

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**21-602/S-015**

***Trade Name:*** Velcade

***Generic Name:*** bortezomib

***Sponsor:*** Millennium Pharmaceuticals, Inc.

***Approval Date:*** June 20, 2008

***Purpose:*** Provides for the use of Velcade (bortezomib) for Injection, single use vial, 3.5 mg to treat patients with multiple myeloma

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*APPLICATION NUMBER:*

**21-602/S-015**

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*APPLICATION NUMBER:*

**21-602/S-015**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-602/S-015

Millennium Pharmaceuticals, Inc.  
40 Landsdowne Street  
Cambridge, MA 02139

Attention: Tanya Lewis, MS  
Sr. Director, Regulatory Affairs

Dear Ms. Lewis:

Please refer to your supplemental new drug application dated December 20, 2007, received December 20, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Velcade® (bortezomib) for Injection, single use vial, 3.5 mg.

We acknowledge receipt of your submissions dated January 15, January 30, March 14, March 19, March 21, April 4, April 16, April 23, April 24, April 29, May 12, May 22, May 28, and June 19, 2008(electronic).

This supplemental new drug application provides for the use of Velcade® (bortezomib) for Injection, single use vial, 3.5 mg to treat patients with multiple myeloma.

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.

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

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. 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-015.**" Approval of this submission by FDA is not required before the labeling is used.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] 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.

We have received your submission dated June 8, 2006, regarding the following postmarketing commitment:

4. Conduct additional investigations of the cardiovascular effects of bortezomib at acutely toxic doses that explore bortezomib induced lethality at 12–14 hours post-dose. Studies should be conducted in a species that most closely models the human response. An investigational study in cynomolgus monkeys would be appropriate, with a focus on potential interventions that could both explore mechanisms of cardiovascular effects and possible clinically relevant interventional therapies. Study protocols may be submitted to the Division for review prior to the conduct of the study. (This study will be completed in the second quarter of 2004.)

We have received your submissions dated March 30, 2007 and June 04, 2007, reporting on the following postmarketing commitments:

11. Conduct PK and PK/PD (pharmacokinetics/pharmacodynamics) studies to examine the potential for drug-drug interactions between bortezomib and drugs that are inhibitors (e.g., ketoconazole), or inducers (e. g., rifampin) of cytochrome P450 3A4. You should also collect adverse reactions noted in this study and evaluate any relationship between plasma levels and adverse reactions. (The draft protocol for this study will be submitted to the Agency for review in the third quarter of 2003.)

We have reviewed your submissions and have concluded that the above commitments were fulfilled.

We remind you of your open postmarketing study commitment #7 agreed upon in your submission dated May 13, 2003:

7. As bortezomib is metabolized and eliminated by the liver, a pharmacokinetic and pharmacokinetic/safety (PK and PK/Safety) study should be conducted in patients with hepatic impairment to provide dosing recommendations for this patient population. (A draft protocol will be submitted to the Agency for review in the fourth quarter of 2003. It is anticipated that this study will take approximately 12 months from initial patient enrollment to completion. A final Clinical Pharmacology report will be made available to the Agency within 3 months of clinical study completion.)

Protocol Submission: November 13, 2003

Study Start: February 13, 2004

Final Report Submission: July 13, 2005

Submit clinical protocols to your IND for this product. Submit non-clinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled “**Postmarketing Study Commitment Protocol**”, “**Postmarketing Study Commitment Final Report**”, or “**Postmarketing Study Commitment Correspondence.**”

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  
Suite 12B05  
5600 Fishers Lane  
Rockville, MD 20857

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 Kim J. Robertson, Consumer Safety Officer, at (301) 796-1441.

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, M.D.  
Deputy Division Director  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Enclosure (label)

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/s/

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Ann Farrell  
6/20/2008 12:41:06 PM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-602/S-015**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VELCADE safely and effectively. See full prescribing information for VELCADE.

### VELCADE (bortezomib) for Injection

Initial US Approval: 2003

#### -----RECENT MAJOR CHANGES-----

Patients with Renal Impairment (8.6) 10/2007

Indications and Usage, Multiple Myeloma (1.1) 06/2008

#### -----INDICATIONS AND USAGE-----

VELCADE is a proteasome inhibitor indicated for:

- treatment of patients with multiple myeloma (1.1)
- treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy (1.2)

#### -----DOSAGE AND ADMINISTRATION-----

The recommended dose of VELCADE is 1.3 mg/m<sup>2</sup> administered as a 3 to 5 second bolus intravenous injection. (2.1, 2.3)

Dose adjustment may be used to manage adverse events that occur during treatment (2.2, 2.4)

#### -----DOSAGE FORMS AND STRENGTHS-----

- 1 single use vial contains 3.5 mg of bortezomib. Dose must be individualized to prevent overdose. (3)

#### -----CONTRAINDICATIONS-----

- VELCADE is contraindicated in patients with hypersensitivity to bortezomib, boron, or mannitol. (4)

#### -----WARNINGS AND PRECAUTIONS-----

- Women should avoid becoming pregnant while being treated with VELCADE. Pregnant women should be apprised of the potential harm to the fetus. (5.1, 8.1)
- Peripheral neuropathy, including severe cases, may occur - manage with dose modification or discontinuation. (2.2, 2.4) Patients with preexisting severe neuropathy should be treated with VELCADE only after careful risk-benefit assessment. (2.2, 2.4, 5.2)

- Hypotension can occur. Caution should be used when treating patients receiving antihypertensives, those with a history of syncope, and those who are dehydrated. (5.3)
- Patients with risk factors for, or existing heart disease, should be closely monitored. (5.4)
- Acute diffuse infiltrative pulmonary disease has been reported. (5.5)
- Nausea, diarrhea, constipation, and vomiting have occurred and may require use of antiemetic and antidiarrheal medications or fluid replacement. (5.7)
- Thrombocytopenia or neutropenia can occur; complete blood counts should be regularly monitored throughout treatment. (5.8)
- Tumor Lysis Syndrome (5.9), Reversible Posterior Leukoencephalopathy Syndrome (5.6), and acute hepatic failure (5.10) have been reported.

#### -----ADVERSE REACTIONS-----

Most commonly reported adverse reactions (incidence ≥30%) in clinical studies include asthenic conditions, diarrhea, nausea, constipation, peripheral neuropathy, vomiting, pyrexia, thrombocytopenia, psychiatric disorders, anorexia and decreased appetite, neutropenia, neuralgia, leukopenia and anemia. Other adverse reactions, including serious adverse reactions, have been reported. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Millennium Pharmaceuticals at (1-866 VELCADE or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### -----USE IN SPECIFIC POPULATIONS-----

- Women should be advised against breast feeding or becoming pregnant while being treated with VELCADE. (5.1, 8.1, 8.3)
- Patients with diabetes may require close monitoring of blood glucose and adjustment of anti-diabetic medication. (8.8)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: [06/2008]

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\*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Multiple Myeloma

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

#### 1.2 Mantle Cell Lymphoma

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

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Dosage in Previously Untreated Multiple Myeloma

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

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

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

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

#### 2.2 Dose Modification Guidelines for Combination Therapy with VELCADE, Melphalan and Prednisone

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

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

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

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

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

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

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

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

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

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

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

<b>Severity of Peripheral Neuropathy Signs and Symptoms</b>	<b>Modification of Dose and Regimen</b>
Grade 1 (paresthesias, weakness and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce VELCADE to 1 mg/m <sup>2</sup>
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold VELCADE therapy until toxicity resolves. When toxicity resolves reinstate with a reduced dose of VELCADE at 0.7 mg/m <sup>2</sup> and change treatment schedule to once per week.
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue VELCADE

Grading based on NCI Common Toxicity Criteria CTCAE v3.0

## 2.5 Administration Precautions

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

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

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

## 2.6 Reconstitution/Preparation for Intravenous Administration

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

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

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

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

## 3 DOSAGE FORMS AND STRENGTHS

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

## 4 CONTRAINDICATIONS

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

## 5 WARNINGS AND PRECAUTIONS

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

### 5.1 Use in Pregnancy

#### Pregnancy Category D

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

### 5.2 Peripheral Neuropathy

VELCADE treatment causes a peripheral neuropathy that is predominantly sensory. However, cases of severe sensory and motor peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral neuropathy (including ≥Grade 3) during treatment with VELCADE. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy may require change in the dose and schedule of VELCADE [*see Dosage and Administration (2.2, 2.4)*]. Following dose adjustments, improvement in or resolution of peripheral neuropathy was reported in 51% of patients with ≥Grade 2 peripheral neuropathy in the relapsed multiple myeloma study. Improvement in or resolution of peripheral neuropathy was reported in 73% of patients who discontinued due to Grade 2 neuropathy or who had ≥Grade 3 peripheral neuropathy in the phase 2 multiple myeloma studies [*see Adverse Reactions (6)*]. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

### 5.3 Hypotension

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

### 5.4 Cardiac Disorders

Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have been reported, including reports in patients with no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or existing heart disease should be closely monitored. In the relapsed multiple myeloma study, the incidence of any treatment-emergent cardiac disorder was 15% and 13% in the VELCADE and dexamethasone groups, respectively. The incidence of heart failure events (acute pulmonary

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

### **5.5 Pulmonary Disorders**

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

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

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

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

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

There have been reports of RPLS in patients receiving VELCADE. 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.

### **5.7 Gastrointestinal Adverse Events**

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

### **5.8 Thrombocytopenia/Neutropenia**

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

**Table 4: Severity of Thrombocytopenia Related to Pretreatment Platelet Count in the Relapsed Multiple Myeloma Study**

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

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

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

## 5.9 Tumor Lysis Syndrome

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

## 5.10 Hepatic Events

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

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

## 6 ADVERSE REACTIONS

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

- Peripheral Neuropathy [see *Warnings and Precautions (5.2); Dosage and Administration (Table 3)*]
- Hypotension [see *Warnings and Precautions (5.3)*]
- Cardiac Disorders [see *Warnings and Precautions (5.4)*]
- Pulmonary Disorders [see *Warnings and Precautions (5.5)*]
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) [see *Warnings and Precautions (5.6)*]
- Gastrointestinal Adverse Events [see *Warnings and Precautions (5.7)*]
- Thrombocytopenia/Neutropenia [see *Warnings and Precautions (5.8)*]
- Tumor Lysis Syndrome [see *Warnings and Precautions (5.9)*]
- Hepatic Events [see *Warnings and Precautions (5.10)*]

## 6.1 Clinical Trials Safety Experience

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

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

Table 5 describes safety data from 340 patients with previously untreated multiple myeloma who received VELCADE ( $1.3 \text{ mg/m}^2$ ) in combination with melphalan ( $9 \text{ mg/m}^2$ ) and prednisone ( $60 \text{ mg/m}^2$ ) in a prospective randomized study.

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

**Table 5-Most Commonly Reported Adverse Events ( $\geq 10\%$  in VELCADE, Melphalan and Prednisone arm) with Grades 3 and  $\geq 4$  Intensity in the Previously Untreated Multiple Myeloma Study**

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

**Musculoskeletal and Connective****Tissue Disorders**

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

**Metabolism and Nutrition****Disorders**

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

**Skin and Subcutaneous Tissue****Disorders**

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

**Respiratory, Thoracic and****Mediastinal Disorders**

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

**Psychiatric Disorders**

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

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

**Relapsed Multiple Myeloma Randomized Study**

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

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

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

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

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

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

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

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

The most common adverse events from the relapsed multiple myeloma study are shown in **Table 6**. All adverse events with incidence  $\geq 10\%$  in the VELCADE arm are included.

