICANT Millennium Pharmaceuticals, Inc.	DATE OF SUBMISSION October 24, 2006
TELEPHONE NO. (Include Area Code) (617) 679-7000	FACSIMILE (FAX) Number (Include Area Code) (617) 551-3742
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 40 Landsdowne Street Cambridge, Massachusetts 02139	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21,602		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) bortezomib	PROPRIETARY NAME (trade name) IF ANY VELCADE® (bortezomib) for Injection	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) [(1R)-3-methyl-1-[[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]boronic acid	CODE NAME (If any) PS-341	
DOSAGE FORM: lyophilized powder for injection	STRENGTHS: 3.5mg	ROUTE OF ADMINISTRATION: Intravenous
(PROPOSED) INDICATION(S) FOR USE: Treatment of patients with mantle cell lymphoma who have received at least one prior therapy		

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION
Response to a Request for Information, e-mail October 22, 2006

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

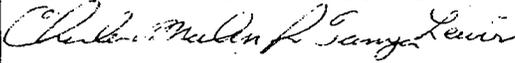
NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Not Applicable

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 56, 515

This application contains the following items: (Check all that apply)		
<input type="checkbox"/>	1. Index	
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling	
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))	
<input type="checkbox"/>	4. Chemistry section	
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
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<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	
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<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)	
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))	
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)	
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))	
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))	
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA-3397)	
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)	
<input checked="" type="checkbox"/>	20. OTHER (Specify) Response to a Request for Information, e-mail October 22, 2006	
CERTIFICATION		
<p>I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:</p> <ol style="list-style-type: none"> 1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820. 2. Biological establishment standards in 21 CFR Part 600. 3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809. 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202. 5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12. 6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81. 7. Local, state and Federal environmental impact laws. <p>If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.</p> <p>The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.</p> <p>Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.</p>		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT		DATE:
		October 24, 2006
TYPED NAME AND TITLE		
Tanya Lewis, M.S. Director, Regulatory Affairs		
ADDRESS (Street, City, State, and ZIP Code)		Telephone Number
40 Landsdowne Street, Cambridge MA 02139		(617) 551-8951
<p>Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p>		
Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Central Document Room 5901-B Ammendale Road Beltsville, MD 20705-1266		Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research (HFM-99) 1401 Rockville Pike Rockville, MD 20852-1448
An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.		

Brent-Steele, Tammie

From: Monahan III, Chuck [Chuck.Monahan@mpi.com]
Sent: Thursday, October 26, 2006 10:38 AM
To: Kane, Robert
Cc: Lewis, Tanya; Brent-Steele, Tammie
Subject: Response to Request Info, sNDA VELCADE ILD

Attachments: ILD_Response.zip; emfalert.txt



ILD_Response.zip emfalert.txt (2 KB)
(1 MB)

This e-mail is being sent on Behalf of Tanya Lewis, Director

Regulatory
Affairs. 617-551-8951
Dear Dr. Kane

Please find attached a response to your question regarding ILD that you sent in an e-mail on October 17, 2006. Copies of this electronic file has been submitted to the Central Document Room.

Please let us know if you have any issues accessing the files.

Regards,
Chuck Monahan
Manager, Regulatory Affairs
Millennium Pharmaceuticals, Inc.
617-444-3144
chuck.monahan@mpi.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER
21-602

APPLICANT INFORMATION

NAME OF APPLICANT Millennium Pharmaceuticals, Inc.	DATE OF SUBMISSION October 25, 2006
TELEPHONE NO. (Include Area Code) (617) 679-7000	FACSIMILE (FAX) Number (Include Area Code) (617) 551-3742
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 40 Landsdowne Street Cambridge, Massachusetts 02139	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE N/A

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ESTABLISHED NAME (e.g., Proper name, USP/USAN name) bortezomib	PROPRIETARY NAME (trade name) IF ANY VELCADE® (bortezomib) for Injection	
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IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)

REASON FOR SUBMISSION
Response to a Request for Information, October 17, 2006

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

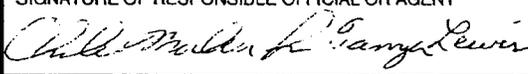
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Not Applicable

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 56, 515

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<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
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<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))	
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)	
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)	
<input checked="" type="checkbox"/>	20. OTHER (Specify) Response to a Request for Information, October 17, 2006	
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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	Tanya Lewis, M.S. Director, Regulatory Affairs	October 25, 2006
ADDRESS (Street, City, State, and ZIP Code)		Telephone Number
40 Landsdowne Street, Cambridge MA 02139		(617) 551-8951
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Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Central Document Room 5901-B Ammendale Road Beltsville, MD 20705-1266	Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research (HFM-99) 1401 Rockville Pike Rockville, MD 20852-1448	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

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(PROPOSED) INDICATION(S) FOR USE: Treatment of patients with mantle cell lymphoma who have received at least one prior therapy	

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IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION
Response to a Request for Information, WorldCare Site Inspection

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

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<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Response to a Request for Information, WorldCare Site Inspection

CERTIFICATION

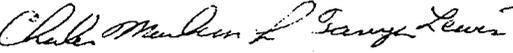
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Tanya Lewis, M.S. Director, Regulatory Affairs	DATE: October 25, 2006
---	---	---------------------------

ADDRESS (Street, City, State, and ZIP Code) 40 Landsdowne Street, Cambridge MA 02139	Telephone Number (617) 551-8951
---	--------------------------------------

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Brent-Steele, Tammie

To: Kane, Robert; Johnson, J. Lloyd
Subject: FW: EDR - NDA021602 from MILLENNIUM PHARMS drug name VELCADE (BORTEZOMIB) INJ 3.5MG

Hi Bob and Lloyd,

Submission from Millennium regarding the _____ inspection. Lloyd, you may have already seen this, however, just thought I'd pass it along.

b(4)

Thanks,
Tammie

-----Original Message-----

From: CDER-EDRADMIN
Sent: Tuesday, October 31, 2006 4:00 PM
To: Brent-Steele, Tammie; Mejia, Bertha*; Padua, Alex*; Pease, Dorothy W; Prather, Mia; Wilder, Lisa C
Cc: Talastas, Hercules*; Emmons, Prentiss*; Langhnoja, Urvi *; Tokoli, Thomas*; CDER-EDRADMIN
Subject: EDR - NDA021602 from MILLENNIUM PHARMS drug name VELCADE (BORTEZOMIB) INJ 3.5MG

Hi !

The EDR has received an Electronic Document on CD-ROM for division HFD-150:

NDA# N21602
Incoming Document Type: N
Incoming Document Type Sequence Number: 000
Supplement Modification Type: C
Letter Date: 10/25/2006

It has sections 1, 20.
The network path location is: \\CDSESUB1\N21602\N_000\2006-10-25A
It is now available on the network. You can review this submission by entering EDR in your browser.

Please address any questions concerning this electronic submission to:

EDRAdmin@cder.fda.gov

Thanks,
EDR Staff

Brent-Steele, Tammie

To: Kane, Robert
Subject: FW: Resp Req Info, ~~_____~~ Inspection

Attachments: Response Req Info, ~~_____~~ Inspection.pdf; emfalert.txt

b(4)



Response Req Info, emfalert.txt (2 KB)
~~_____~~ Inspect...

b(4)

Hi Bob,

Millennium has forwarded the attached documents regarding the ~~_____~~ inspection. They asked that I forward the document to you. I think this is the basis for the request to T-con with you. Let me know if you need anything regarding this.

Thanks,
Tammie.

-----Original Message-----

From: Monahan III, Chuck [mailto:Chuck.Monahan@mpi.com]
Sent: Wednesday, October 25, 2006 12:50 PM
To: Brent-Steele, Tammie
Cc: Lewis, Tanya
Subject: Resp Req Info, ~~_____~~ Inspection

b(4)

This e-mail is being sent on behalf of Tanya Lewis, Director Regulatory Affairs, 617 551-8951
Dear Tammie

Please find attached a copy of the documentation that was requested by Ms. Ellen Madigan, during her site inspection of ~~_____~~, our contracted imaging vendor. Representatives from Millennium provided this report to Ms. Madigan on October 16, 2006 during her wrap up meeting of the ~~_____~~ inspection.

b(4)

Please provide this document to Dr. Kane to support our future discussions.
Hard copies are being submitted to the Central Document Room.

Chuck Monahan
Manager, Regulatory Affairs
Millennium Pharmaceuticals, Inc.
617-444-3144
chuck.monahan@mpi.com

Brent-Steele, Tammie

From: Monahan III, Chuck [Chuck.Monahan@mpi.com]
Sent: Wednesday, October 25, 2006 12:50 PM
To: Brent-Steele, Tammie
Cc: Lewis, Tanya
Subject: Resp Req Info, ~~_____~~ Inspection
Attachments: Response Req Info, ~~_____~~Inspection.pdf; emfalert.txt

b(4)



Response Req Info, emfalert.txt (2 KB)
Inspect...

This e-mail is being sent on behalf of Tanya Lewis, Director

Regulatory
Affairs, 617 551-8951
Dear Tammie

Please find attached a copy of the documentation that was requested by Ms. Ellen Madigan, during her site inspection of _____, our contracted imaging vendor. Representatives from Millennium provided this report to Ms. Madigan on October 16, 2006 during her wrap up meeting of the _____ inspection.

b(4)

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Hard copies are being submitted to the Central Document Room.

Chuck Monahan
Manager, Regulatory Affairs
Millennium Pharmaceuticals, Inc.
617-444-3144
chuck.monahan@mpi.com

Brent-Steele, Tammie

To: Chan, Samuel
Subject: RE: velcade labeling meeting

Hi Sam,

Below is the link to the EDR and the submission for the velcade supplement. The labeling is included in the supplement. I have not finished my review yet, but I plan to do so by tomorrow. We have not discussed any labeling as of yet. Based on the response to my email by the rest of the team, we may start working on labeling on Wednesday.

Thank very much, and please let me know if you need any thing at all.

Tammie

Link to electronic submission:

The network path location is: \\CDSESUB1\N21602\S_010\2006-06-08

From: Chan, Samuel
Sent: Monday, October 23, 2006 9:33 AM
To: Brent-Steele, Tammie
Subject: velcade labeling meeting

Hi, Tammie,

I am the new DDRE project manager. Please provide the labeling material to be discussed at this Wednesday velcade meeting. Thanks.

) Sam

10/23/04

Brent-Steele, Tammie

To: Levine, Alexandra
Subject: Velcade Supplement briefing Document
Attachments: Velcade Executive Summary for Dr. Levine.doc

Dear Dr. Levine:

Thank you for agreeing to review the Velcade sNDA for patients with mantle cell lymphoma after one prior therapy. We have abridged the data to reduce the review burden for you, but if you would like to receive any additional information, please contact us.

Our questions appear at the end of this document. Thank you again for your thoughts and advice.

Tammie Brent for Dr. Bob Kane



Velcade Executive
Summary for ...

Dr. Levine,

Please let me know if you need anything else. Have a great day.

Tammie Brent

FDA/CDER/OND/OODP
10903 New Hampshire Ave.
Bldg 22 Rm 2161
Silver Spring MD 20993
Ph: 301-796-1409
Fax 301-796-9845
Email tammie.brentsteele@fda.hhs.gov

Brent-Steele, Tammie

From: Zhou, Liang
Sent: Tuesday, October 24, 2006 8:28 AM
To: Brent-Steele, Tammie
Cc: Jimenez, Valerie; Liang, Cheng Yi; Patel, Hasmukh B; Jenney, Susan
Subject: FW: sNDA 21-602 Team/Labeling Meeting #2 Velcade

Tammie:

Please refer to Chengyi's e-mail below regarding your labeling review request. Therefore, we don't have any labeling issues at this time.

Thanks,
Liang

From: Liang, Cheng Yi
Sent: Monday, October 23, 2006 1:13 PM
To: Jimenez, Valerie
Cc: Zhou, Liang
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

Valerie:

I do not have CMC question for this supplement. The EA review will be finished soon.

Chengyi

From: Jimenez, Valerie
Sent: Monday, October 23, 2006 11:58 AM
To: Liang, Cheng Yi
Cc: Zhou, Liang
Subject: FW: sNDA 21-602 Team/Labeling Meeting #2 Velcade

Cheng Yi,
Status?

Valerie

From: Booth, Brian P
Sent: Monday, October 23, 2006 11:52 AM
To: Brent-Steele, Tammie; Justice, Robert; Farrell, Ann T; Dagher, Ramzi; Kane, Robert; Morse, David E (CDER); Sridhara, Rajeshwari; Abraham, Sophia; Ko, Chia-wen (Kiki); Liang, Cheng Yi; Zhou, Liang; Grillo, Joseph; Johnson, J. Lloyd; Dempsey, Mary; Lu, Susan; Ball, Leslie; Patel, Hasmukh B; Jimenez, Valerie; Bradley, Sean; Pease, Dorothy W
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

I am doing the secondary now.

B

From: Brent-Steele, Tammie
Sent: Monday, October 23, 2006 11:51 AM
To: Justice, Robert; Farrell, Ann T; Dagher, Ramzi; Kane, Robert; Morse, David E (CDER); Sridhara, Rajeshwari; Abraham, Sophia; Booth, Brian P; Ko, Chia-wen (Kiki); Liang, Cheng Yi; Zhou, Liang; Grillo, Joseph; Johnson, J. Lloyd; Dempsey, Mary; Lu, Susan; Ball, Leslie; Patel, Hasmukh B; Jimenez, Valerie; Bradley, Sean; Pease, Dorothy W
Subject: sNDA 21-602 Team/Labeling Meeting #2 Velcade

Hello,

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discussing labeling? Please let me know what you think should be part of the agenda.

Thanks very much,

Tammie

Brent-Steele, Tammie

From: Zhou, Liang
Sent: Tuesday, October 24, 2006 12:51 PM
To: Brent-Steele, Tammie
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

You too. Tammie. Please let me know if there is any issues which may be raised in tomorrow meeting since I may not attend tomorrow meeting.

Liang

From: Brent-Steele, Tammie
Sent: Tuesday, October 24, 2006 8:41 AM
To: Zhou, Liang
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

Thanks Liang. Have a great day!
Tammie

From: Zhou, Liang
Sent: Tuesday, October 24, 2006 8:28 AM
To: Brent-Steele, Tammie
Cc: Jimenez, Valerie; Liang, Cheng Yi; Patel, Hasmukh B; Jenney, Susan
Subject: FW: sNDA 21-602 Team/Labeling Meeting #2 Velcade

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From: Jimenez, Valerie
Sent: Monday, October 23, 2006 11:58 AM
To: Liang, Cheng Yi
Cc: Zhou, Liang
Subject: FW: sNDA 21-602 Team/Labeling Meeting #2 Velcade

Cheng Yi,
Status?

Valerie

From: Booth, Brian P
Sent: Monday, October 23, 2006 11:52 AM
To: Brent-Steele, Tammie; Justice, Robert; Farrell, Ann T; Dagher, Ramzi; Kane, Robert; Morse, David E (CDER); Sridhara, Rajeshwari; Abraham, Sophia; Ko, Chia-wen (Kiki); Liang, Cheng Yi; Zhou, Liang; Grillo, Joseph; Johnson,

Brent-Steele, Tammie

From: Morse, David E (CDER)
Sent: Tuesday, October 24, 2006 10:57 AM
To: Kane, Robert; Brent-Steele, Tammie
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

We're thrilled (as always).

From: Kane, Robert
Sent: Monday, October 23, 2006 11:54 AM
To: Brent-Steele, Tammie
Cc: Morse, David E (CDER)
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

pharm-tox can confirm they are happy with the changes since the last Velcade label revision also (see overdose)

From: Brent-Steele, Tammie
Sent: Monday, October 23, 2006 11:51 AM
To: Justice, Robert; Farrell, Ann T; Dagher, Ramzi; Kane, Robert; Morse, David E (CDER); Sridhara, Rajeshwari; Abraham, Sophia; Booth, Brian P; Ko, Chia-wen (Kiki); Liang, Cheng Yi; Zhou, Liang; Grillo, Joseph; Johnson, J. Lloyd; Dempsey, Mary; Lu, Susan; Ball, Leslie; Patel, Hasmukh B; Jimenez, Valerie; Bradley, Sean; Pease, Dorothy W
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Thanks very much,

Tammie

J. Lloyd; Dempsey, Mary; Lu, Susan; Ball, Leslie; Patel, Hasmmukh B; Jimenez, Valerie; Bradley, Sean; Pease, Dorothy W

Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

I am doing the secondary now.

B

From: Brent-Steele, Tammie
Sent: Monday, October 23, 2006 11:51 AM
To: Justice, Robert; Farrell, Ann T; Dagher, Ramzi; Kane, Robert; Morse, David E (CDER); Sridhara, Rajeshwari; Abraham, Sophia; Booth, Brian P; Ko, Chia-wen (Kiki); Liang, Cheng Yi; Zhou, Liang; Grillo, Joseph; Johnson, J. Lloyd; Dempsey, Mary; Lu, Susan; Ball, Leslie; Patel, Hasmmukh B; Jimenez, Valerie; Bradley, Sean; Pease, Dorothy W
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Thanks very much,

Tammie

Brent-Steele, Tammie

From: Johnson, J. Lloyd
Sent: Monday, October 23, 2006 1:48 PM
To: Brent-Steele, Tammie; Justice, Robert; Farrell, Ann T; Dagher, Ramzi; Kane, Robert; Morse, David E (CDER); Sridhara, Rajeshwari; Abraham, Sophia; Booth, Brian P; Ko, Chia-wen (Kiki); Liang, Cheng Yi; Zhou, Liang; Grillo, Joseph; Dempsey, Mary; Lu, Susan; Ball, Leslie; Patel, Hasmukh B; Jimenez, Valerie; Bradley, Sean; Pease, Dorothy W
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

Tammie.
Hi Brenda,

With regard to DSI clinical data inspections, we have 4 study sites scheduled for clinical inspection for this NDA.

The central radiology independent review site, _____ has just recently been inspected. Preliminary reports from the inspection indicates that study records and study conduct at that site were in good shape, there were no violative findings, no FDA 483 was issued. **b(4)**

The inspection of the three clinical investigator sites are currently being scheduled. The inspection of Dr. Sagar Lonial, Emory Univ., Atlanta is scheduled to start this week. We have no updates for the other two sites at this time.

Lloyd

From: Brent-Steele, Tammie
Sent: Monday, October 23, 2006 11:51 AM
To: Justice, Robert; Farrell, Ann T; Dagher, Ramzi; Kane, Robert; Morse, David E (CDER); Sridhara, Rajeshwari; Abraham, Sophia; Booth, Brian P; Ko, Chia-wen (Kiki); Liang, Cheng Yi; Zhou, Liang; Grillo, Joseph; Johnson, J. Lloyd; Dempsey, Mary; Lu, Susan; Ball, Leslie; Patel, Hasmukh B; Jimenez, Valerie; Bradley, Sean; Pease, Dorothy W
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Thanks very much,

Tammie

Brent-Steele, Tammie

From: Kane, Robert
Sent: Monday, October 23, 2006 11:51 AM
To: Brent-Steele, Tammie
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

begin labeling

From: Brent-Steele, Tammie
Sent: Monday, October 23, 2006 11:51 AM
To: Justice, Robert; Farrell, Ann T; Dagher, Ramzi; Kane, Robert; Morse, David E (CDER); Sridhara, Rajeshwari; Abraham, Sophia; Booth, Brian P; Ko, Chia-wen (Kiki); Liang, Cheng Yi; Zhou, Liang; Grillo, Joseph; Johnson, J. Lloyd; Dempsey, Mary; Lu, Susan; Ball, Leslie; Patel, Hasmukh B; Jimenez, Valerie; Bradley, Sean; Pease, Dorothy W
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Tammie

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From: Booth, Brian P
Sent: Monday, October 23, 2006 11:52 AM
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B

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Thanks very much,

Tammie

Brent-Steele, Tammie

From: Kane, Robert
Sent: Monday, October 23, 2006 11:54 AM
To: Brent-Steele, Tammie
Cc: Morse, David E (CDER)
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

pharm-tox can confirm they are happy with the changes since the last Velcade label revision also (see overdose)

From: Brent-Steele, Tammie
Sent: Monday, October 23, 2006 11:51 AM
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Thanks very much,

Tammie

Brent-Steele, Tammie

From: Ko, Chia-wen (Kiki)
Sent: Monday, October 23, 2006 12:09 PM
To: Brent-Steele, Tammie; Justice, Robert; Farrell, Ann T; Dagher, Ramzi; Kane, Robert; Morse, David E (CDER); Sridhara, Rajeshwari; Abraham, Sophia; Booth, Brian P; Liang, Cheng Yi; Zhou, Liang; Grillo, Joseph; Johnson, J. Lloyd; Dempsey, Mary; Lu, Susan; Ball, Leslie; Patel, Hasmukh B; Jimenez, Valerie; Bradley, Sean; Pease, Dorothy W
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

Stat evaluation is almost done. I am putting the results and evaluations into the template this week.

Kiki

From: Brent-Steele, Tammie
Sent: Monday, October 23, 2006 11:51 AM
To: Justice, Robert; Farrell, Ann T; Dagher, Ramzi; Kane, Robert; Morse, David E (CDER); Sridhara, Rajeshwari; Abraham, Sophia; Booth, Brian P; Ko, Chia-wen (Kiki); Liang, Cheng Yi; Zhou, Liang; Grillo, Joseph; Johnson, J. Lloyd; Dempsey, Mary; Lu, Susan; Ball, Leslie; Patel, Hasmukh B; Jimenez, Valerie; Bradley, Sean; Pease, Dorothy W
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Thanks very much,

Tammie

Brent-Steele, Tammie

From: Dempsey, Mary
Sent: Monday, October 23, 2006 12:31 PM
To: Brent-Steele, Tammie
Cc: Lu, Susan
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

Hi Tammie,

Believe that San Chan is the PM assigned to this product.
Please let me know if you need any further info from the RMP Team.
Thanks,
MaryD

*Mary Dempsey
Risk Management Program Officer
Office of Surveillance & Epidemiology (OSE)
Center for Drug Evaluation and Research
Phone: 301-796-0147*

*10903 New Hampshire Avenue
CDER Building #22, Room 4326
Silver Spring, MD 20993
New Email Address: Mary.Dempsey@fda.hhs.gov*

From: Brent-Steele, Tammie
Sent: Monday, October 23, 2006 12:24 PM
To: Dempsey, Mary
Cc: Lu, Susan
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

Hi Mary and Susan,

I think the DDRE SE is Samuel Chan, if I'm not mistaken. He contacted me this morning on a separate email. I will contact him regarding the meeting.

Thanks very much.
Tammie

From: Dempsey, Mary
Sent: Monday, October 23, 2006 12:01 PM
To: Brent-Steele, Tammie
Cc: Lu, Susan; Dempsey, Mary
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

Hi Tammie,

Because this is an sNDA for a new indication for an approved product, the OSE RMP Team has not been involved in this review.

I see that you copied Susan Lu on your correspondence and we'll work together to make sure that our DDRE SE is aware of the pending action.

SUSAN: if appropriate, please let SE know about upcoming labeling meeting.

Thanks,
MaryD

Mary Dempsey
Risk Management Program Officer
Office of Surveillance & Epidemiology (OSE)
Center for Drug Evaluation and Research
Phone: 301-796-0147

10903 New Hampshire Avenue
CDER Building #22, Room 4326
Silver Spring, MD 20993
New Email Address: Mary.Dempsey@fda.hhs.gov

From: Brent-Steele, Tammie
Sent: Monday, October 23, 2006 11:51 AM
To: Justice, Robert; Farrell, Ann T; Dagher, Ramzi; Kane, Robert; Morse, David E (CDER); Sridhara, Rajeshwari; Abraham, Sophia; Booth, Brian P; Ko, Chia-wen (Kiki); Liang, Cheng Yi; Zhou, Liang; Grillo, Joseph; Johnson, J. Lloyd; Dempsey, Mary; Lu, Susan; Ball, Leslie; Patel, Hasmukh B; Jimenez, Valerie; Bradley, Sean; Pease, Dorothy W
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Thanks very much,

Tammie

Brent-Steele, Tammie

From: Lu, Susan
Sent: Monday, October 23, 2006 3:45 PM
To: Brent-Steele, Tammie
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

Thanks Tammie!

From: Brent-Steele, Tammie
Sent: Monday, October 23, 2006 1:58 PM
To: Lu, Susan
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

Hi Sue,
I sent the meeting appointments to Jennifer as well as to Sam Chan. Thank you for telling me. Have a great afternoon!

Tammie

From: Lu, Susan
Sent: Monday, October 23, 2006 12:54 PM
To: Dempsey, Mary; Brent-Steele, Tammie
Cc: Rouine, Jennifer; Chan, Samuel
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

Jennifer Rouine (Steele) is the safety evaluator for Velcade and I forwarded the e-mails to her. Tammie, kindly include her for future meeting invitations/correspondence. Thanks-Sue

From: Dempsey, Mary
Sent: Monday, October 23, 2006 12:31 PM
To: Brent-Steele, Tammie
Cc: Lu, Susan
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

Hi Tammie,

Believe that Sam Chan is the PM assigned to this product.
Please let me know if you need any further info from the RMP Team.
Thanks,
MaryD

*Mary Dempsey
Risk Management Program Officer
Office of Surveillance & Epidemiology (OSE)
Center for Drug Evaluation and Research
Phone: 301-796-0147*

*10903 New Hampshire Avenue
CDER Building #22, Room 4326
Silver Spring, MD 20993
New Email Address: Mary.Dempsey@fda.hhs.gov*

From: Brent-Steele, Tammie
Sent: Monday, October 23, 2006 12:24 PM
To: Dempsey, Mary
Cc: Lu, Susan
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

Hi Mary and Susan,

I think the DDRE SE is Samuel Chan, if I'm not mistaken. He contacted me this morning on a separate email. I will contact him regarding the meeting.

Thanks very much.
Tammie

From: Dempsey, Mary
Sent: Monday, October 23, 2006 12:01 PM
To: Brent-Steele, Tammie
Cc: Lu, Susan; Dempsey, Mary
Subject: RE: sNDA 21-602 Team/Labeling Meeting #2 Velcade

Hi Tammie,

Because this is an sNDA for a new indication for an approved product, the OSE RMP Team has not been involved in this review.

I see that you copied Susan Lu on your correspondence and we'll work together to make sure that our DDRE SE is aware of the pending action.

SUSAN: if appropriate, please let SE know about upcoming labeling meeting.

Thanks,
MaryD

Mary Dempsey
Risk Management Program Officer
Office of Surveillance & Epidemiology (OSE)
Center for Drug Evaluation and Research
Phone: 301-796-0147

10903 New Hampshire Avenue
CDER Building #22, Room 4326
Silver Spring, MD 20993
New Email Address: Mary.Dempsey@fda.hhs.gov

From: Brent-Steele, Tammie
Sent: Monday, October 23, 2006 11:51 AM
To: Justice, Robert; Farrell, Ann T; Dagher, Ramzi; Kane, Robert; Morse, David E (CDER); Sridhara, Rajeshwari; Abraham, Sophia; Booth, Brian P; Ko, Chia-wen (Kiki); Liang, Cheng Yi; Zhou, Liang; Grillo, Joseph; Johnson, J. Lloyd; Dempsey, Mary; Lu, Susan; Ball, Leslie; Patel, Hasmmukh B; Jimenez, Valerie; Bradley, Sean; Pease, Dorothy W
Subject: sNDA 21-602 Team/Labeling Meeting #2 Velcade

Hello,

I just wanted to touch base with everyone regarding an agenda for the team meeting on Wednesday 10-25-06 at 3pm in 2201. Can everyone update me with where you are with reviews or inspections? Are we ready to start discussing labeling? Please let me know what you think should be part of the agenda.

Thanks very much,

Tammie

Brent-Steele, Tammie

To: Ko, Chia-wen (Kiki)
cc: Kane, Robert
Subject: sNDA 21-602 S-010 Question from ODAC consultant

Hi Kiki,

Dr. Levine, our ODAC consultant for the above supplement call with a question this afternoon. She asked "What is the duration of response for PR patients?" She noted that the duration of response for all responders was 9.2 months, and for CR or CRu it was 13.5 months. She will send us a response to our submission to her, however, would like the answer to this question prior to responding to us. Please let me know what the response is. Here is her contact information should you require to speak with her.

Dr. Alexandra Levine

b(6)

Thanks very much,
Tammie

Brent-Steele, Tammie

To: Pease, Dorothy W; Cross Jr, Frank H; Spillman, Dianne D
Subject: COI, Schwartz, Velcade, sNDA 21-602 serial number 010

Hi Dotti, Frank and Dianne,

I'm sending this email to get clearance to use following patient consultant:

Karl Schwartz
3774 Buckwampum Road
Springfield Township, Bucks County
Riegelsville, PA 18077
610-346-8419
F 801-409-5736
karls@lymphomation.org

There is no meeting type, the consultant needs to be on hand for consultation during the sNDA review process.

sNDA: 21-602 serial number 010

Drug: Velcade (bortezomib) for injection

Sponsor: Millennium Pharmaceutical, Inc.

Indication: Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy

Competing Products:

Reviewing MO: Bob Kane, MD

Med. Team Lead: Ramzi Dagher, MD

Project Manager: Tammie Brent

Thanks,
Tammie

Brent-Steele, Tammie

To: _____
Subject: Response to your question

b(6)

Hello Dr. Levine,

Please find below an answer to your question regarding the duration of response for PR patients. Response provided by Dr. Kiki Ko, our statistical reviewer, and agreed to by Dr. Bob Kane our clinical reviewer:

The sponsor didn't report the duration of response for PR responders. According to my calculation, the duration of response for PR responders is 217 days (95% CI: 143, 279) for investigator-determined response, and is 186 days (95% CI: 129, 285) for sponsor-derived response.

Please let me know if you need anything else.

Have a great afternoon.