**Table 6: Most Commonly Reported Adverse Events (≥10% in VELCADE arm),with Grades 3 and 4 Intensity in the Relapsed Multiple Myeloma Study (N=663)**

Adverse Event	Treatment Group					
	VELCADE (n=331) [n (%)]			Dexamethasone (n=332) [n (%)]		
	All Events	Grade 3 Events	Grade 4 Events	All Events	Grade 3 Events	Grade 4 Events
Adverse Event	331 (100)	203 (61)	45 (14)	327 (98)	146 (44)	52 (16)
Asthenic conditions	201 (61)	39 (12)	1 (<1)	148 (45)	20 (6)	0
Diarrhea	190 (57)	24 (7)	0	69 (21)	6 (2)	0
Nausea	190 (57)	8 (2)	0	46 (14)	0	0
Constipation	140 (42)	7 (2)	0	49 (15)	4 (1)	0
Peripheral neuropathy	120 (36)	24 (7)	2 (<1)	29 (9)	1 (<1)	1 (<1)
Vomiting	117 (35)	11 (3)	0	20 (6)	4 (1)	0
Pyrexia	116 (35)	6 (2)	0	54 (16)	4 (1)	1 (<1)
Thrombocytopenia	115 (35)	85 (26)	12 (4)	36 (11)	18 (5)	4 (1)
Psychiatric disorders	117 (35)	9 (3)	2 (<1)	163 (49)	26 (8)	3 (<1)
Anorexia and appetite decreased	112 (34)	9 (3)	0	31 (9)	1 (<1)	0
Paresthesia and dysesthesia	91 (27)	6 (2)	0	38 (11)	1 (<1)	0
Anemia	87 (26)	31 (9)	2 (<1)	74 (22)	32 (10)	3 (<1)
Headache	85 (26)	3 (<1)	0	43 (13)	2 (<1)	0
Cough	70 (21)	2 (<1)	0	35 (11)	1 (<1)	0
Dyspnea	65 (20)	16 (5)	1 (<1)	58 (17)	9 (3)	2 (<1)
Neutropenia	62 (19)	40 (12)	8 (2)	5 (2)	4 (1)	0
Rash	61 (18)	4 (1)	0	20 (6)	0	0
Insomnia	60 (18)	1 (<1)	0	90 (27)	5 (2)	0
Abdominal pain	53 (16)	6 (2)	0	12 (4)	1 (<1)	0
Bone pain	52 (16)	12 (4)	0	50 (15)	9 (3)	0
Lower respiratory/ lung infections	48 (15)	12 (4)	2 (<1)	69 (21)	24 (7)	1 (<1)
Pain in limb	50 (15)	5 (2)	0	24 (7)	2 (<1)	0
Back pain	46 (14)	10 (3)	0	33 (10)	4 (1)	0
Arthralgia	45 (14)	3 (<1)	0	35 (11)	5 (2)	0
Dizziness (excl. vertigo)	45 (14)	3 (<1)	0	34 (10)	0	0
Nasopharyngitis	45 (14)	1 (<1)	0	22 (7)	0	0
Herpes zoster	42 (13)	6 (2)	0	15 (5)	4 (1)	1 (<1)
Muscle cramps	41 (12)	0	0	50 (15)	3 (<1)	0
Myalgia	39 (12)	1 (<1)	0	18 (5)	1 (<1)	0
Rigors	37 (11)	0	0	8 (2)	0	0
Edema lower limb	35 (11)	0	0	43 (13)	1 (<1)	0

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

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

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

Safety data from phase 2 and 3 studies of single agent VELCADE 1.3 mg/m<sup>2</sup>/dose twice weekly for 2 weeks followed by a 10-day rest period in 1163 patients with previously treated multiple myeloma (N=1008) and previously treated 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. [see *Clinical Studies (14)*]

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 ≥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 7. All adverse events occurring at ≥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 7: Most Commonly Reported ( $\geq 10\%$  Overall) Adverse Events in Integrated Analyses of Relapsed Multiple Myeloma and Mantle Cell Lymphoma Studies using the 1.3 mg/m<sup>2</sup> Dose (N=1163)**

Adverse Events	All Patients (N=1163)		Multiple Myeloma (N=1008)		Mantle Cell Lymphoma (N=155)	
	All Events	$\geq$ 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	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

## **Description of Selected Adverse Events from the Phase 2 and 3 Relapsed 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 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 Warnings and Precautions (5.7)*]

### ***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 Warnings and Precautions (5.8)*]. 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%). [*see Warnings and Precautions (5.8)*]

### ***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 relapsed 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 Warnings and Precautions (5.2)*]

### ***Hypotension***

The incidence of hypotension (postural hypotension, orthostatic hypotension and hypotension NOS) was 13% in patients treated with VELCADE. 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 Warnings and Precautions (5.3)*]

### ***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  $\geq$ 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  $\geq$ Grade 3 neutropenia also was higher in patients with multiple myeloma (14%) compared to patients with mantle cell lymphoma (4%). [*see Warnings and Precautions (5.8)*]

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

Asthenic conditions were reported in 64% of patients. Asthenia was Grade 3 for 16% and  $\geq$ 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 ( $>38^{\circ}\text{C}$ ) was reported as an adverse event for 34% of patients. The event was Grade 3 in 3% and  $\geq$ 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  $\geq$ Grade 3 pyrexia was 3% in patients with multiple myeloma and 1% in patients with mantle cell lymphoma.

### ***Herpes Virus Infection***

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

### **Additional Adverse Events from Clinical Studies**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## 6.2 Postmarketing Experience

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

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

## 7 DRUG INTERACTIONS

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

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

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

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

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

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

Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits at the highest dose tested (0.075 mg/kg; 0.5 mg/m<sup>2</sup> in the rat and 0.05 mg/kg; 0.6 mg/m<sup>2</sup> in the rabbit) when administered during organogenesis. These dosages are approximately half the clinical dose of 1.3 mg/m<sup>2</sup> based on body surface area.

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

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

### 8.3 Nursing Mothers

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

### 8.4 Pediatric Use

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

## 8.5 Geriatric Use

Of the 669 patients enrolled in the relapsed multiple myeloma study, 245 (37%) were 65 years of age or older: 125 (38%) on the VELCADE arm and 120 (36%) on the dexamethasone arm. Median time to progression and median duration of response for patients  $\geq 65$  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  $\geq 65$  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  $\leq 50$ , 51-64 and  $\geq 65$  years old, respectively. [*see Adverse Reactions (6.1); Clinical Studies (14)*]

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.

## 8.6 Patients with Renal Impairment

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

## 8.7 Patients with Hepatic Impairment

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

## 8.8 Patients with Diabetes

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

## 10 OVERDOSAGE

There is no known specific antidote for VELCADE overdose [*see Warnings and Precautions (5.3) and Dosage and Administration (2.5)*]. 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  $\text{mg}/\text{m}^2$  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.

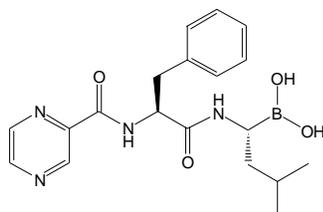
## 11 DESCRIPTION

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

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

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

Bortezomib has the following chemical structure:



The molecular weight is 384.24. The molecular formula is C<sub>19</sub>H<sub>25</sub>BN<sub>4</sub>O<sub>4</sub>. The solubility of bortezomib, as the monomeric boronic acid, in water is 3.3 to 3.8 mg/mL in a pH range of 2 to 6.5.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

### 12.2 Pharmacodynamics

Following twice weekly administration of 1 mg/m<sup>2</sup> and 1.3 mg/m<sup>2</sup> 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 maximum inhibition of 20S proteasome activity was observed between 1 and 1.3 mg/m<sup>2</sup> doses. Maximal inhibition ranged from 70% to 84% and from 73% to 83% for the 1 mg/m<sup>2</sup> and 1.3 mg/m<sup>2</sup> dose regimens, respectively.

### 12.3 Pharmacokinetics

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

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

**Distribution:** The mean distribution volume of bortezomib ranged from approximately 498 to 1884 L/m<sup>2</sup> following single- or repeat-dose administration of 1 mg/m<sup>2</sup> or 1.3mg/m<sup>2</sup> to patients 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.

**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 mg/m<sup>2</sup> and 1.3 mg/m<sup>2</sup> showed that both dose-normalized AUC and C<sub>max</sub> tend to be less in younger patients. Patients < 65 years of age (n=26) had about 25% lower mean dose-normalized AUC and C<sub>max</sub> than those ≥ 65 years of age (n=13).

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

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

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

**Renal Impairment:** A pharmacokinetic study was conducted in patients with various degrees of renal impairment who were classified according to their creatinine clearance values (CrCl) into the following groups: Normal (CrCl ≥60 mL/min/1.73 m<sup>2</sup>, N=12), Mild (CrCl=40-59 mL/min/1.73 m<sup>2</sup>, N=10), Moderate (CrCl=20-39 mL/min/1.73 m<sup>2</sup>, N=9), and Severe (CrCl < 20 mL/min/1.73 m<sup>2</sup>, N=3). A group of dialysis patients who were dosed after dialysis was also included in the study (N=8). Patients were administered intravenous doses of 0.7 to 1.3 mg/m<sup>2</sup> of bortezomib twice weekly. Exposure of bortezomib (dose-normalized AUC and C<sub>max</sub>) was comparable among all the groups. [see **Use in Specific Populations (8.6)**]

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

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

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

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

**Cytochrome P450:** Bortezomib is a poor inhibitor of human liver microsomal cytochrome P450 1A2, 2C9, 2D6, and 3A4, with IC<sub>50</sub> values of >30 μM (>11.5 μg/mL). Bortezomib may inhibit 2C19 activity (IC<sub>50</sub> = 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. [see *Drug Interactions (7.4)*]

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with bortezomib.

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

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

### 13.2 Animal Toxicology

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

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

## 14 CLINICAL STUDIES

### 14.1 Multiple Myeloma

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

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

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

Efficacy results for the trial are presented in Table 8. Median follow-up was 16.3 months. At a pre-specified interim analysis, the primary endpoint, time to progression, was found to be significantly superior, and patients in the Melphalan and Prednisone arm were offered VELCADE, Melphalan and Prednisone treatment.

**Table 8: Summary of Efficacy Analyses in the Previously Untreated Multiple Myeloma Study**

<b>Efficacy Endpoint</b>	<b>VELCADE, Melphalan and Prednisone n=344</b>	<b>Melphalan and Prednisone n=338</b>
<b>Time to Progression</b>		
Events n (%)	101 (29)	152 (45)
Median <sup>a</sup> (95% CI)	20.7 mo (17.6, 24.7)	15.0 mo (14.1, 17.9)
Hazard ratio <sup>b</sup> (95% CI)	0.54 (0.42, 0.70)	
p-value <sup>c</sup>	0.000002	
<b>Progression-free Survival</b>		
Events n (%)	135 (39)	190 (56)
Median <sup>a</sup> (95% CI)	18.3 mo (16.6, 21.7)	14.0 mo (11.1, 15.0)
Hazard ratio <sup>b</sup> (95% CI)	0.61 (0.49, 0.76)	
p-value <sup>c</sup>	0.00001	
<b>Overall Survival</b>		
Events (deaths) n (%)	45 (13)	76 (23)
Hazard ratio <sup>b</sup> (95% CI)	0.61 (0.42, 0.88)	
p-value <sup>c</sup>	0.00782	
<b>Response Rate</b>		
CR <sup>d</sup> n (%)	102 (30)	12 (4)
PR <sup>d</sup> n (%)	136 (40)	103 (30)
nCR n (%)	5 (1)	0
CR + PR <sup>d</sup> n (%)	238 (69)	115 (34)
p-value <sup>e</sup>	<10 <sup>-10</sup>	

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

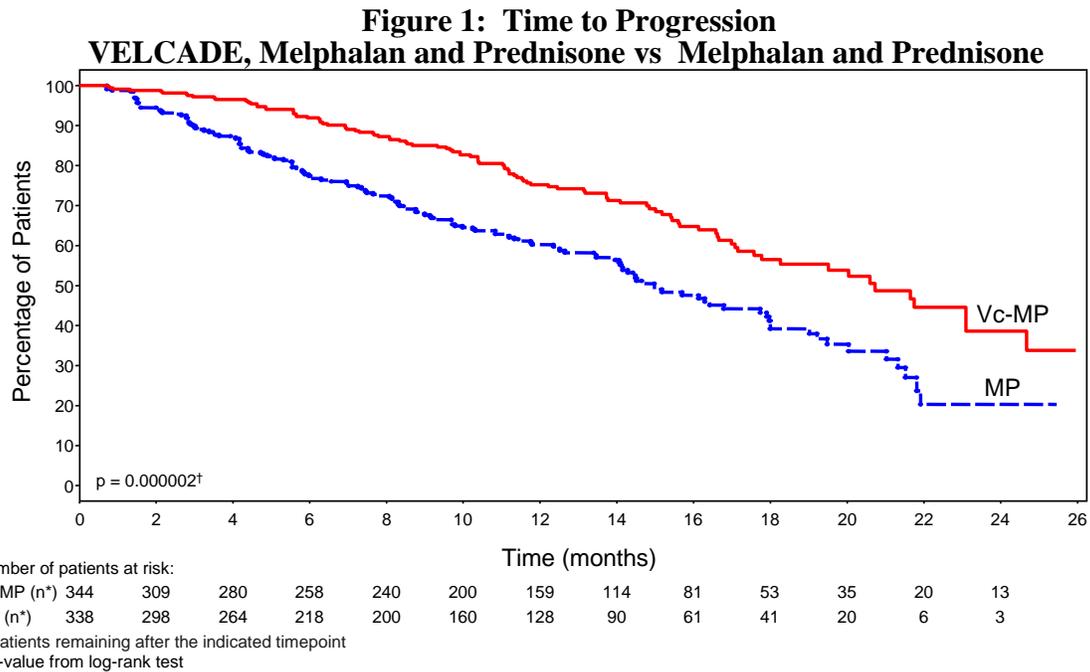
<sup>b</sup> Hazard ratio estimate is based on a Cox proportional-hazard model adjusted for stratification factors: beta2-microglobulin, albumin, and region. A hazard ratio less than 1 indicates an advantage for VELCADE, Melphalan and Prednisone

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

<sup>d</sup> EBMT criteria

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

TTP was statistically significantly longer on the VELCADE, Melphalan and Prednisone arm (see **Figure 1**).