Tammie

Tammie Brent RN MSN
FDA/CDER/OND/OODP
10903 New Hampshire Ave.
Bldg 22 Rm 2161
Silver Spring MD 20993
Ph: 301-796-1409
Fax 301-796-9845
Email tammie.brentsteele@fda.hhs.gov

Brent-Steele, Tammie

From: Kane, Robert
Sent: Tuesday, October 17, 2006 1:28 PM
To: 'Lewis, Tanya'
Cc: Brent-Steele, Tammie
Subject: RE: Questions

Request regarding the 3 patients reported to have SAE of dyspnea - CSR page 158 and table 12-9

"Three patients had a breathing abnormality reported as an SAE (Patients 10-009, 35-001, and 38-003); for all 3 patients, the event was assessed as Grade 3 in intensity and unrelated to VELCADE. Furthermore, for all 3 patients the breathing abnormality did not occur concurrent with a respiratory infection, but was accompanied by weakness and/or fatigue. No patient discontinued VELCADE because of a breathing abnormality.

In table 12-9, three patients are listed as :

Parenchymal lung disorders NEC 3 (2%) 1 (<1%) 1 (<1%) 1 (<1%) 1 (<1%)

It looks like one patient did discontinue for dyspnea?

Could any of these have had ILD?

thanks

Brent-Steele, Tammie

From: Kane, Robert
Sent: Monday, October 16, 2006 4:26 PM
To: 'Lewis, Tanya'
Cc: Brent-Steele, Tammie
Subject: Questions

In your MCL protocol, on page 42 and in the stat plan, you state that the ITT population will be used for all efficacy analyses.

Why then are you using the RP-final for the response analysis?

Brent-Steele, Tammie

To: Kane, Robert
Subject: RE: Velcade

No, not to my knowledge. I checked on this when the submission first came in, however, I will double check, just to be safe. Thanks.
Tammie

From: Kane, Robert
Sent: Tuesday, October 17, 2006 4:16 PM
To: Brent-Steele, Tammie
Subject: Velcade

Does Velcade have orphan drug status for mantle cell lymphoma?

thanks

Brent-Steele, Tammie

From: Johnson, J. Lloyd
Sent: Thursday, October 12, 2006 3:33 PM
To: Kane, Robert
Cc: Brent-Steele, Tammie
Subject: FW: _____ **b(4)**

Hi Bob,

We got pretty lucky in terms of timing for the _____ inspection, the inspection is almost complete and it looking pretty good with no major significant violative findings at this point. It is very unusual to get this lucky in getting the assignment issued, scheduled and completed this soon. Please note that the three different Field Offices are still working on getting the three study sites (PI – inspection) scheduled at this time. **b(4)**

Attached below is an update from our Field Inspector from the New England District Office who is currently inspecting _____.

The inspection will close out this Monday, please let me know if there is anything more you want covered at _____. In addition to the Bioresearch Monitoring Program audit instructions, this inspection will also try to address the following questions as I noted to you previously on my e-mail: **b(4)**

Special Instructions for the inspection of _____ :

- Verify how study blinding was preserved during the independent radiology review of the CT scans performed by _____ radiologists; Is there any indication that blinding was compromised? If so, please provide documentation. **b(4)**
- Determine if _____ applied consistent methodology and procedure in the conduct and review of the CT images, tumor identification, and tumor size measurements, Ascertain if the radiologists performing the readings received specific training on Study Protocol M34103-053.
- Review and compare tumor measurements documented by _____ radiologists against accuracy of source document records, CRFs, and sponsor's data listings. Did the sponsor conduct any audits to monitor the conduct of the independent reading of the radiology scans at _____? **b(4)**
- Based on your review of the source documents, including tumor measurement records on- site, ascertain if the sponsor consistently followed their derived response assessment algorithm in the assessment and final classification of tumor responses from the radiology data provided by _____
- Determine if there were discrepancies between the initial CT scan readings by _____ radiologists and sponsor's tumor response assessment final classification. Document the extent of data discrepancies and determine if the discrepancies were adequately resolved. **b(4)**

Thanks,
Lloyd

*J. Lloyd Johnson, Pharm.D.
 Good Clinical Practice Branch II
 Division of Scientific Investigations
 MPN-1, HFD-47, Rm. 1422
 CDER, USFDA
 phone: 301-827-5459
 fax: 301-827-5290
 Lloyd.Johnson@fda.hhs.gov*

10/12/2006

Brent-Steele, Tammie

From: Kane, Robert
Sent: Sunday, October 22, 2006 7:00 PM
To: 'Lewis, Tanya'
Cc: Brent-Steele, Tammie; Kane, Robert
Subject: RE: questions re sNDA 010

regarding the RP-final population, you describe 9 who were removed from the ATP group because they had no post-baseline assessments.

Was one of the #010-001 ?

Did any (others) of these 9 have neck disease and post-baseline assessments by exam only?

Thanks



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-602S-010
Millennium Pharmaceuticals, Inc.
Attention: Tanya Lewis, M.S.
Director, Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Lewis:

Please refer to your supplemental new drug application(s) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Velcade.

We also refer to your, submission requesting a Waiver from the 120 Day Safety Report.

We have reviewed the referenced material and your request for a Waiver from the 120 day safety report is granted.

If you have any questions, call Tammie Brent-Steele, Regulatory Project Manager, at 301-796-1409.

Sincerely,

{See appended electronic signature page}

Robert Justice, M.D.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ann Farrell
9/28/2006 04:57:17 PM
Farrell for Justice

Brent-Steele, Tammie

From: Verbois, Leigh
Sent: Tuesday, September 26, 2006 3:25 PM
To: Brent-Steele, Tammie
Subject: RE: EDR - NDA021602 from MILLENNIUM PHARMS drug name VELCADE (BORTEZOMIB) INJ 3.5MG

I checked it out and there are no P/T issues.

-----Original Message-----

From: Brent-Steele, Tammie
Sent: Tuesday, September 26, 2006 3:18 PM
To: Verbois, Leigh
Subject: FW: EDR - NDA021602 from MILLENNIUM PHARMS drug name VELCADE (BORTEZOMIB) INJ 3.5MG

Hi Leigh,

Bob Kane has reviewed the submission below already and has okayed it. Just wanted to pass it by you. Thanks very much.

Tammie

-----Original Message-----

From: CDER-EDRADMIN
Sent: Friday, September 01, 2006 5:20 PM
To: Brent-Steele, Tammie; Mejia, Bertha*; Padua, Alex*; Pease, Dorothy W; Prather, Mia; Wilder, Lisa C
Cc: Talastas, Hercules*; Emmons, Prentiss*; Langhnoja, Urvi *; Tokoli, Thomas*; CDER-EDRADMIN
Subject: EDR - NDA021602 from MILLENNIUM PHARMS drug name VELCADE (BORTEZOMIB) INJ 3.5MG

Hi !

The EDR has received an Electronic Document on CD-ROM for division HFD-150:

NDA# N21602
Incoming Document Type: SE1
Incoming Document Type Sequence Number: 010
Supplement Modification Type: C
Letter Date: 8/30/2006

It has sections 1, 20.

The network path location is: \\CDSESUB1\N21602\S_010\2006-08-30A
It is now available on the network. You can review this submission by entering EDR in your browser.

Please address any questions concerning this electronic submission to:

EDRAdmin@cderr.fda.gov

Thanks,
EDR-T-L

57 Page(s) Withheld

 Trade Secret / Confidential (b4)

 √ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

FAX



**FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS**

Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To: Tanya Lewis, M.S.

From: Tammie Brent, RN MSN

Fax: 617-551-3742

Fax: (301) 796-9845

Phone: 617-551-8951

Phone: (301) 796-1409

Pages, including cover sheet: 7

Date: 9/20/06

Re: sNDA 21-602/010 Velcade New Indication

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Please refer to sNDA 21-602 supplement number 010 re: New Indication: Velcade (bortezomib) for Injection is indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

We have the following comments from our Statistical Reviewer:

Question 1: Table 11-1 of the M34103-053 study report indicates there were 12 subjects in the RP-final population without any post-baseline assessment. However, by RP-final definition, anyone in this population should have at least one post-baseline assessment. Please clarify.

Question 2: Please refer to the attached document for comparison of sponsor-derived and investigator-determined best responses for RP-Final population. It appears that there were discrepancies in best response determination between the two methods. Do you have any clarifications or explanations?

Please contact me with any questions you may have.

**Thanks,
Tammie**

Best Response in RP-Final (n=141)

Obs	CNOPATNO	Sponsor	Investigator
1	001-001		PD
2	001-002	SD	PR
3	001-003	SD	PR
4	001-004	CR	CR
5	001-005	SD	SD
6	001-006	SD	SD
7	001-007	SD	PR
8	001-008	SD	SD
9	001-009	SD	PD
10	001-010	SD	PD
11	002-001	PR	PD
12	002-002	CR	PR
13	002-003	PD	PD
14	003-001	PD	PD
15	004-001	SD	PR
16	004-002	PR	PR
17	004-003		PD
18	004-004	SD	SD
19	004-005	PD	SD
20	004-006	SD	PD
21	006-002	CR	CR
22	006-003	CR	CRu
23	006-004	SD	PR
24	006-005		
25	006-006	PR	PR
26	007-001	SD	SD
27	007-003	PR	PR
28	007-004	PR	PR
29	007-005	SD	SD
30	007-006		PD
31	007-008	PD	SD
32	008-001	CR	CR
33	009-001	PR	PR
34	009-002	SD	SD
35	010-001		CR

Best Response in RP-Final (n=141)

Obs	CNOPATNO	Sponsor	Investigator
36	010-002	PR	PR
37	010-003	CR	CR
38	010-005	PR	PR
39	010-006	PD	PD
40	010-007	PR	SD
41	010-008	SD	PR
42	010-009	PD	PD
43	011-001	CRu	CRu
44	011-002		PD
45	011-003	PD	SD
46	011-004	PR	PR
47	011-005	SD	SD
48	011-006	PD	PD
49	011-008	SD	SD
50	012-001	SD	SD
51	012-003	PR	SD
52	012-004	PD	PR
53	012-005	PR	PR
54	013-001	PD	PD
55	013-002		PD
56	013-003	PD	PD
57	013-004	SD	SD
58	013-005	PD	SD
59	013-006	SD	SD
60	014-002	PD	PR
61	014-003	PD	SD
62	014-004	PR	CR
63	014-005	CRu	CR
64	015-001	PR	PR
65	015-002	SD	SD
66	015-003	PR	PR
67	015-004	CR	PR
68	017-001	PR	PR
69	018-001	PR	CRu
70	018-002		PD

Best Response in RP-Final (n=141)

Obs	CNOPATNO	Sponsor	Investigator
71	018-003	PD	PD
72	018-004	PD	SD
73	018-005	PD	PD
74	019-001	PR	PR
75	019-002	SD	SD
76	019-003	SD	SD
77	020-001	SD	PD
78	020-002	SD	SD
79	020-003	PD	PR
80	020-005	SD	SD
81	021-001	SD	SD
82	021-002	SD	SD
83	022-001	PR	PR
84	022-002	SD	SD
85	023-001	PD	PD
86	024-001	PR	PR
87	024-002	SD	PR
88	024-004	PR	PR
89	027-001	SD	PR
90	027-002		PD
91	027-003		PD
92	027-004	PD	PD
93	027-005	SD	SD
94	027-006	PR	PR
95	027-008		SD
96	027-009	PD	PD
97	028-002	PD	SD
98	028-003	PR	PR
99	028-005	SD	PD
100	028-007	SD	SD
101	029-001	PD	PD
102	029-002	SD	SD
103	029-003	PD	PD
104	029-004	SD	PR
105	031-001	PD	SD

Best Response in RP-Final (n=141)

Obs	CNOPATNO	Sponsor	Investigator
106	031-003	SD	PD
107	031-004	SD	SD
108	031-005	SD	SD
109	031-006	PR	PR
110	034-001	PR	PR
111	034-002	PD	PD
112	034-003	PD	PD
113	034-005	PR	PR
114	034-006	PD	SD
115	034-007	PD	PD
116	034-008	SD	SD
117	034-009	SD	PR
118	034-011	PD	SD
119	034-012	PR	PR
120	034-013	PR	PR
121	035-001		PD
122	038-001	PR	SD
123	038-002	SD	SD
124	038-003	SD	SD
125	039-001	PD	PD
126	041-001	PR	PR
127	041-002	PD	PD
128	041-003	PR	PR
129	041-004	SD	SD
130	042-001	SD	SD
131	042-002	PD	PD
132	042-003	CR	PR
133	042-004	PR	SD
134	043-001	PD	PD
135	043-002	PR	PR
136	048-001	SD	PR
137	049-001	PR	PR
138	049-002	PR	PR
139	049-003	PD	SD

Best Response in RP-Final (n=141)

Obs	CNOPATNO	Sponsor	Investigator
140	049-004	PR	PR
141	049-005	CR	CR

Cross-Tabulation of Sponsor-Derived and Investigator-Determined Best Response

The *FREQ* Procedure

Table of bresp_sp by bresp_inv							
bresp_sp (Best Response - Sponsor Derived)	bresp_inv (Best Response - Investigator Determined)						
Frequency Percent Row Pct Col Pct		CR	CRu	PD	PR	SD	Total
	1	1	0	9	0	1	12
	0.71	0.71	0.00	6.38	0.00	0.71	8.51
	8.33	8.33	0.00	75.00	0.00	8.33	
	100.00	12.50	0.00	24.32	0.00	2.17	
CR	0	5	1	0	3	0	9
	0.00	3.55	0.71	0.00	2.13	0.00	6.38
	0.00	55.56	11.11	0.00	33.33	0.00	
	0.00	62.50	33.33	0.00	6.52	0.00	
CRu	0	1	1	0	0	0	2
	0.00	0.71	0.71	0.00	0.00	0.00	1.42
	0.00	50.00	50.00	0.00	0.00	0.00	
	0.00	12.50	33.33	0.00	0.00	0.00	
PD	0	0	0	21	3	11	35
	0.00	0.00	0.00	14.89	2.13	7.80	24.82
	0.00	0.00	0.00	60.00	8.57	31.43	
	0.00	0.00	0.00	56.76	6.52	23.91	
PR	0	1	1	1	29	4	36
	0.00	0.71	0.71	0.71	20.57	2.84	25.53
	0.00	2.78	2.78	2.78	80.56	11.11	
	0.00	12.50	33.33	2.70	63.04	8.70	
SD	0	0	0	6	11	30	47
	0.00	0.00	0.00	4.26	7.80	21.28	33.33
	0.00	0.00	0.00	12.77	23.40	63.83	
	0.00	0.00	0.00	16.22	23.91	65.22	
Total	1	8	3	37	46	46	141
	0.71	5.67	2.13	26.24	32.62	32.62	100.00

Note: bresp_sp = _bresp in the KEYEFF data set with rpfinal=1 and tsource='WC2'
 bresp_inv = _bresp in the KEYEFF data set with rpfinal=1 and tsource='BOX'

Ko, Chia-wen (Kiki)

From: Ko, Chia-wen (Kiki)
Sent: Tuesday, September 19, 2006 4:26 PM
to: Brent-Steele, Tammie
Cc: Kane, Robert; Ko, Chia-wen (Kiki)
Subject: NDA 21602 - two questions need clarifications from the sponsor

Attachments: response_compare.rtf

Dear Tammie,

Could you kindly forward my two questions to the Millennium for NDA 21602?

Question 1: Table 11-1 of the M34103-053 study report indicates there were 12 subjects in the RP-final population without any post-baseline assessment. However, by RP-final definition, anyone in this population should have at least one post-baseline assessment. Please clarify.

Question 2: Please refer to the attached document for comparison of sponsor-derived and investigator-determined best responses for RP-Final population. It appears that there were discrepancies in best response determination between the two methods. Do you have any clarifications or explanations?



response_compare.
rtf (230 KB)

Thanks so much,

Chia-Wen Ko (Kiki)
Math Stat
DBV/OB/CDER/FDA
WO22, RM1221
10903 New Hampshire Ave, Silver Spring, MD 20993
301-796-2058

Best Response in RP-Final (n=141)

Obs	CNOPATNO	Sponsor	Investigator
1	001-001		PD
2	001-002	SD	PR
3	001-003	SD	PR
4	001-004	CR	CR
5	001-005	SD	SD
6	001-006	SD	SD
7	001-007	SD	PR
8	001-008	SD	SD
9	001-009	SD	PD
10	001-010	SD	PD
11	002-001	PR	PD
12	002-002	CR	PR
13	002-003	PD	PD
14	003-001	PD	PD
15	004-001	SD	PR
16	004-002	PR	PR
17	004-003		PD
18	004-004	SD	SD
19	004-005	PD	SD
20	004-006	SD	PD
21	006-002	CR	CR
22	006-003	CR	CRu
23	006-004	SD	PR
24	006-005		
25	006-006	PR	PR
26	007-001	SD	SD
27	007-003	PR	PR
28	007-004	PR	PR
29	007-005	SD	SD
30	007-006		PD
31	007-008	PD	SD
32	008-001	CR	CR
33	009-001	PR	PR
34	009-002	SD	SD
35	010-001		CR

Best Response in RP-Final (n=141)

Obs	CNOPATNO	Sponsor	Investigator
36	010-002	PR	PR
37	010-003	CR	CR
38	010-005	PR	PR
39	010-006	PD	PD
40	010-007	PR	SD
41	010-008	SD	PR
42	010-009	PD	PD
43	011-001	CRu	CRu
44	011-002		PD
45	011-003	PD	SD
46	011-004	PR	PR
47	011-005	SD	SD
48	011-006	PD	PD
49	011-008	SD	SD
50	012-001	SD	SD
51	012-003	PR	SD
52	012-004	PD	PR
53	012-005	PR	PR
54	013-001	PD	PD
55	013-002		PD
56	013-003	PD	PD
57	013-004	SD	SD
58	013-005	PD	SD
59	013-006	SD	SD
60	014-002	PD	PR
61	014-003	PD	SD
62	014-004	PR	CR
63	014-005	CRu	CR
64	015-001	PR	PR
65	015-002	SD	SD
66	015-003	PR	PR
67	015-004	CR	PR
68	017-001	PR	PR
69	018-001	PR	CRu
70	018-002		PD

Best Response in RP-Final (n=141)

Obs	CNOPATNO	Sponsor	Investigator
71	018-003	PD	PD
72	018-004	PD	SD
73	018-005	PD	PD
74	019-001	PR	PR
75	019-002	SD	SD
76	019-003	SD	SD
77	020-001	SD	PD
78	020-002	SD	SD
79	020-003	PD	PR
80	020-005	SD	SD
81	021-001	SD	SD
82	021-002	SD	SD
83	022-001	PR	PR
84	022-002	SD	SD
85	023-001	PD	PD
86	024-001	PR	PR
87	024-002	SD	PR
88	024-004	PR	PR
89	027-001	SD	PR
90	027-002		PD
91	027-003		PD
92	027-004	PD	PD
93	027-005	SD	SD
94	027-006	PR	PR
95	027-008		SD
96	027-009	PD	PD
97	028-002	PD	SD
98	028-003	PR	PR
99	028-005	SD	PD
100	028-007	SD	SD
101	029-001	PD	PD
102	029-002	SD	SD
103	029-003	PD	PD
104	029-004	SD	PR
105	031-001	PD	SD

Best Response in RP-Final (n=141)

Obs	CNOPATNO	Sponsor	Investigator
106	031-003	SD	PD
107	031-004	SD	SD
108	031-005	SD	SD
109	031-006	PR	PR
110	034-001	PR	PR
111	034-002	PD	PD
112	034-003	PD	PD
113	034-005	PR	PR
114	034-006	PD	SD
115	034-007	PD	PD
116	034-008	SD	SD
117	034-009	SD	PR
118	034-011	PD	SD
119	034-012	PR	PR
120	034-013	PR	PR
121	035-001		PD
122	038-001	PR	SD
123	038-002	SD	SD
124	038-003	SD	SD
125	039-001	PD	PD
126	041-001	PR	PR
127	041-002	PD	PD
128	041-003	PR	PR
129	041-004	SD	SD
130	042-001	SD	SD
131	042-002	PD	PD
132	042-003	CR	PR
133	042-004	PR	SD
134	043-001	PD	PD
135	043-002	PR	PR
136	048-001	SD	PR
137	049-001	PR	PR
138	049-002	PR	PR
139	049-003	PD	SD

Best Response in RP-Final (n=141)

Obs	CNOPATNO	Sponsor	Investigator
140	049-004	PR	PR
141	049-005	CR	CR

Cross-Tabulation of Sponsor-Derived and Investigator-Determined Best Response

Table of bresp_sp by bresp_inv							
bresp_sp (Best Response - Sponsor Derived)	bresp_inv (Best Response - Investigator Determined)						Total
	CR	CRu	PD	PR	SD		
Frequency Percent Row Pct Col Pct							
	1 0.71 8.33 100.00	1 0.71 8.33 12.50	0 0.00 0.00 0.00	9 6.38 75.00 24.32	0 0.00 0.00 0.00	1 0.71 8.33 2.17	12 8.51
CR	0 0.00 0.00 0.00	5 3.55 55.56 62.50	1 0.71 11.11 33.33	0 0.00 0.00 0.00	3 2.13 33.33 6.52	0 0.00 0.00 0.00	9 6.38
CRu	0 0.00 0.00 0.00	1 0.71 50.00 12.50	1 0.71 50.00 33.33	0 0.00 0.00 0.00	0 0.00 0.00 0.00	0 0.00 0.00 0.00	2 1.42
PD	0 0.00 0.00 0.00	0 0.00 0.00 0.00	0 0.00 0.00 0.00	21 14.89 60.00 56.76	3 2.13 8.57 6.52	11 7.80 31.43 23.91	35 24.82
PR	0 0.00 0.00 0.00	1 0.71 2.78 12.50	1 0.71 2.78 33.33	1 0.71 2.78 2.70	29 20.57 80.56 63.04	4 2.84 11.11 8.70	36 25.53
SD	0 0.00 0.00 0.00	0 0.00 0.00 0.00	0 0.00 0.00 0.00	6 4.26 12.77 16.22	11 7.80 23.40 23.91	30 21.28 63.83 65.22	47 33.33
Total	1 0.71	8 5.67	3 2.13	37 26.24	46 32.62	46 32.62	141 100.00

Note: bresp_sp = _bresp in the KEYEFF data set with rpfinal=1 and tsource='WC2'
 bresp_inv = _bresp in the KEYEFF data set with rpfinal=1 and tsource='BOX'

Brent-Steele, Tammie

From: Pease, Dorothy W
Sent: Tuesday, September 05, 2006 8:45 AM
To: Clifford, Johanna; Kane, Robert; Brent-Steele, Tammie; Cross Jr, Frank H; Spillman, Dianne D
Subject: RE: Consultant Request sNDA 21-602 Velcade

I already forwarded the request to clear her and two others last week or the week before. There are no competing products.

Dotti

From: Clifford, Johanna
Sent: Monday, September 04, 2006 8:22 AM
To: Kane, Robert; Brent-Steele, Tammie; Pease, Dorothy W; Cross Jr, Frank H; Spillman, Dianne D
Subject: RE: Consultant Request sNDA 21-602 Velcade

She will certainly need a waiver, but it would depend on how much \$\$ she received from OSI. If you'd like to proceed, please forward and request for screening with the appropriate competings.

Thanks, Johanna

From: Kane, Robert
Sent: Thursday, August 24, 2006 11:43 AM
To: Brent-Steele, Tammie; Pease, Dorothy W; Cross Jr, Frank H; Spillman, Dianne D
Cc: Clifford, Johanna
Subject: RE: Consultant Request sNDA 21-602 Velcade

I'd say it is not. Johanna, we await the verdict on this - thanks

From: Brent-Steele, Tammie
Sent: Thursday, August 24, 2006 11:41 AM
To: Pease, Dorothy W; Cross Jr, Frank H; Spillman, Dianne D; Kane, Robert
Subject: FW: Consultant Request sNDA 21-602 Velcade

Hello,

FYI. Response from Dr. Levine attached. She has one question regarding conflict of interest as stated below. Thanks.

Tammie

From: Levine, Alexandra [mailto:alevine@usc.edu]
Sent: Thursday, August 24, 2006 11:36 AM
To: Brent-Steele, Tammie
Subject: RE: Consultant Request

Dear Tammie -

9/5/2006

I would be happy to participate. I have had no relationship with Millennium, but I did receive funding from OSI for a research grant using mitoxantrone, fludarabine, and rituxan for mantle cell lymphoma. That might be seen as a conflict, although I do not think so.

Let me know what you want to do.

Alexandra M. Levine, M.D.
Distinguished Professor of Medicine
Chief, Division of Hematology
Keck School of Medicine of USC
Medical Director, USC/Norris Cancer Hospital

From: Brent-Steele, Tammie [mailto:tammie.brentsteele@fda.hhs.gov]
Sent: Tuesday, August 22, 2006 9:48 AM
To: Levine, Alexandra
Subject: Consultant Request

Dr. Levine:

I'm a project manager in the Division of Drug Oncology Products at the FDA. Members of the Division are reviewing a supplemental NDA (sNDA) for a new indication from Millennium Pharmaceuticals, Inc. for Velcade (bortezomib) for injection in the Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

We want you to serve as a consultant during the review process of this sNDA. The due date for this sNDA is December 8, 2006. During the review process, you may be contacted by our medical officer, Dr. Robert Kane, MD.

Please contact me as soon as possible at (301) 796-1409, or via e-mail at tammie.brentsteele@fda.hhs.gov, and let me know if you are (1) interested in helping us on this project, (2) have any reason to believe that your participation on this project may be construed as a conflict of interest. If you decide to serve as our outside expert, our Advisors & Consultants Staff will contact you regarding conflict of interest (COI) screening. Once COI screening is completed, I will contact you to inform you of your clearance status and send you more information.

Thank you very much,

Tammie

Tammie Brent RN MSN
LCDR USPHS
Consumer Safety Officer/Project Manager
FDA/CDER/OND/OODP
10903 New Hampshire Ave.
Bldg 22 Rm 2161
Silver Spring MD 20993
Ph: 301-796-1409

Fax 301-796-9845

Email tammie.brentsteele@fda.hhs.gov

9/5/2006

Brent-Steele, Tammie

From: Kane, Robert
Sent: Tuesday, September 05, 2006 8:28 AM
To: Clifford, Johanna; Brent-Steele, Tammie; Pease, Dorothy W; Cross Jr, Frank H; Spillman, Dianne D
Subject: RE: Consultant Request sNDA 21-602 Velcade

please proceed

From: Clifford, Johanna
Sent: Monday, September 04, 2006 8:22 AM
To: Kane, Robert; Brent-Steele, Tammie; Pease, Dorothy W; Cross Jr, Frank H; Spillman, Dianne D
Subject: RE: Consultant Request sNDA 21-602 Velcade

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Sent: Thursday, August 24, 2006 11:43 AM
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Cc: Clifford, Johanna
Subject: RE: Consultant Request sNDA 21-602 Velcade

I'd say it is not. Johanna, we await the verdict on this - thanks

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Sent: Thursday, August 24, 2006 11:41 AM
To: Pease, Dorothy W; Cross Jr, Frank H; Spillman, Dianne D; Kane, Robert
Subject: FW: Consultant Request sNDA 21-602 Velcade

Hello,

FYI. Response from Dr. Levine attached. She has one question regarding conflict of interest as stated below. Thanks.

Tammie

From: Levine, Alexandra [mailto:alevine@usc.edu]
Sent: Thursday, August 24, 2006 11:36 AM
To: Brent-Steele, Tammie
Subject: RE: Consultant Request

Dear Tammie -

I would be happy to participate. I have had no relationship with Millennium, but I did receive funding from OSI for a research grant using mitoxantrone, fludarabine, and rituxan for mantle cell lymphoma. That might be seen as a conflict, although I do not think so.

Let me know what you want to do.

Alexandra M. Levine, M.D.
Distinguished Professor of Medicine
Chief, Division of Hematology
Keck School of Medicine of USC
Medical Director, USC/Norris Cancer Hospital

From: Brent-Steele, Tammie [mailto:tammie.brentsteele@fda.hhs.gov]
Sent: Tuesday, August 22, 2006 9:48 AM
To: Levine, Alexandra
Subject: Consultant Request

Dr. Levine:

I'm a project manager in the Division of Drug Oncology Products at the FDA. Members of the Division are reviewing a supplemental NDA (sNDA) for a new indication from Millennium Pharmaceuticals, Inc. for Velcade (bortezomib) for injection in the Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

We want you to serve as a consultant during the review process of this sNDA. The due date for this sNDA is December 8, 2006. During the review process, you may be contacted by our medical officer, Dr. Robert Kane, MD.

Please contact me as soon as possible at (301) 796-1409, or via e-mail at tammie.brentsteele@fda.hhs.gov, and let me know if you are (1) interested in helping us on this project, (2) have any reason to believe that your participation on this project may be construed as a conflict of interest. If you decide to serve as our outside expert, our Advisors & Consultants Staff will contact you regarding conflict of interest (COI) screening. Once COI screening is completed, I will contact you to inform you of your clearance status and send you more information.

Thank you very much,

Tammie

Tammie Brent RN MSN
LCDR USPHS
Consumer Safety Officer/Project Manager
FDA/CDER/OND/OODP
10903 New Hampshire Ave.
Bldg 22 Rm 2161
Silver Spring MD 20993
Ph: 301-796-1409
Fax 301-796-9845
Email tammie.brentsteele@fda.hhs.gov

Brent-Steele, Tammie

From: Pease, Dorothy W
Sent: Monday, August 28, 2006 12:25 PM
To: Clifford, Johanna; Somers, Karen M
Cc: Spillman, Dianne D; Brent-Steele, Tammie
Subject: FW: COI, Schwartz, Velcade, sNDA 21-602 serial number 010

Attachments: FW: Consultant Request sNDA 21-602 Velcade; COI for ODAC Consultants Levine and Hussein, Velcade, sNDA 21-602/010

There are no competing products for this indication.

Please see also attached e-mail for two other consultants for this project (Levine and Hussein) as well as an e-mail from Levine re: possible conflict.

Thanks



FW: Consultant Request sNDA 21...
COI for ODAC Consultants Levin...

Dotti

From: Brent-Steele, Tammie
Sent: Monday, August 21, 2006 3:29 PM
To: Pease, Dorothy W; Cross Jr, Frank H; Spillman, Dianne D
Subject: COI, Schwartz, Velcade, sNDA 21-602 serial number 010

Hi Dotti, Frank and Dianne,

I'm sending this email to get clearance to use following patient consultant:

Karl Schwartz
3774 Buckwampum Road
Springfield Township, Bucks County
Riegelsville, PA 18077
610-346-8419
F 801-409-5736
karls@lymphomation.org

There is no meeting type, the consultant needs to be on hand for consultation during the sNDA review process.

sNDA: 21-602 serial number 010

Drug: Velcade (bortezomib) for injection

Sponsor: Millennium Pharmaceutical, Inc.