### ***Randomized, Clinical Study in Relapsed Multiple Myeloma***

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

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

Baseline patient and disease characteristics are summarized in **Table 9**.

**Table 9: Summary of Baseline Patient and Disease Characteristics in the Relapsed Multiple Myeloma Study**

<b>Patient Characteristics</b>	<b>VELCADE N=333</b>	<b>Dexamethasone N=336</b>
Median age in years (range)	62.0 (33, 84)	61.0 (27, 86)
Gender: Male/female	56% / 44%	60% / 40%
Race: Caucasian/black/other	90% / 6% / 4%	88% / 7% / 5%
Karnofsky performance status score $\leq 70$	13%	17%
Hemoglobin <100 g/L	32%	28%
Platelet count <75 x 10 <sup>9</sup> /L	6%	4%
<b>Disease Characteristics</b>		
Type of myeloma (%): IgG/IgA/Light chain	60% / 23% / 12%	59% / 24% / 13%
Median $\beta_2$ -microglobulin (mg/L)	3.7	3.6
Median albumin (g/L)	39.0	39.0
Creatinine clearance $\leq 30$ mL/min [n (%)]	17 (5%)	11 (3%)
<b>Median Duration of Multiple Myeloma Since Diagnosis (Years)</b>		
	3.5	3.1
<b>Number of Prior Therapeutic Lines of Treatment</b>		
Median	2	2
1 prior line	40%	35%
>1 prior line	60%	65%
<b>Previous Therapy</b>		
Any prior steroids, e.g., dexamethasone, VAD	98%	99%
Any prior anthracyclines, e.g., VAD, mitoxantrone	77%	76%
Any prior alkylating agents, e.g., MP, VBMCP	91%	92%
Any prior thalidomide therapy	48%	50%
Vinca alkaloids	74%	72%
Prior stem cell transplant/other high-dose therapy	67%	68%
Prior experimental or other types of therapy	3%	2%

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

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

interim analysis of time to progression, the dexamethasone arm was halted and all patients randomized to dexamethasone were offered VELCADE, regardless of disease status.

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

The time to event analyses and response rates from the relapsed multiple myeloma study are presented in **Table 10**. Response and progression were assessed using the European Group for Blood and Marrow Transplantation (EBMT) criteria.<sup>1</sup> Complete response (CR) required <5% plasma cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test (IF). Partial response (PR) requires  $\geq 50\%$  reduction in serum myeloma protein and  $\geq 90\%$  reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks along with stable bone disease and normal calcium. Near complete response (nCR) was defined as meeting all the criteria for complete response including 100% reduction in M-protein by protein electrophoresis, however M-protein was still detectable by immunofixation (IF<sup>+</sup>).

**Table 10: Summary of Efficacy Analyses in the Relapsed Multiple Myeloma Study**

Efficacy Endpoint	All Patients		1 Prior Line of Therapy		> 1 Prior Line of Therapy	
	VELCADE	Dex	VELCADE	Dex	VELCADE	Dex
	n=333	n=336	n=132	n=119	n=200	n=217
<b>Time to Progression</b>						
Events n (%)	147 (44)	196 (58)	55 (42)	64 (54)	92 (46)	132 (61)
Median <sup>a</sup> (95% CI)	6.2 mo (4.9, 6.9)	3.5 mo (2.9, 4.2)	7.0 mo (6.2, 8.8)	5.6 mo (3.4, 6.3)	4.9 mo (4.2, 6.3)	2.9 mo (2.8, 3.5)
Hazard ratio <sup>b</sup> (95% CI)	0.55 (0.44, 0.69)		0.55 (0.38, 0.81)		0.54 (0.41, 0.72)	
p-value <sup>c</sup>	<0.0001		0.0019		<0.0001	
<b>Overall Survival</b>						
Events (deaths) n (%)	51 (15)	84 (25)	12 (9)	24 (20)	39 (20)	60 (28)
Hazard ratio <sup>b</sup> (95% CI)	0.57 (0.40, 0.81)		0.39 (0.19, 0.81)		0.65 (0.43, 0.97)	
p-value <sup>c,d</sup>	<0.05		<0.05		<0.05	
<b>Response Rate</b>						
Population <sup>e</sup> n = 627	n=315	n=312	n=128	n=110	n=187	n=202
CR <sup>f</sup> n (%)	20 (6)	2 (<1)	8 (6)	2 (2)	12 (6)	0 (0)
PR <sup>f</sup> n (%)	101 (32)	54 (17)	49 (38)	27 (25)	52 (28)	27 (13)
nCR <sup>f,g</sup> n (%)	21 (7)	3 (<1)	8 (6)	2 (2)	13 (7)	1 (<1)
CR + PR <sup>f</sup> n (%)	121 (38)	56 (18)	57 (45)	29 (26)	64 (34)	27 (13)
p-value <sup>h</sup>	<0.0001		0.0035		<0.0001	

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

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

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

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

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

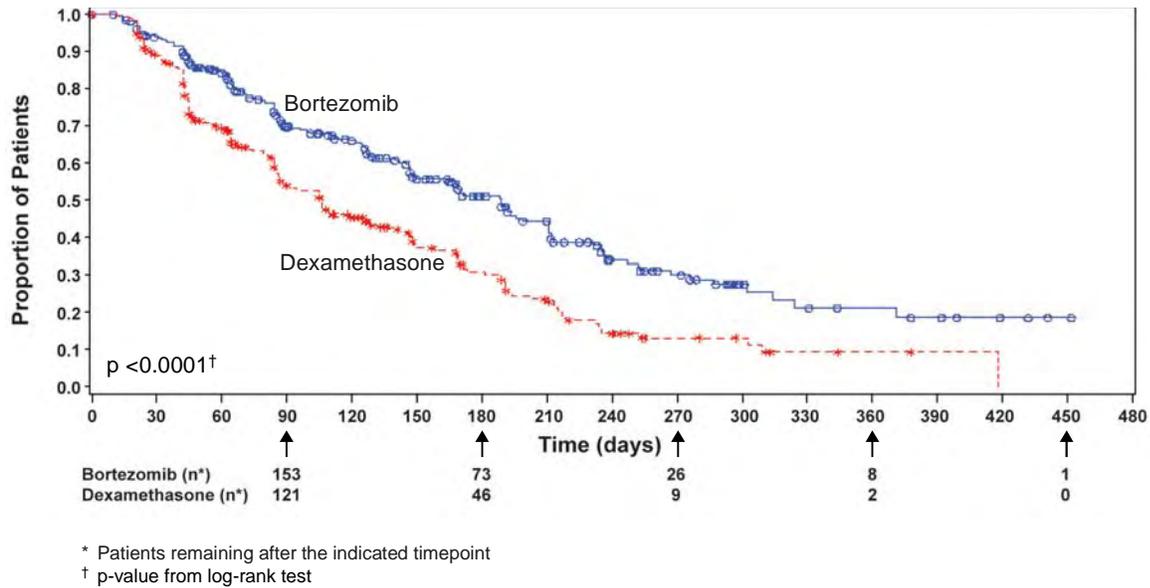
<sup>f</sup> EBMT criteria<sup>1</sup>; nCR meets all EBMT criteria for CR but has positive IF. Under EBMT criteria nCR is in the PR category.

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

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

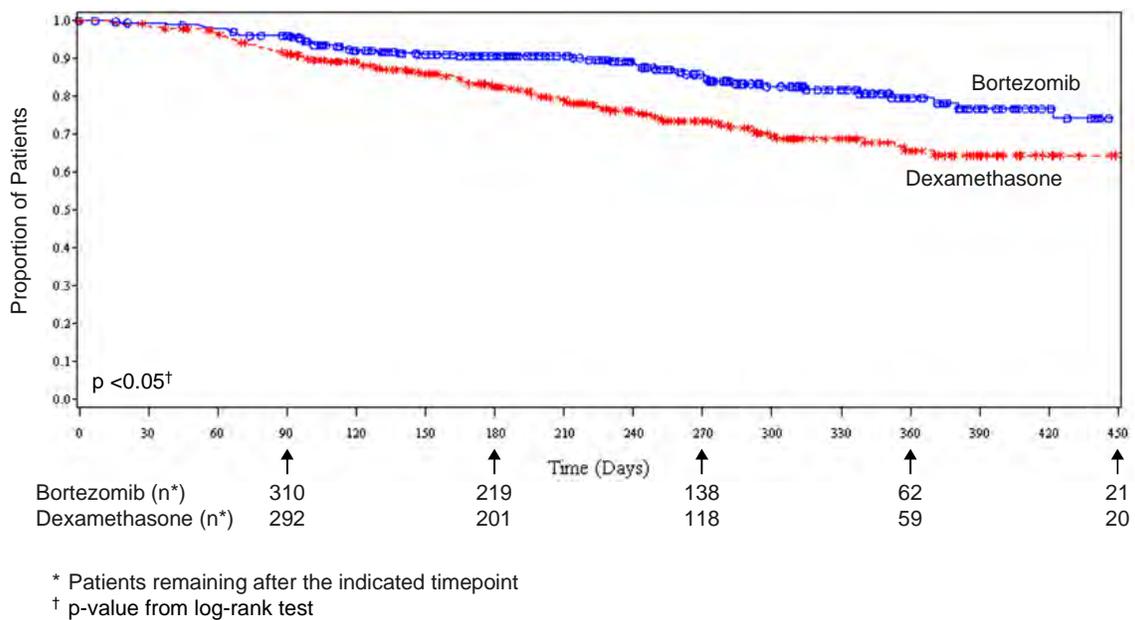
TTP was statistically significantly longer on the VELCADE arm (see Figure 2).

**Figure 2: Time to Progression**  
**Bortezomib vs. Dexamethasone (relapsed multiple myeloma study)**



As shown in **Figure 3** VELCADE had a significant survival advantage relative to dexamethasone ( $p < 0.05$ ). The median follow-up was 8.3 months.