Indication: Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy

Competing Products:

Reviewing MO: Bob Kane, MD

Med. Team Lead: Ramzi Dagher, MD

Project Manager: Tammie Brent

Thanks,
Tammie

Brent-Steele, Tammie

From: Brent-Steele, Tammie
Sent: Thursday, August 24, 2006 11:41 AM
To: Pease, Dorothy W; Cross Jr, Frank H; Spillman, Dianne D; Kane, Robert
Subject: FW: Consultant Request sNDA 21-602 Velcade

Hello,

FYI. Response from Dr. Levine attached. She has one question regarding conflict of interest as stated below. Thanks.

Tammie

From: Levine, Alexandra [mailto:alevine@usc.edu]
Sent: Thursday, August 24, 2006 11:36 AM
To: Brent-Steele, Tammie
Subject: RE: Consultant Request

Dear Tammie -

I would be happy to participate. I have had no relationship with Millennium, but I did receive funding from OSI for a research grant using mitoxantrone, fludarabine, and rituxan for mantle cell lymphoma. That might be seen as a conflict, although I do not think so.

Let me know what you want to do.

Alexandra M. Levine, M.D.
Distinguished Professor of Medicine
Chief, Division of Hematology
Keck School of Medicine of USC
Medical Director, USC/Norris Cancer Hospital

From: Brent-Steele, Tammie [mailto:tammie.brentsteele@fda.hhs.gov]
Sent: Tuesday, August 22, 2006 9:48 AM
To: Levine, Alexandra
Subject: Consultant Request

Dr. Levine:

I'm a project manager in the Division of Drug Oncology Products at the FDA. Members of the Division are reviewing a supplemental NDA (sNDA) for a new indication from Millennium Pharmaceuticals, Inc. for Velcade (bortezomib) for injection in the Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

We want you to serve as a consultant during the review process of this sNDA. The due date for this sNDA is December 8, 2006. During the review process, you may be contacted by our medical officer, Dr. Robert Kane, MD.

8/28/2006

Please contact me as soon as possible at (301) 796-1409, or via e-mail at tammie.brentsteele@fda.hhs.gov, and let me know if you are (1) interested in helping us on this project, (2) have any reason to believe that your participation on this project may be construed as a conflict of interest. If you decide to serve as our outside expert, our Advisors & Consultants Staff will contact you regarding conflict of interest (COI) screening. Once COI screening is completed, I will contact you to inform you of your clearance status and send you more information.

Thank you very much,

Tammie

Tammie Brent RN MSN
LCDR USPHS
Consumer Safety Officer/Project Manager
FDA/CDER/OND/OODP
10903 New Hampshire Ave.
Bldg 22 Rm 2161
Silver Spring MD 20993
Ph: 301-796-1409
Fax 301-796-9845
Email tammie.brentsteele@fda.hhs.gov

8/28/2006

Brent-Steele, Tammie

Dog + Pony

Subject: SPON PRESENTATION/sNDA 21-602/010 Millennium Velcade DDOP (Kane) TB
Location: CDER OODP MEETING CALENDAR; CDER WO 1309 conf rm Bldg22

Start: Wed 8/23/2006 2:00 PM
End: Wed 8/23/2006 3:00 PM

Recurrence: (none)

Meeting Status: Meeting organizer

Required Attendees: ~~Brent-Steele, Tammie; Justice, Robert; Farrell, Ann T; Dagher, Ramzi; Kane, Robert; Morse, David E; Girdhara, Rajeshwari; Ko, Chia-wen (Kiki); Abraham, Sophia; Booth, Brian P; Patel, Hasmukh B; Jimenez, Valerie~~

Optional Attendees: Grillo, Joseph; Johnson, J Lloyd; Dempsey, Mary; Lu, Susan; Pratt, Robert; Weiss, Karen; Pazdur, Richard; Ball, Leslie; Brown, Tiffany; Mills, George; Rieves, Rafel; Kress, Scheldon; Stinson, Barbara; Mcfadden, Emily; Spillman, Dianne D; CDER 150 Calendar; Gorovets, Alex; Verbois, Leigh

Resources: CDER OODP MEETING CALENDAR; CDER WO 1309 conf rm Bldg22

FYI Attendees: J. Grillo, J. L. Lloyd, M. Dempsey, S. Lu, R. Pratt, K. Weiss, R. Pazdur, L. Ball, H. Patel, V. Jimenez, T. Brown, G. Mills, R. Rieves, S. Kress, B. Stinson, E. McFadden, D. Spillman

Product: Velcade (bortezomib)

Indication: Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy

Purpose: Sponsor presentation for efficacy supplement 21-602/010

MO: Kane

SPONSOR: August 23, 2006, 2:00 pm - 3:00 pm, WO 1309 In-Person

If you have any questions, contact the Regulatory Project Manager, Tammie Brent-Steele at 301-796-1409.

Brent-Steele, Tammie

From: Brent-Steele, Tammie
Sent: Wednesday, August 23, 2006 1:33 PM
To: Pease, Dorothy W; Cross Jr, Frank H; Spillman, Dianne D
Subject: COI for ODAC Consultants Levine and Hussein, Velcade, sNDA 21-602/010

Hello,

I have two ODAC consultants that need clearance.

Dr. Maha Hussein

Maha Hussain, M.D., FACP
Professor of Medicine & Urology
7314 CCGC
University of Michigan Comprehensive
Cancer Center
1500 E. Medical Center Dr.
Ann Arbor, MI 48109-0946
tel: 734-936-8906
Fax: 734-615-2719

Dr. Alexandra Levine

Alexandra M. Levine, M.D.
Medical Director
USC/Norris Cancer Hospital
Division of Hematology, MS34
1441 Eastlake Avenue
Los Angeles, CA 90033
Phone 323-865-3913
alevine@usc.edu

No meeting scheduled, but will need to be available to be contacted by our review team during the review time. Due date 12-8-06

NDA: 21-602

Drug: Velcade (bortezomib) for Injection

Sponsor: Millennium Pharmaceuticals, Inc.

Indication: Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy

Competing Products:

Reviewing MO: Bob Kane

Med. Team Lead: Ramzi Dagher

Project Manager: Tammie Brent

Brent-Steele, Tammie

To: Minor, Joann M
cc: Spillman, Dianne D; Pease, Dorothy W
Subject: Request for Patient Consultant for sNDA 21-602 sn 010

Hi Joann,

I need to request a patient consultant for the following sNDA:

Drug: Velcade

Sponsor: Millennium Pharmaceuticals, Inc.

Indication: Treatment of Patients with mantle cell lymphoma who have received at least one prior therapy

The filing meeting was held on August 2, 2006 and the application was filed as a priority review with a due date of 12/8/06.

Please let me know if you need other information.

Thanks very much,
Tammie

Tammie Brent-Steele RN MSN
LCDR USPHS
Consumer Safety Officer/Project Manager
FDA/CDER/OND/OODP
10903 New Hampshire Ave.
Bldg 22 Rm 2161
Silver Spring MD 20993
h: 301-796-1409
Fax 301-796-9845
Email tammie.brentsteele@fda.hhs.gov

Brent-Steele, Tammie

From: Minor, Joann M
Sent: Friday, August 18, 2006 2:20 PM
To: Brent-Steele, Tammie
Subject: RE: Request for patient consultant

Hi Tammie,

Here is our patient consultant --- I talked with him and he has agreed to be the PC:

Karl Schwartz\3774 Buckwampum Road
Springfield Township, Bucks County
Riegelsville, PA 18077
610-346-8419
F 801-409-5736
karls@lymphomation.org

JoAnn

From: Brent-Steele, Tammie
Sent: Friday, August 18, 2006 11:31 AM
To: Minor, Joann M
Subject: Request for patient consultant

Hi Joann,

I need to request a patient consultant regarding the following information:

Submission: sNDA 21-602 serial number 010. This is supplement for the new indication, "Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

Drug: Velcade (bortezomib) for Injection

We don't have a specific meeting set up, however, would like to have a patient consultant available for consultation during the review time for this sNDA. The due date is December 8, 2006.

Please let me know what other information you need.

Thank you and have a great weekend.

Tammie
Tammie Brent-Steele RN MSN
LCDR USPHS
Consumer Safety Officer/Project Manager
FDA/CDER/OND/OODP
10903 New Hampshire Ave.
Bldg 22 Rm 2161
Silver Spring MD 20993
Ph: 301-796-1409
Fax 301-796-9845
Email tammie.brentsteele@fda.hhs.gov

Brent-Steele, Tammie

From: Pease, Dorothy W
Sent: Thursday, August 24, 2006 9:12 AM
To: Brent-Steele, Tammie
Subject: RE: COI for ODAC Consultants Levine and Hussein, Velcade, sNDA 21-602/010

Sorry, I see your e-mail is correct already. Once we get the competing products on Monday, I will forward all three consultants (Levine, Hussein, and Schwartz) to ACS at the same time.

Thanks

Dotti

From: Brent-Steele, Tammie
Sent: Wednesday, August 23, 2006 1:33 PM
To: Pease, Dorothy W; Cross Jr, Frank H; Spillman, Dianne D
Subject: COI for ODAC Consultants Levine and Hussein, Velcade, sNDA 21-602/010

Hello,

I have two ODAC consultants that need clearance.

Dr. Maha Hussein

Maha Hussain, M.D., FACP
Professor of Medicine & Urology
7314 CCGC
University of Michigan Comprehensive
Cancer Center
1500 E. Medical Center Dr.
Ann Arbor, MI 48109-0946
tel: 734-936-8906
Fax: 734-615-2719

Dr. Alexandra Levine

Alexandra M. Levine, M.D.
Medical Director
USC/Norris Cancer Hospital
Division of Hematology, MS34
1441 Eastlake Avenue
Los Angeles, CA 90033
Phone 323-865-3913
alevine@usc.edu

No meeting scheduled, but will need to be available to be contacted by our review team during the review time. Due date 12-8-06

NDA: 21-602

Drug: Velcade (bortezomib) for Injection

Sponsor: Millennium Pharmaceuticals, Inc.

Indication: Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy

Competing Products:

Reviewing MO: Bob Kane

Med. Team Lead: Ramzi Dagher

Project Manager: Tammie Brent

Brent-Steele, Tammie

From: Levine, Alexandra [alevine@usc.edu]
Sent: Thursday, August 24, 2006 11:36 AM
To: Brent-Steele, Tammie
Subject: RE: Consultant Request

Dear Tammie -

I would be happy to participate. I have had no relationship with Millennium, but I did receive funding from OSI for a research grant using mitoxantrone, fludarabine, and rituxan for mantle cell lymphoma. That might be seen as a conflict, although I do not think so.

Let me know what you want to do.

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Distinguished Professor of Medicine
Chief, Division of Hematology
Keck School of Medicine of USC
Medical Director, USC/Norris Cancer Hospital

From: Brent-Steele, Tammie [mailto:tammie.brentsteele@fda.hhs.gov]
Sent: Tuesday, August 22, 2006 9:48 AM
To: Levine, Alexandra
Subject: Consultant Request

Dr. Levine:

I'm a project manager in the Division of Drug Oncology Products at the FDA. Members of the Division are reviewing a supplemental NDA (sNDA) for a new indication from Millennium Pharmaceuticals, Inc. for Velcade (bortezomib) for injection in the Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

We want you to serve as a consultant during the review process of this sNDA. The due date for this sNDA is December 8, 2006. During the review process, you may be contacted by our medical officer, Dr. Robert Kane, MD.

Please contact me as soon as possible at (301) 796-1409, or via e-mail at tammie.brentsteele@fda.hhs.gov, and let me know if you are (1) interested in helping us on this project, (2) have any reason to believe that your participation on this project may be construed as a conflict of interest. If you decide to serve as our outside expert, our Advisors & Consultants Staff will contact you regarding conflict of interest (COI) screening. Once COI screening is completed, I will contact you to inform you of your clearance status and send you more information.

Thank you very much,

Tammie

8/24/2006

Tammie Brent RN MSN
LCDR USPHS
Consumer Safety Officer/Project Manager
FDA/CDER/OND/OODP
10903 New Hampshire Ave.
Bldg 22 Rm 2161
Silver Spring MD 20993
Ph: 301-796-1409
Fax 301-796-9845
Email tammie.brentsteele@fda.hhs.gov

Brent-Steele, Tammie

To: mahahuss@umich.edu
Subject: Consultant Request

Dr. Hussein,

I'm a project manager in the Division of Drug Oncology Products at the FDA. Members of the Division are reviewing a supplemental NDA (sNDA) for a new indication from Millennium Pharmaceuticals, Inc. for Velcade (bortezomib) for injection in the Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

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Please contact me as soon as possible at (301) 796-1409, or via e-mail at tammie.brentsteele@fda.hhs.gov, and let me know if you are (1) interested in helping us on this project, (2) have any reason to believe that your participation on this project may be construed as a conflict of interest. If you decide to serve as our outside expert, our Advisors & Consultants Staff will contact you regarding conflict of interest (COI) screening. Once COI screening is completed, I will contact you to inform you of your clearance status and send you more information.

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Tammie

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LCDR USPHS
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Silver Spring MD 20993
Ph: 301-796-1409
Fax 301-796-9845
Email tammie.brentsteele@fda.hhs.gov

Brent-Steele, Tammie

From: Maha Hussain [mahahuss@med.umich.edu]
Sent: Tuesday, August 22, 2006 2:04 PM
To: Brent-Steele, Tammie
Cc: Karen Akans
Subject: Re: Consultant Request

Sure, will be happy to
m

"Electronic Mail is not secure, may not be read every day, and should not be used for urgent or sensitive issues."

Maha Hussain, M.D., FACP
Professor of Medicine & Urology
7314 CCGC
University of Michigan Comprehensive
Cancer Center
1500 E. Medical Center Dr.
Ann Arbor, MI 48109-0946
tel: 734-936-8906
Fax: 734-615-2719

>>> "Brent-Steele, Tammie" <tammie.brentsteele@fda.hhs.gov> 8/22/2006
12:45 PM >>>

Dr. Hussein,

I'm a project manager in the Division of Drug Oncology Products at the FDA. Members of the Division are reviewing a supplemental NDA (sNDA) for a new indication from Millennium Pharmaceuticals, Inc. for Velcade (bortezomib) for injection in the Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

We want you to serve as a consultant during the review process of this sNDA. The due date for this sNDA is December 8, 2006. During the review process, you may be contacted by our medical officer, Dr. Robert Kane, MD.

Please contact me as soon as possible at (301) 796-1409, or via e-mail at tammie.brentsteele@fda.hhs.gov, and let me know if you are (1) interested in helping us on this project, (2) have any reason to believe that your participation on this project may be construed as a conflict of interest. If you decide to serve as our outside expert, our Advisors & Consultants Staff will contact you regarding conflict of interest (COI) screening. Once COI screening is completed, I will contact you to inform you of your clearance status and send you more information.

Thank you very much,

Tammie

Tammie Brent RN MSN
LCDR USPHS
Consumer Safety Officer/Project Manager
FDA/CDER/OND/OODP
10903 New Hampshire Ave.
Bldg 22 Rm 2161
Silver Spring MD 20993
Ph: 301-796-1409
Fax 301-796-9845
Email tammie.brentsteele@fda.hhs.gov

Electronic Mail is not secure, may not be read every day, and should not be used for urgent or sensitive issues.

Brent-Steele, Tammie

To: Pease, Dorothy W; Cross Jr, Frank H; Spillman, Dianne D
Subject: COI for ODAC Consultants Levine and Hussein, Velcade, sNDA 21-602/010

Hello,

I have two ODAC consultants that need clearance.

Dr. Maha Hussein

Maha Hussain, M.D., FACP
Professor of Medicine & Urology
7314 CCGC
University of Michigan Comprehensive
Cancer Center
1500 E. Medical Center Dr.
Ann Arbor, MI 48109-0946
tel: 734-936-8906
Fax: 734-615-2719

Dr. Alexandra Levine

Alexandra M. Levine, M.D.
Medical Director
USC/Norris Cancer Hospital
Division of Hematology, MS34
1441 Eastlake Avenue
Los Angeles, CA 90033
Phone 323-865-3913
levine@usc.edu

No meeting scheduled, but will need to be available to be contacted by our review team during the review time. Due date 12-8-06

NDA: 21-602

Drug: Velcade (bortezomib) for Injection

Sponsor: Millennium Pharmaceuticals, Inc.

Indication: Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy

Competing Products:

Reviewing MO: Bob Kane

Med. Team Lead: Ramzi Dagher

Project Manager: Tammie Brent

Brent-Steele, Tammie

From: Minor, Joann M
Sent: Friday, August 18, 2006 2:20 PM
To: Brent-Steele, Tammie
Subject: RE: Request for patient consultant

Hi Tammie,

Here is our patient consultant --- I talked with him and he has agreed to be the PC:

Karl Schwartz\3774 Buckwampum Road
Springfield Township, Bucks County
Riegelsville, PA 18077
610-346-8419
F 801-409-5736
karls@lymphomation.org

JoAnn

From: Brent-Steele, Tammie
Sent: Friday, August 18, 2006 11:31 AM
To: Minor, Joann M
Subject: Request for patient consultant

Hi Joann,

I need to request a patient consultant regarding the following information:

Submission: sNDA 21-602 serial number 010. This is supplement for the new indication, "Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

Drug: Velcade (bortezomib) for Injection

We don't have a specific meeting set up, however, would like to have a patient consultant available for consultation during the review time for this sNDA. The due date is December 8, 2006.

Please let me know what other information you need.

Thank you and have a great weekend.

Tammie
Tammie Brent-Steele RN MSN
LCDR USPHS
Consumer Safety Officer/Project Manager
FDA/CDER/OND/OODP
10903 New Hampshire Ave.
Bldg 22 Rm 2161
Silver Spring MD 20993
Ph: 301-796-1409
Fax 301-796-9845
Email tammie.brentsteele@fda.hhs.gov

Brent-Steele, Tammie

To: alevine@usc.edu
subject: Consultant Request

Dr. Levine:

I'm a project manager in the Division of Drug Oncology Products at the FDA. Members of the Division are reviewing a supplemental NDA (sNDA) for a new indication from Millennium Pharmaceuticals, Inc. for Velcade (bortezomib) for injection in the Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

We want you to serve as a consultant during the review process of this sNDA. The due date for this sNDA is December 8, 2006. During the review process, you may be contacted by our medical officer, Dr. Robert Kane, MD.

Please contact me as soon as possible at (301) 796-1409, or via e-mail at tammie.brentsteele@fda.hhs.gov, and let me know if you are (1) interested in helping us on this project, (2) have any reason to believe that your participation on this project may be construed as a conflict of interest. If you decide to serve as our outside expert, our Advisors & Consultants Staff will contact you regarding conflict of interest (COI) screening. Once COI screening is completed, I will contact you to inform you of your clearance status and send you more information.

Thank you very much,

Tammie

Tammie Brent RN MSN
LCDR USPHS
Consumer Safety Officer/Project Manager
FDA/CDER/OND/OODP
10903 New Hampshire Ave.
Bldg 22 Rm 2161
Silver Spring MD 20993
Ph: 301-796-1409
Fax 301-796-9845
Email tammie.brentsteele@fda.hhs.gov

Brent-Steele, Tammie

To: Kane, Robert; Dagher, Ramzi
Subject: DSI Inspection Request sNDA 21-602/010 Velcade

Attachments: DSI Inspection Request.doc

Hi Bob and Ramzi,

Attached please find a DSI Inspection Request memo for sNDA 21-602/010 for your review and completion. Please let me know if you have any questions, or if I need to correct anything, as this is the first one I've done.

Thanks very much,
Tammie



DSI Inspection
Request.doc (49...

Brent-Steele, Tammie

From: Pratt, Robert
Sent: Wednesday, August 16, 2006 1:17 PM
To: Brent-Steele, Tammie
Cc: Rouine, Jennifer; Lu, Susan
Subject: Declined: INTMTG Team/Labeling #1 Velcade NDA 21-602/SE1 010 Millennium DDOP TB (Kane)

Hi Tammie,

Would you please remove me from the Velcade distribution list and add Jennifer Rouine? She's the SE now covering the drug.

Thanks,

Bob

Done 8-16-06

Brent-Steele, Tammie

From: Lu, Susan
Sent: Wednesday, August 16, 2006 1:06 PM
To: Brent-Steele, Tammie
Cc: Rouine, Jennifer
Subject: Declined: INTMTG Team/Labeling #1 Velcade NDA 21-602/SE1 010 Millennium DDOP TB (Kane)

Hi Tammie,

I'll be out of the office 9/22 and cannot attend.

Velcade has been reassigned from Bob Pratt to Jennifer Rouine Steele (rouinej). Please include Jennifer on future distribution lists for Velcade related meetings and consults. Thanks-

Sue

Done 8-16-06.

DSI CONSULT: Request for Clinical Inspections

Date: August 10, 2006

To: Constance Lewin, M.D., M.P.H., Branch Chief, GCP1, HFD-46
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47
Lloyd Johnson, HFD-47

Through: Robert Justice, M.D., Director, HFD-150 (for foreign inspection requests)
Joseph Salewski, , Acting Director, DSI, HFD-45

From: Tammie Brent-Steele, Regulatory Project Manager, HFD-150
Division of Drug Oncology Products

Subject: Request for Clinical Site Inspections
NDA 21-602/S-010
Millennium Pharmaceuticals, Inc.
Velcade (bortezomib)

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

This NDA provides data for the following: new indication: Mantle Cell Lymphoma.

Site # (Name and Address)	Number of Subjects
006: Sagar Lonial, MD Emory University Winship Cancer Institute 1365-C Clifton Road Atlanta, GA, USA 30322	6 (in particular, patients 002 and 003)
049 Andre Goy, MD Hackensack University Medical Center 20 Prospect Ave Hackensack, NJ, USA 07601	5 (in particular, patient 049-005)

Request for Clinical Inspections

010 Benjamin Djulbegovic, MD, PhD H. Lee Moffitt Cancer Cntr & Research Institute 12902 Magnolia Drive Tampa, FL, USA 33612	8 (in particular, patient 003)
--	-----------------------------------

Domestic Inspections:

We have requested inspections because (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify:)
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other: SPECIFY – to confirm that source data is present and corresponds to the CRFs information

International Inspections: - NONE**Goal Date for Completion:**

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) November 9, 2006. We intend to issue an action letter on this application by (division action goal date) December 8, 2006. The PDUFA due date for this application is December 9, 2006.

Should you require any additional information, please contact Tammie Brent-Steele.

Concurrence: (if necessary)

Ramzi Dagher, MD, Medical Team Leader
Robert Kane, MD, Medical Reviewer
Robert Justice, MD, Division Director (for foreign inspection requests only)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Tammie Brent-Steele

8/16/2006 03:18:55 PM

DSI Request for Clinical Site Inspection sNDA 21-602 sn010

DSI CONSULT: Request for Clinical Inspections

Date: August 10, 2006

To: Constance Lewin, M.D., M.P.H., Branch Chief, GCP1, HFD-46
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47
Lloyd Johnson, HFD-47

Through: Robert Justice, M.D., Director, HFD-150 (for foreign inspection requests)
Joseph Salewski, , Acting Director, DSI, HFD-45

From: Tammie Brent-Steele, Regulatory Project Manager, HFD-150
Division of Drug Oncology Products

Subject: Request for Clinical Site Inspections
NDA 21-602/S-010
Millennium Pharmaceuticals, Inc.
Velcade (bortezomib)

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

This NDA provides data for the following: new indication: Mantle Cell Lymphoma.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication

Domestic Inspections:

We have requested inspections because (please check all that apply):

Enrollment of large numbers of study subjects

- High treatment responders (specify:)
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other: SPECIFY

International Inspections:

We have requested inspections because (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other: SPECIFY

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) November 9, 2006. We intend to issue an action letter on this application by (division action goal date) December 8, 2006. The PDUFA due date for this application is December 9, 2006.

Should you require any additional information, please contact Tammie Brent-Steele.

Concurrence: (if necessary)

Ramzi Dagher, MD, Medical Team Leader
Robert Kane, MD, Medical Reviewer
Robert Justice, MD, Division Director (for foreign inspection requests only)

Brent-Steele, Tammie

To: Grillo, Joseph
Subject: sNDA 21-602 sn 010 Labeling consult
Attachments: DDMAC Consult 8-10-06.doc

Hello,

Please find attached a consult for sNDA 21-602 sn 010 for Velcade, Millennium Pharmaceuticals, Inc. The submission may be found in the electronic document room. Please let me know what other information you may need.

Thank you very much,
Tammie



DDMAC Consult
8-10-06.doc (67 ...)

Tammie Brent-Steele RN MSN
LCDR USPHS
Consumer Safety Officer/Project Manager
FDA/CDER/OND/OODP
10903 New Hampshire Ave.
Bldg 22 Rm 2161
Silver Spring MD 20993
Ph: 301-796-1409
Fax 301-796-9845
Email tammie.brentsteele@fda.hhs.gov

REQUEST FOR CONSULTATION

TO (Office/Division):

DDMAC

Attention: Joseph Grillo, Pharm. D.
WO22 Rm. 1454
301-796-1200

FROM (Name, Office/Division, and Phone Number of Requestor):

Tammie Brent-Steele, Project Manager
Division of Drug Oncology Products HFD-150
WO22 Rm. 2161
301-796-1409

DATE
8/15/06

IND NO.

NDA NO.
21-602 sn: 010

TYPE OF DOCUMENT
sNDA for new indication

DATE OF DOCUMENT
6/8/06

NAME OF DRUG
Velcade (bortezomib)

PRIORITY CONSIDERATION
Priority Review

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
10/1/06

NAME OF FIRM: Millennium Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: The Division of Drug Oncology Products requests DDMAC review the proposed product labeling and any relevant advertising for this sNDA. Please see the submission in the Electronic Document Room, submission sNDA 21-602 supplement 010. PDUFA due date 12/9/06. Filed as a priority review. First team meeting mid to late September, TBA.

Clinical Reviewer: Robert Kane

Reg. Project Manager: Tammie Brent-Steele

SIGNATURE OF REQUESTOR
Tammie Brent-Steele, RN, MSN

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

	PRINTED NAME AND SIGNATURE OF DELIVERER
--	---

DMIHP Interim Consult Memorandum to the File

NDA: 21-602
Product: Velcade for mantle cell lymphoma
Sponsor: Millennium Pharmaceuticals
Today's date: August 2, 2006
DMIHP Reviewer: Scheldon Kress/Alex Gorovets/Dwaine Rieves

1. This memorandum confirms that the displayed radiographs from Study 053 are viewable and conducive to an informal inspection.
2. DMIHP is working to obtain an SGE radiologist to complete the informal inspection.
3. The displayed radiographs are not submissions to the sNDA. Hence, the displayed radiographs are not a consideration in the filing consideration for the submitted sNDA.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Rafel Rieves
8/2/2006 02:50:31 PM
MEDICAL OFFICER

Brent-Steele, Tammie

From: Kane, Robert
Sent: Monday, July 24, 2006 6:34 PM
To: Rieves, Rafel; Dagher, Ramzi; Farrell, Ann T; Brent-Steele, Tammie
Cc: Brown, Tiffany; Mills, George; Marzella, Libero; Gorovets, Alex
Subject: RE: NDA 21-602 (Velcade)

Thanks, Dwaine, my request was not as clear as it should have been -

Tammie:

(1) please request a patient listing from Millennium indicating the patient ID numbers of all patients whom they have designated as CR or CRu in the MCL study for the NDA filing August 2. Provide me and DMIHP with a copy of the list.

(2) please consult DMIHP

Purpose: The sponsor has submitted a sNDA (21-602) for MCL based on response rates and duration of response. In accordance with the previous meetings between DDOP, DMIHP, and the applicant, in which the submission process for radiographic images and related data from the independent radiologic review has been examined by DMIHP; DDOP requests DMIHP to:

- (a) determine that the imaging submission data is sufficient to allow the filing of the NDA for the filing meeting August 2.
- (b) After the filing meeting, provide a review of the submitted images and independent radiologic review data sufficient to verify that the patients which the sponsor designates as CR or CRu in fact fulfill the protocol imaging criteria for these designations.

Thank you

From: Rieves, Rafel
Sent: Monday, July 24, 2006 5:57 PM
To: Kane, Robert
Cc: Brown, Tiffany; Mills, George; Marzella, Libero; Gorovets, Alex; Brent-Steele, Tammie
Subject: FW: NDA 21-602 (Velcade)

Hey Bob,

we're trying to be sure everyone has a clear understanding of the goal of the consult....can you forward a consult request document to Tiffany summarizing specifically what's requested...perhaps Tammie can do this...

I think you're requesting a Informal Audit of the Endpoint Adjudication...in the consult document, will be useful if you can identify which patients you want examined (perhaps you only want a random sample)...we're prob going to have to clear an SGE to do the actual viewing...still, once a consulting med officer is assigned to the consult request, we can check and make sure the images are viewable (sufficient for the filing)....

Lou, Alex, this will need a consulting med officer assigned to make sure the images are viewable and to facilitate getting an SGE lined up for viewing/development of the endpoint image audit review document...thanks Dwaine

From: Brown, Tiffany
Sent: Monday, July 24, 2006 8:20 AM
To: Rieves, Rafel
Subject: FW: NDA 21-602 (Velcade)

Dr. Rieves,
Please see the email from Dr. Kane below regarding the Velcade submission.

Tiffany

Tiffany J. Brown, M.P.H

Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
301-796-2050 (phone)
301-796-9847 (fax)

From: Kane, Robert
Sent: Saturday, July 22, 2006 2:52 PM
To: Brown, Tiffany; Brent-Steele, Tammie; Stinson, Barbara
Cc: Dagher, Ramzi
Subject: RE: NDA 21-602 (Velcade)

Tiffany, a filing meeting is scheduled for 8/2 for this sNDA. DDOP requests DMIHP to review the images and sponsor's algorithm to confirm the sponsor's determination of CR and CRu patients. I believe the hard drive containing this data is already in house and the hardware was checked at a sponsor meeting in March.

Please take a peek before 8/2 to confirm for us at the filing meeting that this data can be accessed so the sNDA can be filed.

Thanks.