**Figure 3: Overall Survival**  
**Bortezomib vs. Dexamethasone (relapsed multiple myeloma study)**



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

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

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

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

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

### **14.2 Mantle Cell Lymphoma**

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

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. The median age of the patients was 65 years (42, 89), 81% were male, and 92% were Caucasian. Of the total, 75% had one or more extra-nodal sites of disease, and 77% were stage 4. In 91% of the patients, prior therapy included all of the following: an anthracycline or mitoxantrone, cyclophosphamide, and rituximab. A total of thirty seven percent (37%) of patients were refractory to their last prior therapy. An IV bolus injection of VELCADE 1.3 mg/m<sup>2</sup>/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. Patients achieving a CR or CRu were treated for 4 cycles beyond first evidence of CR or CRu. The study employed dose modifications for toxicity. [see *Dosage and Administration* (2.4)]

Responses to VELCADE are shown in Table 11. Response rates to VELCADE were determined according to the International Workshop Response Criteria (IWRC)<sup>2</sup> 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 11: Response Outcomes in a Phase 2 Mantle Cell Lymphoma Study**

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

## 15 REFERENCES

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5. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006;63:1172-1193.
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## 16 HOW SUPPLIED/STORAGE AND HANDLING

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

NDC 63020-049-01

3.5 mg single use vial

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

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

### Caution: R<sub>x</sub> only

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

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## 17 PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

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

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Rev 9

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-602/S-015**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader and DDD Review

<b>Date</b>	6/5/08
<b>From</b>	Ann T. Farrell, M.D.
<b>Subject</b>	Cross-Discipline Team Leader and DDD Review
<b>NDA/BLA # Supplement#</b>	21-602, 015
<b>Applicant</b>	Millennium Pharmaceuticals
<b>Date of Submission</b>	12/20/07
<b>PDUFA Goal Date</b>	6/20/08
<b>Proprietary Name / Established (USAN) names</b>	Velcade
<b>Dosage forms / Strength</b>	Lyophilized powder for Intravenous injection
<b>Proposed Indication(s)</b>	1. For the treatment of patients with multiple myeloma
<b>Recommended:</b>	<i>Approval</i>

## **1. Introduction**

The applicant has submitted the results from a single study titled: "An Open-Label, Randomized Study of Velcade®-Melphalan-Prednisone Versus Melphalan-Prednisone in Patients with Previously Untreated Multiple Myeloma (protocol 26866138-MMY-3002)" to support a change to the indication and update the labeling with additional safety and efficacy information. The sponsor proposes that the clinical study report and data justify the following indication "for the treatment of patients with multiple myeloma". The sponsor has received approval for the treatment of patients with multiple myeloma who have been treated with 1 or more prior therapies. The current application proposes to justify the use of Velcade in the front-line setting.

## **2. Background**

The study protocol was submitted and reviewed by the Division in 2004, and the Division had agreed to the study design under a special protocol assessment (SPA). The use of melphalan prednisone (MP) as an active control is reasonable in this setting.

## **3. CMC/Device**

There are no outstanding issues.

## **4. Nonclinical Pharmacology/Toxicology**

No pharmacology/toxicology information was submitted with this application. There are no outstanding issues.

## **5. Clinical Pharmacology/Biopharmaceutics**

The sponsor submitted pharmacokinetic data of Velcade given alone or with melphalan and prednisone (MP) from a subgroup of 21 patients in the trial. The effect of co-administration of melphalan and prednisone on the exposure of Velcade was evaluated in 20 evaluable patients as a part of the pivotal Phase 3 Study MMY-3002. There was a 17% increase in mean Velcade exposure (AUC). Thus there does not appear to be a significant effect of MP on Velcade PK.

There are no outstanding issues.

## 6. Clinical Microbiology

No microbiology information was submitted with this application. There are no outstanding issues.

## 7. Clinical/Statistical- Efficacy

The applicant submitted the results from a single study titled: "An Open-Label, Randomized Study of Velcade®-Melphalan-Prednisone Versus Melphalan-Prednisone in Patients with Previously Untreated Multiple Myeloma (protocol 26866138-MMY-3002)."

From Dr. Kane's Medical Officer review, "The study is a prospective phase 3, international, randomized (1:1), open-label trial in patients with previously untreated multiple myeloma to compare Velcade (1.3 mg/m<sup>2</sup>) in combination with melphalan and prednisone, versus melphalan and prednisone. The primary endpoint is time to progression (TTP), using a time-to-event analysis for superiority."

Patient and disease demographics were well-balanced between treatment arms as noted in Dr. Kane's review.

*From Dr. Kane's review, "In total, 682 patients from 151 centers in 22 countries were randomized into Study MMY-3002 as of the cutoff time of June 15, 2007; 344 patients randomized to the Vc-MP treatment group and 338 patients randomized to the MP treatment group. The majority (79%) of patients were enrolled at sites in the Europe/Australia region, with most patients from Russia (14%), Germany (10%), Italy (9%), Poland (8%), and Belgium-Luxemburg (7%). A total of 9% of patients were enrolled in North America, including 6% (43 patients) enrolled in the U.S. In the Vc-MP treatment group, 340 patients received at least one dose of treatment compared to 337 in the MP treatment group, and thus 677 patients comprised the safety population.*

*The median age was 71 years, and 30% of patients were age 75 or greater. A total of 23 patients were less than age 65 and were judged not to be transplant-eligible on the basis of cardiovascular disease, emphysema, recurring infections, or other morbidity.*

*The majority (599 patients; 88%) were White; 10% were of Asian origin and 2% were Black. Males and females were evenly distributed. Mean BSA was 1.77 m<sup>2</sup>. The median baseline KPS was 80%; 34% of patients had a KPS of ≤70% and thus about 2/3 were PS 80 or above. Other notable characteristics included high stage disease (ISS Stage III) in 34%, extensive bone lesions (>10 lesions in 27%), and impaired renal function (creatinine clearance <60 mL/min in 54%).*

*For 98% of the patients, a monoclonal protein was present for monitoring, and 2% were considered as oligo-secretory. The protein was IgG in 63%, IgA in 25%, IgD and IgM in 1% each, and light-chain in 8%.*

By ISS staging,<sup>i</sup> 19% were stage 1, 47% were stage 2, and 34% were stage 3 at baseline. Of the 128 patients with Stage I disease, objective myeloma-related organ damage or disease symptoms were reported in all but 3 patients and included objective organ damage documented (baseline bone lesions or baseline plasmacytomas or pre-randomization hemoglobin result <100 g/L or pre-randomization creatinine result >ULN or pre-randomization serum calcium >ULN) or other evidence of myeloma related bone disease (e.g., therapy or symptoms for myeloma-related bone disease reported) or other myeloma-related symptoms (e.g., fatigue, infection, etc.) reported.

Reviewer comments: The median age on study is slightly older than the median age for the disease, since patients eligible for this study were judged not to be candidates for SCT. Enrollment to each arm was well-balanced by demographic factors: country, gender, age; and baseline disease characteristics including: cytogenetics, bone lytic lesions (present in 65% of each group), anemia, beta2-microglobulin levels, percent marrow plasma cells, renal function, baseline history of spinal cord compression, baseline opioid use (30% for each group), and baseline neuropathy (10%). About 15% were receiving bisphosphonates at baseline in each arm.”

The study results demonstrated that time to progression (TTP) was statistically significantly longer in the treatment arm where Velcade was added to MP compared with the MP arm. The results on TTP are also supported by an improvement in Overall Survival for patients who received Velcade.

#### Study MMY-3002 Results

	MP	Velcade plus MP	P-value (stratified log-rank)	Hazard ratio (Cox model) (95% CI)
Efficacy Parameter				
Time to Progression – Median (months) (95% CI)	15 mo (14.1, 17.9 )	20.9 mo (17.6, 24.7 )	< 0.000002	0.537 (0.42, 0.70)
Overall Survival – Median (months)	NE	NE	< 0.0078	0.607 (0.42, 0.88)

Reviewer’s Table

For other secondary endpoints (response rate), please see Dr. Kane’s MO review and Dr. Ko’s statistical review.

Dr. Kane's review notes that the TTP analyses differ between the applicant and the FDA. The TTP calculation differs due to the FDA review team's removal of 6 patients who did not have confirmed progression prior to death. He notes that the applicant chose to include them in the TTP analysis.

Regardless of the method, the results suggest a statistically significant difference in TTP for those on the Velcade combination arm.

These results are not unexpected given that previous studies of Velcade have demonstrated its efficacy in the setting of more refractory and previously treated multiple myeloma.

## 8. Safety

The application represents the fourth indication for Velcade. No new safety issues were identified during this review. However, Dr. Kane did identify the following issues as safety issues for this particular submission: infection, hematology, neuropathy, and cardiac. His review noted that the hematology and neuropathy information were adequately described in the labeling. I concur with his assessment regarding the hematologic and neurologic adverse events.

Reproduced below are his discussions regarding infection and cardiac issues.

From his review

*"Infections:*

*The incidence of Grade  $\geq 3$  infections at any time during treatment was 19% (66 patients) in the Vc-MP treatment group and 18% (60 patients) in the MP treatment group. In the Vc-MP and MP treatment groups, respectively, the most common infections included pneumonia (16% vs. 11%), herpes zoster (13% vs. 4%), and bronchitis (13% vs. 8%). Respiratory tract infections were higher in MP-treated patients (5%) compared with Vc-MP-treated patients (1%).*

*The incidence of herpes zoster was higher in the Vc-MP treatment group (14%) compared with the MP treatment group (4%). The protocol contained a recommendation for antiviral prophylaxis for the Velcade group; 26% (90/340 patients) of patients in the Vc-MP treatment group compared with 4% (14/337 patients) received prophylactic antivirals. Of the 90 patients in the Vc-MP treatment group who received prophylactic antivirals, only 3 patients (3.3%) developed herpes zoster. Of the 250 patients in the Vc-MP treatment group who did not receive antiviral prophylaxis, 43 (17%) patients developed herpes zoster. Prophylactic use of antivirals may have reduced development of herpes zoster for Vc-MP-treated patients but there likely was a selection bias with regard to who received antivirals. In the MP treatment group, 2/14 patients (14%) who received prophylactic antivirals developed herpes zoster, while 12/323 patients (4%) without antiviral prophylaxis developed herpes zoster. Prophylactic antibacterial use prior to the start of treatment was similar in both treatment*

groups (14 patients [4%] and 15 patients [4%] in the Vc-MP and MP treatment groups, respectively).

*Circulatory and cardiac conditions:*

*On the current study, there were 52 (15%) hypotension and orthostatic hypotension cases combined for the Vc-MP arm versus 11 (4%) on the MP arm. Hypotension can precipitate cardiovascular events. Treatment-emergent hypertension occurred in 13% on the Vc-MP arm versus 7% on the MP arm. Some of this hypertensive effect is likely due to the steroid (P), but the asymmetry in the effect is not explained.*

*In the Vc-MP treatment group, 11% of patients experienced a Cardiac Rhythm and Conduction Abnormality (most commonly palpitations and atrial fibrillation each in 3% of patients). In 4% of patients, these Cardiac Rhythm and Conduction Abnormalities were considered related to study drug, were Grade 3 or higher in 4% of patients, were considered serious adverse events in 4% of patients, and resulted in study drug discontinuation in 1% of patients. In the MP treatment group, 11% of patients experienced Cardiac Rhythm and Conduction Abnormalities including palpitations and atrial fibrillation in 3% each of patients. In 2% of patients, these Cardiac Rhythm and Conduction Abnormalities were considered related to study drug, were Grade 3 or higher in 3% of patients, were considered serious adverse events in 3% of patients, and resulted in study drug discontinuation in <1% of patients.*

*Seventeen patients (5%) in the Vc-MP treatment group and 11 patients (3%) in the MP treatment group experienced at least 1 heart failure event. Eleven of the 17 heart failure events reported in the Vc-MP treatment group were considered at least Grade 3 while 10 of the 11 heart failure events reported in the MP treatment group were considered at least Grade 3 toxicity. Note: 43 patients (13%) in the Vc-MP treatment group and 30 patients (9%) in the MP treatment group were reported with heart failure at baseline.*

**Table 1: Time to heart failure events**

	MP (N=11)	Vc-MP (N=17)
<b>Any Heart Failure Event</b>		
N	11	17
Mean (SD) days	179.5 (138.85)	61.1 (81.35)
Median	217.0	39.0
Range	(4; 343)	(9; 355)
<b>Grade ≥ 3 Heart Failure Event</b>		
N	10	11
Mean (SD) days	167.8 (140.48)	43.3 (27.30)
Median	139.5	39.0
Range	(4; 343)	(9; 95)