From: Brown, Tiffany
Sent: Friday, June 23, 2006 1:05 PM
To: Brent-Steele, Tammie
Cc: Dagher, Ramzi; Kane, Robert
Subject: NDA 21-602 (Velcade)

The Division of Medical Imaging and Hematology Products (DMIHP) is in receipt of your consult request for the following application:

NDA: 21-602

Sponsor: Millennium Pharmaceuticals, Inc. **b(4)**

CRO: _____

Drug: Velcade (bortezomib) Injection

Indication: For the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

To support and develop the NDA review process, DMIHP will work with DDOP, Millennium Pharmaceuticals and their CRO to ensure that the images associated with this application are available and formatted in an acceptable manner, if the review of the images submitted with the NDA are necessary for the Agency to review. DMIHP will request that the Sponsor/CRO confirm the required response time for the NDA submission of the images, the availability of one of the Independent imaging reviewers to review images at White Oak with DDOP and DMIHP; and the availability of technical support staff to operate the imaging submission software.

DMIHP will request the actual submission of the images and perform further consultative imaging review processes only if DDOP identifies a subset of cases that require a review of the images.

If DDOP determines that an imaging review of a specific subset is required, please inform Tiffany Brown, DMIHP RPM; and please send to DMIHP a consult defining the specific subset of cases for review and the questions to be addressed in the review.

In follow-up to DDOP's consult request, DMIHP, in conjunction with DDOP, will request the actual submission of the images to the NDA, and develop with the Sponsor/CRO a schedule for an onsite (White Oak) review of the specific imaging cases with the independent imaging reviewer.

If you have any questions, please contact me.

Sincerely,

Tiffany Brown

Tiffany J. Brown, M.P.H
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
301-796-2050 (phone)
301-796-9847 (fax)



NDA 21-602/S-010

PRIOR APPROVAL SUPPLEMENT

Millennium Pharmaceuticals, Inc.
Attention:
Tanya Lewis, M.S.
Director, Regulatory Affairs
40 Landsdowne Street
Cambridge, Massachusetts 01239

Dear Ms. Lewis:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for the following:

Name of Drug Product: Velcade (bortezomib) for Injection 3.5 mg

NDA Number: 21-602

Supplement number: 010

Review Priority Classification: Priority (P)

Date of supplement: June 8, 2006

Date of receipt: June 9, 2006

This supplemental application proposes the following change(s):

A new indication:

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

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 8, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 9, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We

NDA #-###/S-###

Page 2

note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call Tammie Brent-Steele, Regulatory Project Manager, at (301) 796-1409.

Sincerely,

{See appended electronic signature page}

Tammie Brent-Steele, RN MSN
Regulatory Project Manager
Division of Drug Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-602/S-010

Millennium Pharmaceuticals, Inc.
Attention:
Tanya Lewis, M.S.
Director, Regulatory Affairs
40 Landsdowne Street
Cambridge, Massachusetts 02139

Dear Ms. Lewis:

Please refer to your June 8, 2006 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Velcade (boortezomib) for Injection 3.5 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on August 8, 2006 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Tammie Brent-Steele, Regulatory Project Manager, at (301) 796-1409.

Sincerely,

{See appended electronic signature page}

Tammie Brent-Steele, RN MSN
Regulatory Project Manager

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Tammie Brent-Steele
8/8/2006 01:31:58 PM

Brent-Steele, Tammie

From: Pease, Dorothy W
Sent: Monday, August 07, 2006 2:33 PM
To: Brent-Steele, Tammie
Subject: RE: sNDA 21-602/010 documents for your review

Both letters are fine. I wouldn't capitalize your name or Millenium. You will be signing both letters, so you don't need to circulate them through Dr. Justice.

The filing review looks OK, but you should fill in the PDUFA goal date as 12-9-06 and correct the portion that lists the reviewers: Robert Kane is the Medical Reviewer. Sheldon Kress is the Medical Imaging Division Medical Reviewer.

Dotti

From: Brent-Steele, Tammie
Sent: Monday, August 07, 2006 12:52 PM
To: Pease, Dorothy W
Subject: sNDA 21-602/010 documents for your review

Hi Dotti,

Here are the filing review, the acknowledgement letter and the FG letter for your review for sNDA 21-602/010. I'll be leaving in a few minutes to meet the movers at my house. So, I'll make any changes tomorrow morning. Thanks very much for your help with this and for coming to my first filing meeting.

Tammie

<< File: FG 74 Day Ltr 21602-010 8-7-06.doc >> << File: sNDA 21602-010 Acknowledgement ltr 8-7-06.doc >> << File: Velcade filing review.doc >>

DMIHP Interim Consult Memorandum to the File

NDA: 21-602
Product: Velcade for mantle cell lymphoma
Sponsor: Millennium Pharmaceuticals
Today's date: August 2, 2006
DMIHP Reviewer: Scheldon Kress/Alex Gorovets/Dwaine Rieves

1. This memorandum confirms that the displayed radiographs from Study 053 are viewable and conducive to an informal inspection.
2. DMIHP is working to obtain an SGE radiologist to complete the informal inspection.
3. The displayed radiographs are not submissions to the sNDA. Hence, the displayed radiographs are not a consideration in the filing consideration for the submitted.sNDA.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Rafel Rieves
8/2/2006 02:50:31 PM
MEDICAL OFFICER

Brent-Steele, Tammie

From: Gorovets, Alex
Sent: Monday, July 31, 2006 5:05 PM
To: Rieves, Rafel; Brown, Tiffany
Cc: Mills, George; Clifford, Johanna; Brent-Steele, Tammie; Kress, Scheldon; Stinson, Barbara; Gorovets, Alex
Subject: FW: sNDA 21-602/010 Patient list with ID numbers designated CR and CRu
Attachments: sNDA21-602 Patient ID List.pdf

Dwaine,

Thank you for the follow-up.

Tiffany,

Please note that Scheldon from now on is the consulting medical officer/reviewer on this project.

Thank you,

Alex

-----Original Message-----

From: Rieves, Rafel
Sent: Monday, July 31, 2006 4:31 PM
To: Kress, Scheldon; Brent-Steele, Tammie
Cc: Gorovets, Alex; Mills, George; Clifford, Johanna
Subject: FW: sNDA 21-602/010 Patient list with ID numbers designated CR and CRu

Ji Alex and Scheldon,

I was able to open and view images...now we need Scheldon to spend time familiarizing himself with this software (it is not easy--takes time and prob about a day's work going thru it)...such that he can go thru it with the SGE and generate inspection document...there are only 11 subjects with images to examine...

Tammie...we need to get an SGE cleared to do this informal inspection...can you send Scheldon and Alex a list of competing products to Velcade for this application (there may not be any)--then, Alex can you send Johanna Clifford a note with the SGE documents (request/competing products/such that we can get this going before Scheldon comes back...Tom Ju prob should be targeted as SGE/i don't think we have any other SGE's actually up to doing this sort of inspection yet...

thanks DWaine

From: Brown, Tiffany
Sent: Monday, July 31, 2006 3:41 PM
To: Rieves, Rafel; Gorovets, Alex
Subject: FW: sNDA 21-602/010 Patient list with ID numbers designated CR and CRu

FYI

Tiffany J. Brown, M.P.H
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
301-796-2050 (phone)
301-796-9849 (fax)
Email: tiffanyj.brown@fda.hhs.gov

From: Brent-Steele, Tammie

Sent: Monday, July 31, 2006 3:04 PM
To: Kane, Robert; Brown, Tiffany
Subject: sNDA 21-602/010 Patient list with ID numbers designated CR and CRu

Hi Bob and Tiffany,

Per your request Bob, please find attached the patient list with ID numbers designated CR and CRu from Millennium for sNDA 21-602 Velcade MCL study.

Tiffany, could you please let me know if there are reviewer changes? I know there has been some re-organization for you guys, so I just want to make sure I keep everyone in the loop.

Thanks very much,
Tammie



sNDA21-602
Patient ID List.pdf...

Brent-Steele, Tammie

From: Rieves, Rafel
Sent: Monday, July 31, 2006 4:31 PM
To: Kress, Scheldon; Brent-Steele, Tammie
Cc: Gorovets, Alex; Mills, George; Clifford, Johanna
Subject: FW: sNDA 21-602/010 Patient list with ID numbers designated CR and CRu

Attachments: sNDA21-602 Patient ID List.pdf

Hi Alex and Scheldon,

I was able to open and view images...now we need Scheldon to spend time familiarizing himself with this software (it is not easy--takes time and prob about a day's work going thru it)...such that he can go thru it with the SGE and generate inspection document...there are only 11 subjects with images to examine...

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thanks DWaine

From: Brown, Tiffany
Sent: Monday, July 31, 2006 3:41 PM
To: Rieves, Rafel; Gorovets, Alex
Subject: FW: sNDA 21-602/010 Patient list with ID numbers designated CR and CRu

TYI

Tiffany J. Brown, M.P.H
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
301-796-2050 (phone)
301-796-9849 (fax)
Email: tiffanyj.brown@fda.hhs.gov

From: Brent-Steele, Tammie
Sent: Monday, July 31, 2006 3:04 PM
To: Kane, Robert; Brown, Tiffany
Subject: sNDA 21-602/010 Patient list with ID numbers designated CR and CRu

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Per your request Bob, please find attached the patient list with ID numbers designated CR and CRu from Millennium for sNDA 21-602 Velcade MCL study.

Tiffany, could you please let me know if there are reviewer changes? I know there has been some re-organization for you guys, so I just want to make sure I keep everyone in the loop.

Thanks very much,
Tammie



sNDA21-602
Patient ID List.pdf...

Brent-Steele, Tammie

From: Sridhara, Rajeshwari
Sent: Thursday, July 06, 2006 10:05 AM
To: Brent-Steele, Tammie
Cc: Pease, Dorothy W; Ko, Chia-wen (Kiki)
Subject: sNDA21-602 S010

Tammie,
Chia-wen Ko has been assigned as the stat reviewer for this application. Please include her in all the meetings.
Thanks
Raji

Rajeshwari Sridhara, Ph.D.

Team Leader, DBV/OB/CDER/FDA

WO22, Rm 1210, Maildrop 1207

10903 New Hampshire Avenue, Silver Spring, MD 20993

Tel: 301-796-1759, Fax: 301-796-9912

E-mail: rajeshwari.sridhara@fda.hhs.gov

Brent-Steele, Tammie

From: Rouine, Jennifer
Sent: Monday, June 26, 2006 8:52 AM
To: Brent-Steele, Tammie
Subject: RE: INTMTG File Velcade NDA 21-602/SE1 010 Millennium DDOP TB (Kane)

Hi Tammie,

FYI: The following mtg invite was forwarded to me. I am now the OSE/DDRE Safety Evaluator for Velcade (switched to me from Bob Pratt).

Thanks.
Jennifer

Jennifer Rouine Steele, Pharm.D.
Safety Evaluator
Division of Drug Risk Evaluation
Office of Surveillance and Epidemiology
CDER/FDA
301.796.1463

From: Brent-Steele, Tammie
Sent: Friday, June 23, 2006 3:25 PM
To: Brent-Steele, Tammie; Justice, Robert; Farrell, Ann T; Dagher, Ramzi; Kane, Robert; Morse, David E; Sridhara, Rajeshwari; Abraham, Sophia; Booth, Brian P
Cc: Grillo, Joseph; Johnson, J. Lloyd; Dempsey, Mary; Lu, Susan; Pratt, Robert; Weiss, Karen; Pazdur, Richard; Ball, Leslie; Patel, Has Mukh B; Jimenez, Valerie; CDER 150 Calendar; Brown, Tiffany; Mills, George; Rieves, Rafel; Kress, Scheldon; Stinson, Barbara
Subject: INTMTG File Velcade NDA 21-602/SE1 010 Millennium DDOP TB (Kane)
When: Wednesday, August 02, 2006 3:00 PM-4:00 PM (GMT-05:00) Eastern Time (US & Canada).
Where: CDER OODP MEETING CALENDAR; CDER WO 1309 conf rm Bldg22

FYI Attendees: B. Stinson, S. Kress, R. Rieves, G. Mills, T. Brown, V. Jimenez, H. Patel, L. Ball, R. Pazdur, K. Weiss, S. Lu, R. Pratt, M. Dempsey, J.L. Johnson, J. Grillo

Product: Velcade

Indication: Treatment of patients with Mantle Cell Lymphoma who have at least one prior therapy

Purpose: Filing Meeting. New supplemental New Drug Application for new indication, to support the approval of Velcade for treatment of patients with Mantle Cell Lymphoma who have at least one prior therapy.

MO: Robert Kane, MD

INTERNAL: August 2, 2006 3:00 pm WO 1309

Link to electronic submission:

The network path location is: \\CDSESUB1\N21602\S 010\2006-06-08

If you have any questions, contact the Regulatory Project Manager, Tammie Brent-Steele at 301-796-1409.

REQUEST FOR CONSULTATION

TO (Office/Division): Div. of Medical Imaging and Hematology Products		FROM (Name, Office/Division, and Phone Number of Requestor): Div. of Drug Oncology Products Tammie Brent-Steele, Project Manager 301-796-1409		
DATE 7/26/06	IND NO.	NDA NO. 21-602	TYPE OF DOCUMENT sNDA for new indication	DATE OF DOCUMENT 6/8/06
NAME OF DRUG Velcade		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 8/2/06
NAME OF FIRM: Millennium Pharmaceuticals, Inc.				

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: The sponsor has submitted a sNDA (21-602) for MCL based on response rates and duration of response.

In accordance with the previous meetings between DDOP, DMIHP, and the applicant, in which the submission process for radiographic images and related data from the independent radiologic review has been examined by DMIHP; DDOP requests DMIHP to:

- (a) determine that the imaging submission data is sufficient to allow the filing of the NDA for the filing meeting August 2.
- (b) After the filing meeting, provide a review of the submitted images and independent radiologic review data sufficient to verify that the patients which the sponsor designates as CR or CRu in fact fulfill the protocol imaging criteria for these designations.

SIGNATURE OF REQUESTOR

Tammie Brent-Steele

METHOD OF DELIVERY (Check one)

DFS

EMAIL

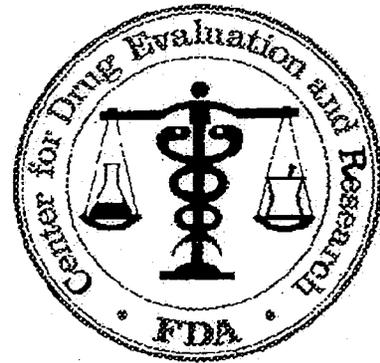
MAIL

HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

FAX



**FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS**

Center for Drug Evaluation and Research
5901-B Ammerdale Road
Beltsville, MD 20705-1266

To: Tanya Lewis

From: Tammie Brent-Steele RN MSN

Fax: 617-551-3742

Fax: (301) 796-9845

Phone: 617-551-8951

Phone: (301) 796-1409

Pages, including cover sheet: 1

Date: July 26, 2006

Re: Clinical reviewer request for sNDA 21-602/010

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Comments:

Please refer to your sNDA 21-602/010 for Velcade in the treatment of patients with Mantle Cell Lymphoma who have received at least one prior therapy.

The Clinical reviewer has the following request:

1. Please submit a patient listing indicating the patient ID numbers of all patients whom you have designated as CR or CRu in the MCL study.

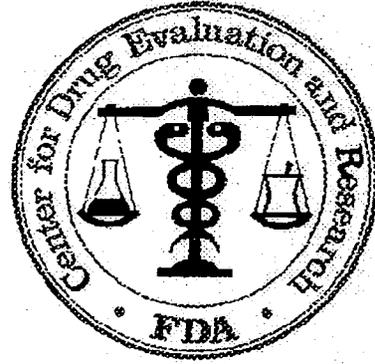
We will need this information as soon as possible as we would like to review it prior to our August 2, 2006 internal meeting.

**Thank you,
Tammie Brent-Steele, RN, MSN**

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS**

Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266



To: Tanya Lewis

From: Tammie Brent-Steele RN MSN

Fax: 617-551-3742

Fax: (301) 796-9845

Phone: 617-551-8951

Phone: (301) 796-1409

Pages, including cover sheet: 1

Date: July 18, 2006

Re: Presentation Meeting for sNDA 21-602/010

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Comments:

The Center for Drug Evaluation and Research's Division of Drug Oncology Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last approximately one hour. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. The applicant should present their reasons for why the Division of the Office of Oncology Drugs should approve their NDA/sNDA.

A date of August 23, 2006, 2:00pm to 3:00pm EST has been chosen by the Division for your presentation. The presentation will take place here at 10903 New Hampshire Ave. WO Bldg 22, Silver Spring, MD 20993. If you are unable to adhere to this date, you may provide us with alternative dates in the cover letter of your NDA/sNDA and the Division will try to accommodate them. Please contact me as soon as possible if you determine that re-scheduling of dates may be necessary.

Additionally, I am requesting that you send your presentation overheads to me a few days before the presentation date electronically.

Thank you,

Tammie Brent-Steele, RN, MSN

Brent-Steele, Tammie

From: Brown, Tiffany
Sent: Friday, June 23, 2006 1:05 PM
To: Brent-Steele, Tammie
Cc: Dagher, Ramzi; Kane, Robert
Subject: NDA 21-602 (Velcade)

The Division of Medical Imaging and Hematology Products (DMIHP) is in receipt of your consult request for the following application:

NDA: 21-602

Sponsor: Millennium Pharmaceuticals, Inc.

b(4)

CRO: _____

Drug: Velcade (bortezomib) Injection

Indication: For the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

To support and develop the NDA review process, DMIHP will work with DDOP, Millennium Pharmaceuticals and their CRO to ensure that the images associated with this application are available and formatted in an acceptable manner, if the review of the images submitted with the NDA are necessary for the Agency to review. DMIHP will request that the Sponsor/CRO confirm the required response time for the NDA submission of the images, the availability of one of the Independent imaging reviewers to review images at White Oak with DDOP and DMIHP; and the availability of technical support staff to operate the imaging submission software.

DMIHP will request the actual submission of the images and perform further consultative imaging review processes only if DDOP identifies a subset of cases that require a review of the images.

If DDOP determines that an imaging review of a specific subset is required, please inform Tiffany Brown, DMIHP RPM; and please send to DMIHP a consult defining the specific subset of cases for review and the questions to be addressed in the review.

In follow-up to DDOP's consult request, DMIHP, in conjunction with DDOP, will request the actual submission of the images to the NDA, and develop with the Sponsor/CRO a schedule for an onsite (White Oak) review of the specific imaging cases with the independent imaging reviewer.

If you have any questions, please contact me.

Sincerely,
Tiffany Brown

Tiffany J. Brown, M.P.H
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
301-796-2050 (phone)
301-796-9847 (fax)

REQUEST FOR CONSULTATION

TO (Office/Division): Div. of Medical Imaging and Hematology
Products

FROM (Name, Office/Division, and Phone Number of Requestor): Div. of
Drug Oncology Products
Tammie Brent-Steele, Project Manager
301-796-1409

DATE
6/19/06

IND NO.

NDA NO.
21-602

TYPE OF DOCUMENT
sNDA for new indication

DATE OF DOCUMENT
6/8/06

NAME OF DRUG
Velcade

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
7/8/06

NAME OF FIRM: Millennium Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Supplemental New Drug Application fo a New Indication

SIGNATURE OF REQUESTOR
Tammie Brent-Steele

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Brent-Steele, Tammie

From: EDRAAdmin@cder.fda.gov
Sent: Friday, June 16, 2006 10:04 AM
To: Zhou, Liang; Brent-Steele, Tammie; Kane, Robert; Rosario, Lilliam; Wang, Yong-Cheng; Mejia, Bertha*; Padua, Alex*; Pease, Dorothy W; Prather, Mia; Wilder, Lisa C
Cc: Talastas, Hercules*; Emmons, Prentiss*; Langhnoja, Urvi *; Tokoli, Thomas*; CDER-EDRADMIN
Subject: EDR - NDA021602 from MILLENNIUM PHARMS drug name VELCADE (BORTEZOMIB) INJ 3.5MG

Hi !

The EDR has received an Electronic Document on CD-ROM for division HFD-150:

NDA# N21602
Incoming Document Type: SE1
Incoming Document Type Sequence Number: 010
Supplement Modification Type:
Letter Date: 6/8/2006

It has sections 1, 2, 3, 8, 10, 11, 12, 13, 16, 18, 19.
The network path location is: \\CDSESUB1\N21602\S_010\2006-06-08
It is now available on the network. You can review this submission by entering EDR in your browser.

Please address any questions concerning this electronic submission to:

EDRAAdmin@cder.fda.gov

Thanks,
EDR-Staff

Brent-Steele, Tammie

From: Sridhara, Rajeshwari
Sent: Friday, June 16, 2006 2:43 PM
to: Brent-Steele, Tammie
Cc: Dagher, Ramzi
Subject: RE: EDR - NDA021602 from MILLENNIUM PHARMS drug name VELCADE (BORTEZOMIB) INJ 3.5MG

Tammie,

I will be assigning this to a new reviewer (Dr. Chia-Wen Ko) who will be joining our team on June 26th. Until then please send all correspondences and meeting notices to me.

Thanks
Raji

Rajeshwari Sridhara, Ph.D.
Team Leader, DBV/OB/CDER/FDA
W022, Rm 1210, Maildrop 1207
10903 New Hampshire Avenue, Silver Spring, MD 20993
Tel: 301-796-1759 Fax: 301-796-9912
E-mail: rajeshwari.sridhara@fda.hhs.gov

-----Original Message-----

From: Brent-Steele, Tammie
Sent: Friday, June 16, 2006 1:10 PM
To: Dagher, Ramzi; Morse, David E; Sridhara, Rajeshwari; Booth, Brian P; Mills, George; Rieves, Rafel; Kress, Scheldon; Stinson, Barbara; Brown, Tiffany
cc: Abraham, Sophia
Subject: FW: EDR - NDA021602 from MILLENNIUM PHARMS drug name VELCADE (BORTEZOMIB) INJ 3.5MG

Hello,

Please note the attached email from the EDR. Please check assignments and let me know if there are any changes. I don't remember that there were any Clin Pharm or Pharm Tox issues in the Pre-NDA meetings for this supplement, however, please let me know so that I can assemble the team.

Thanks very much,
Tammie

-----Original Message-----

From: EDRAAdmin@cder.fda.gov [mailto:EDRAAdmin@cder.fda.gov]
Sent: Friday, June 16, 2006 10:04 AM
To: Zhou, Liang; Brent-Steele, Tammie; Kane, Robert; Rosario, Lilliam; Wang, Yong-Cheng; Mejia, Bertha*; Padua, Alex*; Pease, Dorothy W; Prather, Mia; Wilder, Lisa C
Cc: Talastas, Hercules*; Emmons, Prentiss*; Langhnoja, Urvi *; Tokoli, Thomas*; CDER-EDRADMIN
Subject: EDR - NDA021602 from MILLENNIUM PHARMS drug name VELCADE (BORTEZOMIB) INJ 3.5MG

Hi !

The EDR has received an Electronic Document on CD-ROM for division HFD-150:

NDA# N21602

Incoming Document Type: SE1
Incoming Document Type Sequence Number: 010
Supplement Modification Type:
Letter Date: 6/8/2006

It has sections 1, 2, 3, 8, 10, 11, 12, 13, 16, 18, 19.

The network path location is: \\CDSESUB1\N21602\S_010\2006-06-08

It is now available on the network. You can review this submission by entering EDR in your browser.

Please address any questions concerning this electronic submission to:

EDRAdmin@cderr.fda.gov

Thanks,
EDR-Staff

Brent-Steele, Tammie

To: Brown, Tiffany
Subject: FW: EDR - NDA021602 from MILLENNIUM PHARMS drug name VELCADE (BORTEZOMIB) INJ 3.5MG

Attachments: DMIHP Consult NDA 21-602 sn 010.doc



DMIHP Consult NDA
21-602 sn 01...

Hi Tiffany,

The electronic version of the sNDA for Millennium's Velcade came in on Friday. I'm attaching the consult form to this email. This will be the first time I'm handling a new sNDA, and an electronic one at that. So, any suggestions or pointers you may have I would truly welcome. Let me know if I need to route this to someplace else.

Thanks very much,
Tammie

-----Original Message-----

From: EDRAAdmin@cder.fda.gov [mailto:EDRAAdmin@cder.fda.gov]
Sent: Friday, June 16, 2006 10:04 AM
To: Zhou, Liang; Brent-Steele, Tammie; Kane, Robert; Rosario, Lilliam; Wang, Yong-Cheng; Mejia, Bertha*; Padua, Alex*; Pease, Dorothy W; Prather, Mia; Wilder, Lisa C
Cc: Talastas, Hercules*; Emmons, Prentiss*; Langhnoja, Urvi *; Tokoli, Thomas*; CDER-EDRADMIN
Subject: EDR - NDA021602 from MILLENNIUM PHARMS drug name VELCADE (BORTEZOMIB) INJ 3.5MG

i !

The EDR has received an Electronic Document on CD-ROM for division HFD-150:

NDA# N21602
Incoming Document Type: SE1
Incoming Document Type Sequence Number: 010
Supplement Modification Type:
Letter Date: 6/8/2006

It has sections 1, 2, 3, 8, 10, 11, 12, 13, 16, 18, 19.
The network path location is: \\CDSESUB1\N21602\S_010\2006-06-08
It is now available on the network. You can review this submission by entering EDR in your browser.

Please address any questions concerning this electronic submission to:

EDRAAdmin@cder.fda.gov

Thanks,
EDR-Staff

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER
21-602

APPLICANT INFORMATION

NAME OF APPLICANT Millennium Pharmaceuticals, Inc.	DATE OF SUBMISSION June 8, 2006
TELEPHONE NO. (Include Area Code) (617) 679-7000	FACSIMILE (FAX) Number (Include Area Code) (617) 551-3742
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 40 Landsdowne Street Cambridge, Massachusetts 02139	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE N/A

CDER/CDR
JUN 09 2006
RECEIVED

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-602		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) bortezomib	PROPRIETARY NAME (trade name) IF ANY VELCADE® (bortezomib) for Injection	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) [(1R)-3-methyl-1-[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]boronic acid	CODE NAME (If any) PS-341	
DOSAGE FORM: lyophilized powder for injection	STRENGTHS: 3.5mg	ROUTE OF ADMINISTRATION: Intravenous
(PROPOSED) INDICATION(S) FOR USE: Treatment of patients with mantle cell lymphoma who have received at least one prior therapy		

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input checked="" type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION Supplemental New Drug Application (sNDA) for a new indication
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input checked="" type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Not Applicable

ORIGINAL

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 56, 515

This application contains the following items: (Check all that apply)

<input checked="" type="checkbox"/>	1. Index
<input checked="" type="checkbox"/>	2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input checked="" type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input checked="" type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input checked="" type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input checked="" type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input checked="" type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input checked="" type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input checked="" type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (f)(3))
<input checked="" type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input checked="" type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	20. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT

TYPED NAME AND TITLE

DATE:

Tanya Lewis, M.S.
Director, Regulatory Affairs

June 8, 2006

ADDRESS (Street, City, State, and ZIP Code)

40 Landsdowne Street, Cambridge MA 02139

Telephone Number

(617) 551-8951

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN
SERVICES
FOOD AND DRUG ADMINISTRATIONPRESCRIPTION DRUG USER FEE
COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS MILLENNIUM PHARMACEUTICALS INC Tanya Lewis 40 Landsdowne Street Cambridge MA 02139 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 021-602
2. TELEPHONE NUMBER 617-551-8951	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME VELCADE (bortezomib) for Injection	6. USER FEE I.D. NUMBER PD3006548
---	--------------------------------------

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
 Food and Drug Administration
 CBER, HFM-99
 1401 Rockville Pike
 Rockville, MD 20852-1448

Food and Drug Administration
 CDER, HFD-94
 12420 Parklawn Drive, Room 3046
 Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

Tanya Lewis

TITLE

*Director
 Oncology Regulatory Affairs*

DATE

22 MAY 2006

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
 \$383,700.00

Form FDA 3397 (12/03)

(BE PRMT CLOSE G) (Print Cover sheet)

ACTION PACKAGE CHECKLIST

Application Information		
A # NDA # 21-602	BLA STN# NDA Supplement # 010	If NDA, Efficacy Supplement Type SE1
Proprietary Name: Velcade Established Name: bortezomib Dosage Form: IV		Applicant: Millennium Pharmaceuticals, Inc.
RPM: Tammie Brent		Division: DDOP Phone # 301-796-1409
NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. <input type="checkbox"/> If no listed drug, check here and explain: Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct. <input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date:
❖ User Fee Goal Date		12-9-06
❖ Action Goal Date (if different)		12-8-06
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): NDAs, BLAs and Supplements: <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies NDAs and NDA Supplements: <input type="checkbox"/> OTC drug Other: Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> • Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) • OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Press Office notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other

❖ Exclusivity	
<ul style="list-style-type: none"> • NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> • NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> • NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> • NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> • NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
❖ Patent Information (NDAs and NDA supplements only)	
<ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> • Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(j)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (<i>If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews).</i>) 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	12-8-06
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	12-8-06
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	12-8-06
• Original applicant-proposed labeling	6-8-06
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	12-8-06
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	12-8-06
• Original applicant-proposed labeling	6-8-06
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (full color carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)	<input type="checkbox"/> DMETS <input type="checkbox"/> DSRCS <input checked="" type="checkbox"/> DDMAC <input type="checkbox"/> SEALD <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies <ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) Incoming submission documenting commitment 	<input checked="" type="checkbox"/> None
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) Pre-NDA/BLA meeting (<i>indicate date</i>) EOP2 meeting (<i>indicate date</i>) Other (e.g., EOP2a, CMC pilot programs) 	<input type="checkbox"/> No mtg
	<input type="checkbox"/> No mtg
❖ Advisory Committee Meeting	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available 	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	12-7-06
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications) <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>) (<i>all original applications and all efficacy supplements that could increase the patient population</i>) <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	12-8-06
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	N/A <input type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: N/A <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	12-8-06
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	<input type="checkbox"/> None requested
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	12-6-06
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	page 9
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	N/A
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
<ul style="list-style-type: none"> • Clinical Studies 	12-4-06
<ul style="list-style-type: none"> • Bioequivalence Studies 	
<ul style="list-style-type: none"> • Clin Pharm Studies 	
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11-30-06
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12-6-06

Comment [1]:

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) Or it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) Or it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) And no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) And all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) Or the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) Or the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.