*Sponsor table 61, CSR page 228*

*Reviewer comments: The protocol excluded patients with uncontrolled or severe cardiovascular disease, including myocardial infarction within 6 months of enrollment, New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, clinically significant pericardial disease, or cardiac amyloidosis. Overall the differences in frequency of heart failure on study were similar. Time to onset appeared to be earlier on the Velcade arm.*

*For Vc-MP- and MP-treated patients without a history of hypotension, 47 (14%) patients and 11 (3%) patients respectively reported treatment-emergent hypotension events during the study. Four patients in MP treatment group and 6 patients in Vc-MP treatment group had a history or the presence of orthostatic hypotension at study entry. None of these in the MP treatment group and 2 of these 6 patients (33%) in the Vc-MP treatment group reported treatment-emergent hypotension.*

*Some cardiac ECHO data (for Velcade alone) was available in the randomized study of Velcade + Doxil versus Velcade (MMY-3001), reviewed for the sNDA for Doxil. In that study, a LVEF reduction was defined as an absolute decrease of  $\geq 15\%$  over baseline or a  $\geq 5\%$  decrease below the institutional lower limit of normal. Based on that definition, 25 (8%) patients in the Velcade alone arm and 42 (13%) patients in the Doxil + Velcade arm experienced a reduction in LVEF. In the study, the incidence of heart failure adverse events (ventricular dysfunction, cardiac failure, right ventricular failure, congestive cardiac failure, chronic cardiac failure, acute pulmonary edema and pulmonary edema) was similar (3% each) in the Doxil + Velcade group and the Velcade monotherapy group.*

*Other AEs rates can be summarized as follows:*

<i>Gastrointestinal Disorders</i>	<i>(Vc-MP: 77%, MP: 55%)</i>
<i>Nervous System Disorders</i>	<i>(Vc-MP: 74%, MP: 36%)</i>
<i>General Disorders</i>	<i>(Vc-MP: 70%, MP: 59%)</i>
<i>• Infections and Infestations</i>	<i>(Vc-MP: 69%, MP: 54%)</i>
<i>• Metabolism and Nutrition Disorders</i>	<i>(Vc-MP: 47%, MP: 37%)</i>
<i>• Skin and Subcutaneous Tissue Disorders</i>	<i>(Vc-MP: 41%, MP: 24%)</i>
<i>• Psychiatric Disorders</i>	<i>(Vc-MP: 33%, MP: 23%)</i>
<i>• Vascular Disorders</i>	<i>(Vc-MP: 33%, MP: 20%)</i>

*Reviewer comments: The addition of Velcade did not appear to increase substantially the cardiac AEs (a difference of 6 patients) compared to the MP arm. On the Vc-MP arm, 13 additional patients had entered the study with cardiac history. CHF of grade  $\geq 3$  occurred in equal numbers on each study arm. Hypotension is more common on the Vc-MP arm, and this AE is included in the label but should continue to be emphasized by the applicant in marketing materials...*

Based on review of the study results for infection, no significant change to the labeling is recommended at this time. In this trial, the incidences of grade 3 or greater infection were similar for the treatment arms; however the incidence of respiratory tract infections was higher for the MP arm. The incidence of herpes zoster infection was higher in the Velcade arm. The

higher incidence of herpes zoster infection associated with Velcade was noted previously with Velcade and is already described in the label.

Due to the concern for viral infection, the MMY-003 study protocol recommended the use of anti-viral prophylaxis but did not mandate it. The study information regarding the use of anti-viral prophylaxis should be incorporated into the labeling.

The issues regarding cardiovascular issues are less clear. The review of the data from this trial did not suggest an overall increase in cardiac arrhythmias nor angina or myocardial infarction on the Velcade arm. Although there was a 2% difference in serious cardiac rhythm and conduction abnormalities, no difference was observed in the rate of discontinuation due to cardiac rhythm and conduction abnormalities.

The study noted an increase in cardiovascular/fluid overload/hypotension/hypertension events. The difficulty with the causality assessment is that both Velcade and prednisone can effect fluid shifts partially through effects on vasculature. Information on Velcade's effect on the vasculature has been in the label since the original approval. The information on cardiovascular adverse events should be incorporated into the labeling.

From Dr. Kane's review he recommended that *Continuing emphasis on adequate and optimal hydration is important. Systemic hypotension is a known direct effect of Velcade as well as an expected possibility in patients experiencing symptoms of nausea, vomiting, diarrhea, ileus, asthenia, dyspnea, pneumonia and other respiratory impairments. However, vigorous hydration is circumscribed by the possibility of fluid overload and congestive heart failure occurring as well. These concerns are described in the current label.*

I concur with his assessments regarding the cardiovascular adverse events and labeling.

Both Dr. Kane and I note that European Medicines Agency (EMA) recently recommended that Velcade (bortezomib) should not be used in patients with certain severe pulmonary or heart problems (acute diffuse infiltrative pulmonary and pericardial disease). However, the EMA Committee for Medicinal Products for Human Use (CHMP) also concluded during its March 2008 meeting that the benefits of Velcade are greater than its risks. Thus they recommended that, "in patients with acute diffuse infiltrative pulmonary and pericardial disease," Velcade not be used.

We reviewed our data regarding these adverse events, and this study's data. We performed exploratory analyses for cardiovascular events and individually reviewed the data. At the present time, we do not recommend a labeling change but do recommend continued surveillance for cardiovascular events and pulmonary events in order to be able to inform physicians as quickly as possible.

## **9. Advisory Committee Meeting**

The application was not taken to an Advisory Committee meeting for multiple reasons including:

The Division has previously used TTP and related endpoints such as progression-free survival (PFS) for regular/full approval decisions for the treatment of multiple myeloma.

Velcade has demonstrated a statistically significant efficacy difference for TTP in a patient population with multiple myeloma that has failed other therapies in a randomized control trial.

## **10. Pediatrics**

Velcade has Orphan Drug status and therefore a waiver or deferral is not necessary.

## **11. Other Relevant Regulatory Issues**

The Division of Scientific Investigation (DSI) declined to audit this trial. DSI has previously audited trials used as the basis for approval of prior supplements which included some of the sites.

## **12. Labeling**

Information added to the label from review of the supplement included a change in the indication as well as incorporation of the efficacy and safety information from the trial. The information regarding anti-viral prophylaxis as used during the trial was added to Velcade's label for safe and effective use.

## **13. Recommendations/Risk Benefit Assessment**

- Recommended regulatory action

Dr. Kane recommended approval and I concur.

- Risk Benefit Assessment

Untreated multiple myeloma is a fatal disease. The study results demonstrated an improvement in TTP and OS (although the medians have not been reached). While Velcade treatment is not without risk, the benefit outweighs the risk.

- Recommendation for Postmarketing Risk Management Activities

Continued surveillance for adverse events

- Recommendation for other Postmarketing Study Commitments

None

- Recommended Comments to Applicant

None

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<sup>i</sup> Philip R. Greipp, Jesus San Miguel, Brian G.M. Durie, John J. Crowley et al. International Staging System (ISS) for Multiple Myeloma. J Clin Oncol 2005; 23: 3412-3420.

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Ann Farrell  
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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-602/S-015**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	sNDA
Submission Number	21-602 SE1
Submission Code	015
Letter Date	12/20/2007
EDR Stamp Date	12/31/2007
PDUFA Goal Date	06/17/2008
Reviewer Name	Robert C. Kane, MD
Review Completion Date	05/16/2008
Network path	<a href="\\CDSESUB1\EDRWORK\restore\N21602\S_015">\\CDSESUB1\EDRWORK\restore\N21602\S_015</a>
Established Name	Bortezomib
(Proposed) Trade Name	Velcade
Therapeutic Class	Proteasome inhibitor
Applicant	Millennium, Inc.
Priority Designation	P
Formulation	Lyophilized powder for Intravenous injection
Dosing Regimen	1.3 mg/m <sup>2</sup> twice weekly for 2 weeks every three weeks
Indication	For the treatment of patients with multiple myeloma
Intended Population	Multiple myeloma (first-line)

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## Table of Abbreviations

AE	Adverse Event
ANC	Absolute neutrophil count
AR	Adverse reaction
ASH	American Society of Hematology
CR	Complete response (EBMT criteria)
CSR	Clinical study report
CTCAE	Common Toxicity Criteria, version 3, NCI
Dex	Dexamethasone
EBMT	European bone marrow transplant program
ESA	Erythropoietic stimulating agent (epoietin / darbepoetin)
IDMC	Independent data safety monitoring committee
HDT	High-dose chemotherapy (usually used with stem cell transplantation)
HR	Hazard ratio
IF	Immunofixation electrophoresis
IMWG	International Myeloma Working Group
IRRC	Independent radiologic review committee
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
ISS	International staging system (for myeloma)
ITT	Intention to treat population (all patients' randomized)
IV	Intravenous
LOCF	Last observation carried forward
MOA	Mechanism of action
MP	Melphalan plus prednisone
M-protein	Myeloma protein (refers to the monoclonal product of plasma cells)
NOS	Not otherwise specified
ns	not statistically significant
ORR	Overall response rate, defined as CR plus PR
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PN	Peripheral neuropathy
PO	per os, orally
PR	Partial response (EBMT criteria)
P.S.	Performance status
SAE	Serious adverse event (CTCAE criteria)
SCT	Stem cell transplant (follows high-dose chemotherapy)
SOC	System, organ, class (categories for merging AEs by type)
SPD	Sum of the longest perpendicular diameters
TEAE	Treatment-emergent adverse event
TTP	Time to tumor progression
ULN	Upper limit of normal
Vc-MP	Velcade plus MP

# **1 Recommendations/Risk Benefit Assessment**

## **1.1 Recommendation on Regulatory Action**

I recommend that Velcade receive regular approval for the applicant's proposed indication: "treatment of patients with multiple myeloma." For this sNDA, the applicant has submitted substantial evidence for the efficacy and safety of Velcade from a study in a previously untreated, first-line multiple myeloma population of 682 patients. Velcade has previously received approval as a single agent in the relapsed, refractory setting and for the "second line" setting for myeloma patients after one prior therapy. In this study, time to progression (TTP), the pre-specified primary endpoint and the secondary study endpoints of overall survival (OS), progression-free survival, and response rate, were statistically and clinically superior for the addition of Velcade to melphalan plus prednisone (MP), a standard first-line therapy for symptomatic multiple myeloma (see section 6, table 2). The primary progression endpoint was determined in most cases by changes in laboratory values performed centrally and assessed by a computer algorithm previously validated by the applicant. The progression-free survival (PFS) results, incorporating all deaths, were consistent with the TTP results. For the TTP, PFS, OS, and the response endpoints, exploratory subgroup analyses showed consistent superiority for the addition of Velcade to MP. The study population consisted of patients age 65 and above, as well as a small number of younger patients considered ineligible for high-dose chemotherapy (HDT) plus stem cell transplantation (SCT). The median age at diagnosis for myeloma is 68 years, and SCT is generally limited to those under age 65. While this study does not directly examine the use of Velcade alone or in combination before SCT, other reported studies do support that use and a restriction of the indication based on potential transplant eligibility does not appear necessary for safe use of Velcade in the first-line setting.

The Division had agreed to the study design in 2004 under a special protocol assessment (SPA), and the applicant conducted the study and the analyses diligently. The efficacy and safety findings for the active control group receiving MP are plausible. Safety has already been well-characterized for Velcade as monotherapy, and no new or excessive safety findings were observed in this study in combination with MP. Post-marketing safety reports, when compared with findings from clinical trials, indicate that physicians can use Velcade with acceptable safety and that the label provides useful safety margins for individual patient needs.

## **1.2 Risk Benefit Analysis**

The dose and schedule studied in the protocol confer clear clinical benefits of disease control and survival improvement with well-characterized, acceptable, and manageable safety.

Myelosuppression usually is not excessive. Neuropathy is a common baseline characteristic of patients with MM and also a definite consequence of Velcade therapy, but the dose adjustments in the current label allow acceptably safe use of Velcade in the context of this disease process. The applicant also has studied Velcade use with renal impairment (also common in myeloma) and has determined that dose adjustment is not necessary in renal impairment.

### **1.3 Recommendations for Risk Evaluation and Mitigation Strategies**

While the current label provides detailed clinical guidance for the appropriate use of Velcade, respiratory complications occur prominently in Velcade studies. However, respiratory complications are common in myeloma patients, many of whom have impaired immunity, neutropenia, and an increase in respiratory infections in addition to the potential affects of chemotherapy. The role of Velcade as an additional risk factor is uncertain, but chemotherapy generally has immunosuppressive effects. Given the increased risk of infection in such patients, attention to immunization for pneumococcal and viral respiratory diseases before starting chemotherapy may be of help, even though vaccine efficacy may be impaired. Alternatively, patients may be considered for immunizations following disease response to therapy.

Patients receiving Velcade in this study also received antiviral prophylaxis; consideration for antiviral prophylaxis has been added to the label.

Continuing emphasis on adequate and optimal hydration is important. Systemic hypotension is a known direct effect of Velcade as well as an expected possibility in patients experiencing symptoms of nausea, vomiting, diarrhea, ileus, asthenia, dyspnea, pneumonia and other respiratory impairments. However, vigorous hydration is circumscribed by the possibility of fluid overload and congestive heart failure occurring as well. These concerns are described in the current label.

### **1.4 Recommendations on Post Marketing Activities/Phase 4 studies**

1. The applicant should consider providing additional education to treating physicians to emphasize performing close patient observations to optimize fluid balance to prevent dehydration and hypotension as well as fluid overload during Velcade therapy. Frequent check of patient weight and fluid intake might assist in assessing under- or over-hydration.
2. Velcade alone or when added to MP is associated with an increase in re-activation events of herpes viruses, including zoster. In this protocol, antiviral prophylactic medications were advised in the Velcade combination arm. The sponsor should consider determining the value of antiviral prophylaxis prospectively.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

Unchanged from the previous review of sNDA 21-602, SE1-006 in 2005

## **2.2 Tables of Currently Available Treatments for Proposed Indications**

A table is not provided. Until 2003, MP or its variations (or dexamethasone alone) were the only treatment options for older patients, and a combination of vincristine, adriamycin, and dexamethasone (VAD) was commonly used for younger and transplant-eligible patients. Since then, Velcade, thalidomide, and lenalidomide have been approved as single agents. They are being studied in various combinations in first-line and subsequent lines of MM therapy.

## **2.3 Availability of Proposed Active Ingredient in the United States**

Velcade has been available commercially in the U.S. since 2003.

## **2.4 Important Safety Issues with Consideration to Related Drugs**

There are no other marketed drugs with a similar mechanism of action to Velcade. It is unlikely that Velcade can be combined with thalidomide due to overlapping neuropathy toxicity.

## **2.5 Summary of Pre-submission Regulatory Activity Related to Submission**

- In 2003, Velcade was approved under subchapter H for relapsed and refractory myeloma.
- In 2005, Velcade received regular approval for the treatment of myeloma progressing after one prior therapy, based on a single randomized study in 669 patients with progressive myeloma after one prior therapy who then were treated either with Velcade or dexamethasone. In that study, time to progression (TTP), the primary endpoint, was improved from a median of 3 months on dexamethasone to 6 months on Velcade. Overall survival, a secondary endpoint, was significantly improved also.
- In 2006, Velcade received regular approval for treatment of mantle cell lymphoma after one prior therapy.
- Velcade has exclusivity under orphan drug status for both of the above indications through 2012
- A pediatric waiver has previously been granted for MM and is requested for this indication with the sNDA.
- Millennium Pharmaceuticals, Inc. also is seeking exclusivity, pursuant to 21 CFR 314.108(b)(5), for Velcade (bortezomib) for Injection for the treatment of patients with previously untreated multiple myeloma.

Reviewer comments: For this application, the EOP2 meeting was held in February 2004. The applicant subsequently submitted a special protocol assessment which was accepted after amendment. The Agency accepted the use of TTP as the primary efficacy endpoint with the study powered to assess OS. TTP was used in the regular approval of Velcade in 2005 (for treatment after one prior therapy) with improved OS as a supportive analysis. TTP is plausible since (1) this myeloma population is older and patients have co-morbidities and competing mortality, (2) multiple subsequent therapies are available which may confound the OS analysis, and (3) TTP is assessed by results of laboratory protein measurements using a validated computer algorithm which functions essentially as a blinded independent adjudication procedure.

Also, while TTP quantifies a progression state, most patients receiving the therapy also show at least some level of response and clinical benefits such as reduced transfusions, increased hemoglobin, reduction in pain, delay in skeletal adverse events, etc.

## **2.6 Other Relevant Background Information**

MM is predominately a disease of the elderly, with a median age of 68 years. For eligible patients under age 65, high-dose therapy and stem-cell transplantation (SCT) is usually offered based on evidence of improved PFS and OS in some earlier randomized studies. The transplant-eligible population was excluded from the present study, although the overall benefit of SCT in patients currently experiencing high-level responses to contemporary combination therapies is not clear.

Velcade has been studied with dexamethasone (Dex) as first-line therapy. Anderson et al<sup>1</sup> reported results of 66 patients receiving the approved dose and schedule of Velcade along with Dex in which the ORR was 38% (including 10% CR and 28% PR). Peripheral neuropathy (PN) occurred in 55% (with 66% grade 1 and 33% grade 2) with 1 patient discontinuing for grade 3 PN. In this phase 2 study in "elderly, previously untreated patients, high response rates with toxicity judged as consistent with that expected was reported (this study was not submitted for this NDA).<sup>1</sup> Previous approvals have been based on the use of Velcade as a single agent and with dexamethasone (Dex) for myeloma patients after initial therapy.

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

The applicant has provided an electronic application with excellent clarity, organization, and analyses. The statistical reviewer has verified the accuracy of all of the principal analyses. DSI was consulted regarding an audit of 2 sites (one in Boston and one in Edmonton, Alberta) selected for their relatively high enrollment and geographic proximity. Subsequently, Dr. Robert Young, DSI, advised the Division that an inspection for this sNDA will not be conducted and noted that, in this sNDA, while TTP is the primary endpoint, the study shows a strongly positive overall survival finding and this is the third regulatory submission for Velcade in the myeloma population (and the fourth overall) with no prior concerns identified by DSI.

### **3.2 Compliance with Good Clinical Practices**

The trial was designed to be performed in accordance with the Declaration of Helsinki and each site had an IRB/IEC protocol review. Compliance has been attested by the applicant.

### **3.3 Financial Disclosures**

The applicant provided financial statements on all site PIs and many sub-investigators but not all. No conflicts of interest have been identified except for 2 sub-investigators who either

held stock or received fees for providing services to the applicant. Only one patient was entered and followed by one of these two individuals.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

No new information was submitted

### **4.2 Clinical Microbiology**

No new information was submitted

### **4.3 Preclinical Pharmacology/Toxicology**

No new information was submitted

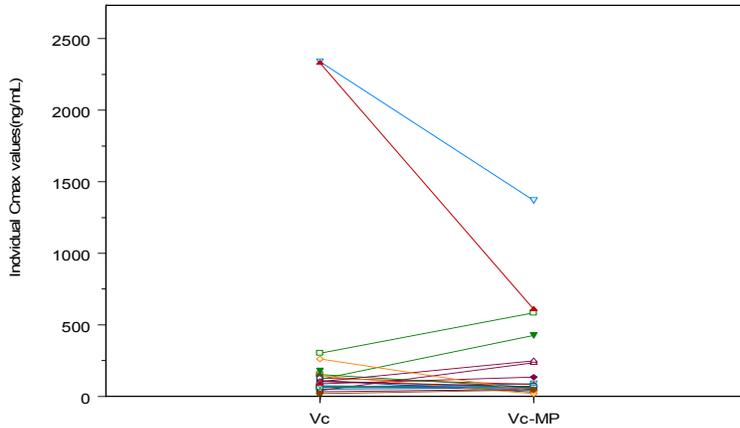
### **4.4 Clinical Pharmacology**

The PK of Velcade given alone or with MP was studied in a subgroup of 21 patients in the trial. The effect of co-administration of melphalan and prednisone on the exposure of VELCADE was evaluated in 20 evaluable patients as a part of the pivotal Phase 3 Study MMY-3002. It is not known whether melphalan or prednisone inhibits CYP3A4, the principal enzyme involved in Velcade metabolism. The effect of Velcade on the PK of melphalan and prednisone has not been examined in this study. Melphalan is eliminated from plasma primarily by chemical hydrolysis and there is no evidence of cytochrome P450-mediated metabolism. Prednisone is metabolized by the liver to the active metabolite prednisolone through the  $11\beta$ -hydroxydehydrogenase enzyme, which is not part of the CYP system.

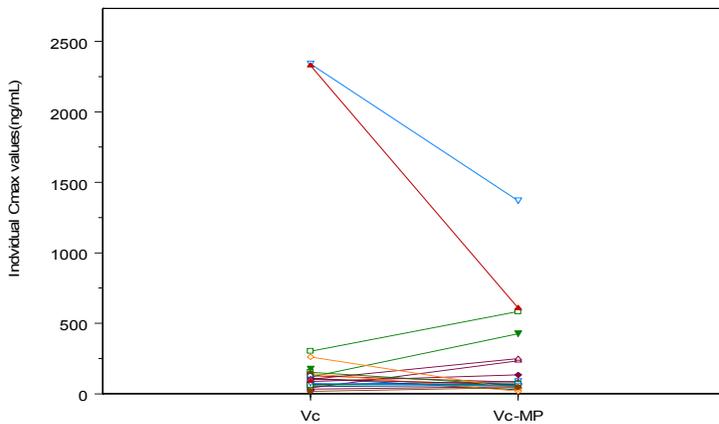
The graphs below, provided by Dr. S. Abraham, clinical pharmacology reviewer, display individual patient data. Apart from the outliers, there was no substantial difference in daily exposure ( $AUC_{0-24h}$ ) to VELCADE after MP administration when compared to VELCADE alone. A similar observation was made for  $AUC_{0-\infty}$ .

The variability was high for both AUCs (71% for  $AUC_{0-24h}$  and 52% for  $AUC_{0-\infty}$  for VELCADE alone and for VELCADE + MP treatments, respectively). As noted in the graphs, one patient appeared to drive the high variability in  $C_{max}$  and AUC values.

**Figure 1:** Comparison of Individual and Mean  $C_{max}$  of VELCADE With or Without Co-Administration with Melphalan+Prednisone in 21 Evaluable Patients



**Figure 2:** Comparison of Individual and Mean Exposure ( $AUC_{0-24h}$ ) of VELCADE With or Without Co-Administration with Melphalan+Prednisone in 21 Evaluable Patients



Additionally, no significant relationships were observed between polymorphisms in the genes (CYP2C19, CYP2D6, CYP3A4, and CYP3A5) and pharmacokinetic endpoints ( $AUC_{\infty}$  and

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Robert Kane, MD

C<sub>max</sub>) in patients who received VELCADE alone or in the presence of MP. See the clin-pharm review.

Reviewer comments: These findings were reviewed with the clinical pharmacology team. While the effect of MP on Velcade, studied under a bioequivalence design, showed a 17% increase in mean Velcade exposure (AUC), inspection of the individual patient data points shows that for all patients except the 2 of 21 outliers, the exposure of Velcade was not appreciably changed by co-administration of MP. The reason for the 2 outliers is not explained. It is reasonable to conclude that there is not a significant effect of MP on Velcade PK.

#### 4.4.1 Mechanism of Action

No new data submitted

#### 4.4.2 Pharmacodynamics

No new data submitted

## 5 Sources of Clinical Data

### 5.1 Tables of Clinical Studies

One clinical study is submitted

**Table 1: Studies submitted for the NDA**

Study number	design	N	Schedule	Outcome
26866138- MMY-3002	Phase 3, 2 arm, open-label, add-on design	682	Vc-MP versus MP	TTP and OS improvement

### 5.2 Review Strategy

Since Velcade is approved for use following first-line therapy and also in refractory and relapsed myeloma patients, the primary concern for this application is the strength of evidence to support the first-line use of the drug in the general population of myeloma patients not previously treated. This review examines that support, including the characteristics of the population studied as representative of previously untreated and symptomatic myeloma patients, the magnitude of effect demonstrated for the primary and secondary endpoints, toxicity, the plausibility of the effect size in the control group, and the conduct of the study. While the study is open-label in design, the endpoint is determined primarily by an algorithm applied to central lab results.

### 5.3 Discussion of Individual Studies

The applicant has submitted one study titled: "An Open-Label, Randomized Study of Velcade®-Melphalan-Prednisone Versus Melphalan-Prednisone in Patients with Previously Untreated Multiple Myeloma (protocol 26866138-MMY-3002)." The study is a prospective phase 3, international, randomized (1:1), open-label trial in patients with previously untreated multiple myeloma to compare Velcade (1.3 mg/m<sup>2</sup>) in combination with melphalan and prednisone, versus melphalan and prednisone. The primary endpoint is time to progression (TTP), using a time-to-event analysis for superiority. The principal investigator is Jesus San Miguel, M.D., Hospital Clinico de Salamanca, Salamanca, Spain. The efficacy and safety results will be reviewed in sections 6 and 7.

## 6 Review of Efficacy

**Table 2: FDA efficacy analysis overview table**

N = 682 (ITT population) Efficacy endpoints	MP n = 338	Vc-MP n = 344
<b>Time to Progression</b>		
Events n (%) 247/390	148 (43.8%)	99 (28.8%)
Median (months) (95% CI)	15 mo (14.1, 17.9)	20.9 mo (17.6, 24.7)
P value (stratified logrank) a	< 0.000002	
Hazard ratio (Cox model) b (95% CI)	0.537 (0.42, 0.70)	
<b>Progression-free Survival</b>		
Events n (%)	190 (56)	135 (39)
Median (month) (95% CI)	14.0 mo (11.1, 15.0)	18.3 mo (16.6, 21.7)
P value (stratified logrank) a	0.00001	
Hazard ratio <sup>b</sup> (95% CI)	0.61 (0.49, 0.76)	
<b>Overall Survival</b>		
Events (deaths) n (%) 121 events	76 (23%)	45 (13%)
Overall Survival – Median (months) (median not reached)	NE	NE
Hazard ratio (Cox model) (95% CI)	0.607 (0.42, 0.88)	
p value (stratified logrank)	< 0.0078	
<b>Response</b>		
Response rate CR n (%)	12 (4%)	102 (30%)
Response rate PR n (%)	103 (30%)	136 (40%)
Response rate total (CR + nCR + PR) n (%)	115 (34%)	238 (69%)
P value (CMH chi-square) c	p < 10 <sup>-10</sup>	

### Reviewer table

a: The interim analysis TTP alpha boundary was 0.0096 with 63% (247/390) of the total TTP events. The logrank test stratification factors were the stratifications used at randomization, as pre-specified

b: The Cox regression model covariates used the same stratification factors: beta<sub>2</sub> micro-globulin, albumin, and region, as pre-specified

c: Stratified Cochran-Mantel-Haenszel chi-square test

### Reviewer comments:

This table differs from the applicant's analysis in two areas. First, the TTP calculation differs due to the removal of 6 patients who did not have confirmed progression prior to death. The applicant chose to include them in the TTP analysis. Second, the response rates are calculated on the ITT population, not the response-evaluable as used by the applicant. The FDA method maintains the phase 3 intention-to-treat design. Please see the FDA statistical review which discusses these choices in more detail.

## 6.1 Indication

The sponsor's proposed indication is: "Velcade (bortezomib) is indicated for the treatment of patients with multiple myeloma."

Reviewer comment: This is a broad indication and could include patients eligible for SCT used as a consolidation therapy following their initial chemotherapy. This study does not define the safety of a subsequent SCT since patients considered SCT-eligible were excluded from this trial. However, less than 50% of myeloma patients are eligible for SCT, and the sponsor has performed other studies showing that SCT after induction with other Velcade combinations (using this same Velcade dose) does not impair stem cell collection or SCT results.<sup>2</sup>

### 6.1.1 Methods/Study design

There is one large phase 3 trial supporting this sNDA.

Study 26866138-MMY-3002:

- Design: Open-label, prospective, randomized, active-control, international phase 3 study
- Randomization and analysis stratified by:
  - baseline beta<sub>2</sub>-microglobulin ((<2.5 mg/L, 2.5 to 5.5 mg/L, >5.5 mg/L)
  - baseline albumin (<3.5 g/dL and ≥3.5 g/dL [SI Units: <35 g/L, ≥35 g/L])
  - Geographic regions – 3 groups (North America, Europe, other)
- Population: Previously untreated, symptomatic multiple myeloma or asymptomatic with related organ/tissue damage (also defined using EBMT criteria)
  - Measurable disease (M protein): Blood and 24-hour urine samples for M-protein measurements were analyzed by a central laboratory.
  - KPS ≥ 60
  - Adequate baseline organ function (platelets > 100,000; ANC > 1000)
  - Not candidates for high dose chemotherapy-stem cell transplant
    - Based on age 65 or greater, or
    - Co-morbid conditions precluding SCT (sponsor approval needed)
  - No radiation or major surgery within 30 days
  - No peripheral neuropathy (or neuropathic pain) grade 2 or higher at entry
- Treatment: MP versus Vc-MP
  - Active control arm is a standard regimen for this population
  - MP: Cycles every 6 weeks times 9 cycles maximum
    - Melphalan by mouth 9 mg/m<sup>2</sup> daily times 4 days, days 1-4
    - Prednisone 60 mg/m<sup>2</sup> by mouth daily times 4 days, days 1-4
  - Vc-MP: Cycles every 6 weeks times 9 cycles maximum
    - MP same as the control arm

- Vc – Velcade 1.3 mg/m2 given IV bolus:
  - First 4 cycles: Given on days 1, 4, 8, 11, 22, 25, 29, 32
  - Next 5 cycles: Given weekly X 4 weeks; days 1, 8, 22, 29

Study drug administration schedule for the Vc-MP arm.

**Four 6-Week Treatment Cycles**

Week	1				2		3	4		5		6
Day	1	2	3	4	8	11	-	22	25	29	32	-
Vc	X			X	X	X	-	X	X	X	X	-
MP	X	X	X	X								

**Five 6-Week Treatment Cycles**

Week	1				2	3	4	5	6
Day	1	2	3	4	8	-	22	29	-
Vc	X				X	-	X	X	-
MP	X	X	X	X					

- Clinic visits: every 3 weeks for the first 54 weeks then every 6 weeks
  - Dose omissions for up to 3 weeks allowed; dose reductions also provided
  - The neuropathic pain dose-reduction chart in the current label was used
  - Upon evidence of PD, further therapy to be selected by investigator choice
- Concomitant drugs
  - Bisphosphonates for all patients with lytic bone lesions
  - Anti-viral prophylaxis for herpes zoster advised for the Vc-MP arm
- Sample size based on TTP, to detect a 33% improvement with 80% power, assuming median TTP of 18 months in control; N = 680 to provide 390 events. This same sample size is estimated to detect a 42% improvement in OS (HR=1.42) assuming that the median OS for the control is 30 months and 45 months for the Vc-MP arm.
- Primary endpoint: TTP; superiority analysis; defined as evidence of PD or relapse from CR as defined by EBMT criteria and assessed by the sponsor's algorithm.
- Analysis population – ITT (all randomized); all tests use 2 sided alpha = 0.05
- TTP Logrank analysis (stratified) using the ITT population and randomization co-variables
  - Three formal interim analyses (IA) and one final (390 events) with alpha spending
  - First IA to occur after 100 patients completed cycle 1, for safety
  - Second IA at 570 enrollments to re-assess sample size (efficacy alpha = 0.0001, assuming at least 120 events)
  - Third IA at 2/3 of the TTP events (~ 260) or one year after the second IA, which ever occurs first
- IDMC – charter for pre-defined oversight and analyses
- Secondary efficacy endpoints:
  - OS and PFS based on the ITT population
  - Response rate: CR rate and ORR using EBMT criteria (EBMT CR definition requires a negative IF test both in serum and in urine
    - One marrow exam for IF negative patients
    - Two marrow exams performed 6 weeks apart if non-secretory myeloma

- analysis by CMH test
- Note: immunofixation-positive CR requires all CR criteria to be fulfilled, except for the requirement of negative IF tests. This IF-positive CR category was not described by the original EBMT criteria and if analyzed, is to be reported under the PR category. Serum free light chain results were not analyzed in this study.
- time to and duration of response
- Other objectives
  - Safety, using CTCAE version 3 for reporting AEs and lab events
  - To characterize the PK of bortezomib used in combination with MP
  - Pharmacogenomic and proteomic exploratory studies
- Dates
  - Enrollment: December 2004 – June 15, 2007 (clinical cutoff for the 3<sup>rd</sup> IA)
- Protocol amendments - 4
  - June 2004: Before the study opened - to clarify protocol items, add a PFS analysis, and change age eligibility to allow patients under age 65 if they are not SCT eligible
  - April 2005: Clarifications and recommendation for anti-viral prophylaxis with Vc
  - March 2006: 440 patients were randomized by this time - Added a third interim analysis for TTP; allowed eligibility if baseline platelets 70-100K if extensive marrow involvement with myeloma
  - January 2007: All patients had been randomized – changed the timing of the third IA to allow it at 1 year after the second IA. Added the definition of clinical relapse, IMWG response and progression criteria and to assess stringent CR (sCR) if possible. However, the primary TTP endpoint remains defined by the original EBMT criteria specified.

Reviewer comments: The study design was accepted by FDA as suitable for regulatory evaluation for the first-line use of Velcade. The open-label choice was acceptable because it would not be appropriate to expose the control patients to repeated IV access procedures without benefit. The eligibility criteria, primary and secondary endpoints, and the method of determining the progression status are appropriate. The treatment effect in the control group, as noted above, was estimated for a median TTP of 18 months and median OS of 30 months. The applicant's estimates were accurate and provided an efficient protocol design.

### 6.1.2 Demographics

In total, 682 patients from 151 centers in 22 countries were randomized into Study MMY-3002 as of the cutoff time of June 15, 2007; 344 patients randomized to the Vc-MP treatment group and 338 patients randomized to the MP treatment group. The majority (79%) of patients were enrolled at sites in the Europe/Australia region, with most patients from Russia (14%), Germany (10%), Italy (9%), Poland (8%), and Belgium-Luxemburg (7%). A total of 9% of patients were enrolled in North America, including 6% (43 patients) enrolled in the U.S. In the Vc-MP treatment group, 340 patients received at least one dose of treatment compared to 337 in the MP treatment group, and thus 677 patients comprised the safety population.

The median age was 71 years, and 30% of patients were age 75 or greater. A total of 23 patients were less than age 65 and were judged not to be transplant-eligible on the basis of cardiovascular disease, emphysema, recurring infections, or other morbidity.

The majority (599 patients; 88%) were White; 10% were of Asian origin and 2% were Black. Males and females were evenly distributed. Mean BSA was 1.77 m<sup>2</sup>. The median baseline KPS was 80%; 34% of patients had a KPS of  $\leq 70\%$  and thus about 2/3 were PS 80 or above. Other notable characteristics included high stage disease (ISS Stage III) in 34%, extensive bone lesions (>10 lesions in 27%), and impaired renal function (creatinine clearance <60 mL/min in 54%).

For 98% of the patients, a monoclonal protein was present for monitoring, and 2% were considered as oligo-secretory. The protein was IgG in 63%, IgA in 25%, IgD and IgM in 1% each, and light-chain in 8%.

By ISS staging,<sup>3</sup> 19% were stage 1, 47% were stage 2, and 34% were stage 3 at baseline. Of the 128 patients with Stage I disease, objective myeloma-related organ damage or disease symptoms were reported in all but 3 patients and included objective organ damage documented (baseline bone lesions or baseline plasmacytomas or pre-randomization hemoglobin result <100 g/L or pre-randomization creatinine result >ULN or pre-randomization serum calcium >ULN) or other evidence of myeloma related bone disease (e.g., therapy or symptoms for myeloma-related bone disease reported) or other myeloma-related symptoms (e.g., fatigue, infection, etc.) reported.

Reviewer comments: The median age on study is slightly older than the median age for the disease, since patients eligible for this study were judged not to be candidates for SCT. Enrollment to each arm was well-balanced by demographic factors: country, gender, age; and baseline disease characteristics including: cytogenetics, bone lytic lesions (present in 65% of each group), anemia, beta2-microglobulin levels, percent marrow plasma cells, renal function, baseline history of spinal cord compression, baseline opioid use (30% for each group), and baseline neuropathy (10%). About 15% were receiving bisphosphonates at baseline in each arm.

### 6.1.3 Patient Disposition

All patients received the treatment to which they were randomized. More patients in the Vc-MP treatment group completed the 9 cycles of study treatment (154 [45%] compared to 138 [41%] patients in the MP treatment group), and 47 patients (14%) in the Vc-MP treatment group versus 33 patients (10%) in the MP treatment group were still in the treatment phase at the time of data cut-off. Fifteen percent of patients discontinued treatment due to adverse events in the Vc-MP treatment group compared with 14% of patients in the MP treatment group. On Vc-MP, therapy discontinuation after achieving confirmed IF-negative CR state was 3%, compared with <1% in the MP treatment group. There were more discontinuations due to PD in the MP treatment group (21%) than in the Vc-MP treatment group (7%). Discontinuation from study treatment after IF-negative CR was initially a protocol-specified reason for treatment termination; after implementation of Amendment 2, patients with an IF-negative CR were expected to continue in the study until 9 cycles (54 weeks) were completed.

Reviewer comment: Overall, 4% of patients were considered as protocol entry deviations. Most were minor lab variations from baseline requirements and are unlikely to have influenced the results. On-therapy deviations occurred in 12% of Velcade-treated patients and 3% of the controls, likely influenced by the additional complexity of following the Velcade dosing schedule. These events were judged as not likely to have altered the results.

#### 6.1.4 Applicant's Analysis of Primary Endpoint - TTP

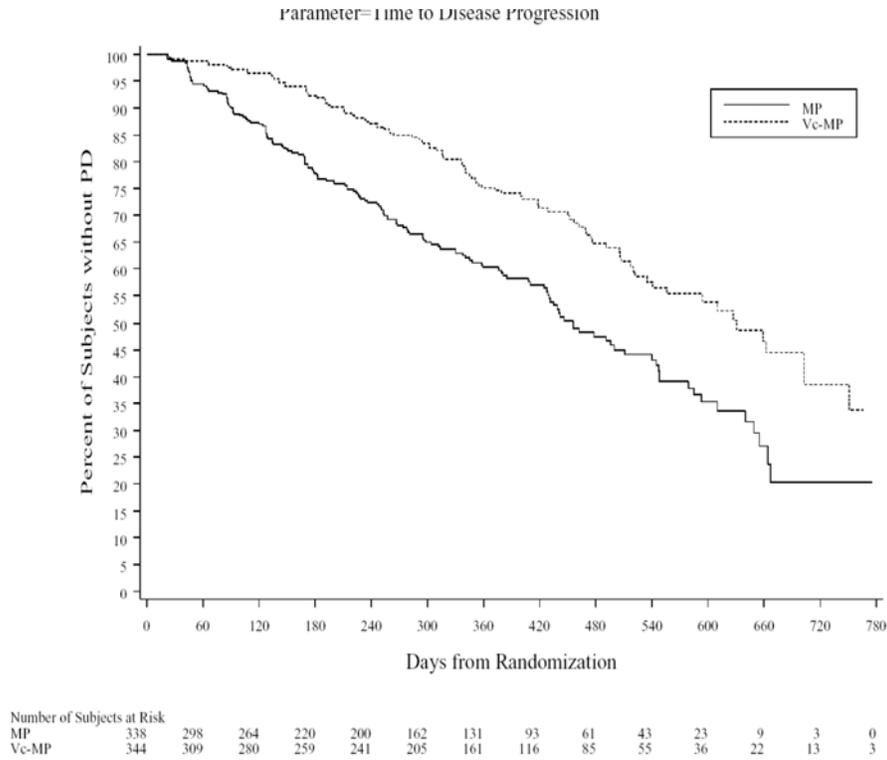
The primary analysis of TTP was conducted on the ITT population. Progression (or relapse from CR) was evaluated by the EBMT criteria as pre-specified and used the applicant's computer algorithm, as previously described and validated. The determination of PD and response was largely based on M-protein changes reported by the central laboratory and less often by new bone lesions or measurements of plasmacytomas provided by the investigators (see table below). Sites were required to fax (within 24 hours) to the Sponsor's Medical Monitor supporting documentation of the diagnosis of progressive disease. After the IDMC reviewed the data from the third interim analysis, the Sponsor was notified that the pre-specified statistical boundary for the primary endpoint of TTP was crossed, as of the clinical cut-off date, with 65% (253/390 events) of the required TTP events of PD or relapse (Vc-MP: 101 events, MP: 152 events) reported. Results were reported in days, and months were calculated using the following formula: number of months = number of days divided by 30.4375. The median TTP was 20.7 months (631 days) in the Vc-MP treatment group compared with 15.0 months (456 days) in the MP treatment group. The hazard ratio (Vc-MP vs. MP treatment group) was 0.540 (95% CI: 0.417, 0.699), and the stratified log-rank test p-value was 0.000002.

The O'Brien Fleming boundary significance level of 0.0108 for the third interim analysis of TTP, based on 253 observed events (65% of pre-specified required events), and the applicant's TTP analysis, were verified by the FDA statistical reviewer. Overall, 34% of patients were censored at the time of the TTP analysis. The Hazard ratio (HR) is based on a Cox regression model adjusted for the stratification factors: beta<sub>2</sub> micro-globulin, albumin, and region, as pre-specified.

Reviewer comment:

Note that, for its analysis, FDA defined TTP as excluding deaths that were not preceded by documented progression. Please see table 2 above for the FDA results. The applicant's analysis includes 6 additional patients that were censored by FDA, accounting for small statistical differences. Regardless, the results remain statistically robust and fully supported by the PFS analysis which also includes deaths from any cause as events.

**Figure 3: Applicant Kaplan-Meier curves for TTP based on the ITT population**



Applicant graph, CSR, page 138; module 5.3.5.1

Reviewer comment: An early and consistent separation in outcome occurred favoring Vc-MP. Based on the similarity in the slopes of the two curves after an early Velcade treatment effect, it may be that the total duration of Velcade in this study did not further augment the early improvement.

The specific finding (event) indicating the progression determination is shown in the next table.

**Table 3: Basis for determination of progression for the ITT population**

	MP (N=338)	Vc-MP (N=344)	Total (N=682)
Progressive Disease Reason	n (%)	n (%)	n (%)
<b>Yes</b>	152	101	253
Serum M-protein	76 (50)	75 (74)	151 (60)
Urine M-protein	39 (26)	12 (12)	51 (20)
Bone lesions	17 (11)	3 (3)	20 (8)
Bone marrow results	12 (8)	6 (6)	18 (7)
Death due to PD	6 (4)	5 (5)	11 (4)
Extramedullary plasmacytoma	8 (5)	5 (5)	13 (5)
Hypercalcemia	1 (1)	0	1 (<1)
<b>No</b>	186	243	429
Study cut-off	117 (63)	178 (73)	295 (69)
Death	22 (12)	27 (11)	49 (11)
Subsequent therapy	35 (19)	22 (9)	57 (13)
Lost to follow-up	12 (6)	16 (7)	28 (7)

Applicant data table 29, CSR page 139, module 5.3.5.1

MP = melphalan-prednisone; Vc-MP = VELCADE-melphalan-prednisone;

PD = progressive disease.

Note: Percentages calculated with the number of patients per progressive disease as denominator.

Note: A patient may show PD based on more than one criterion

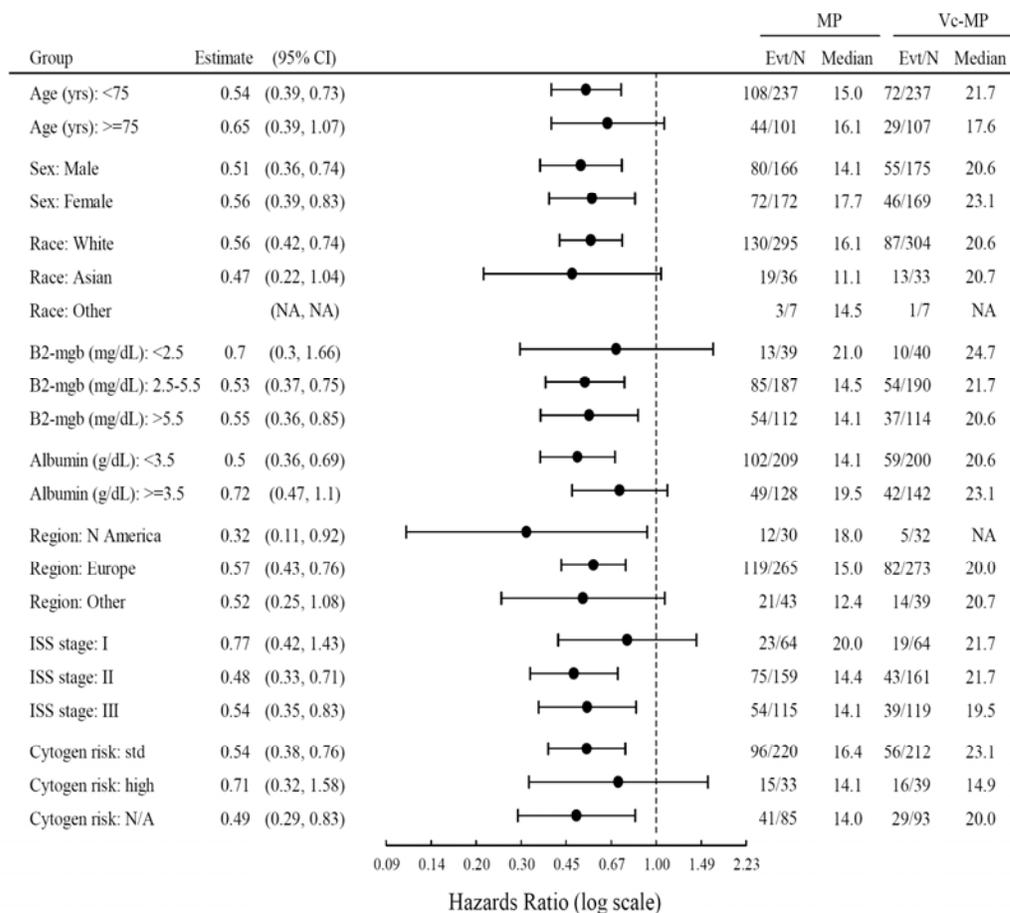
Note: Three patients and 1 patient in both the Vc-MP and MP treatment group, respectively had PD by both serum and urine M-protein.

Reviewer comments:

The large majority of progressions were based on changes in protein measurements (80% overall) using the EBMT criteria. There were fewer bone lesion progressions on the Vc-MP arm than on the MP arm. Other progression events were similar.

TTP assessed by investigator was examined as a sensitivity analysis, using the investigator-reported date of progression or relapse. With a total of 229 progression and relapse events as reported by the investigators (83 events and 146 events in the Vc-MP and MP treatment groups, respectively), the Vc-MP treatment group also showed a significant improvement in TTP over the MP treatment group. The median TTP per investigator assessment was 24.0 months (732 days) for the Vc-MP treatment group compared with 16.6 months (505 days) for the MP treatment group (Table 30). The hazard ratio (Vc-MP vs. MP treatment group) was 0.483 (95% CI: 0.367, 0.636), and the p-value was 0.0000001 (stratified log-rank test).

**Figure 4: Exploratory analysis of TTP by subgroups, ITT population**



Applicant figure 4, CSR page 144

Reviewer comment:

The above subgroup analyses, while exploratory, provide strong support for the primary analysis and for the generalizability of the treatment effect of Vc-MP.

6.1.5 Analysis of Secondary Endpoints(s)

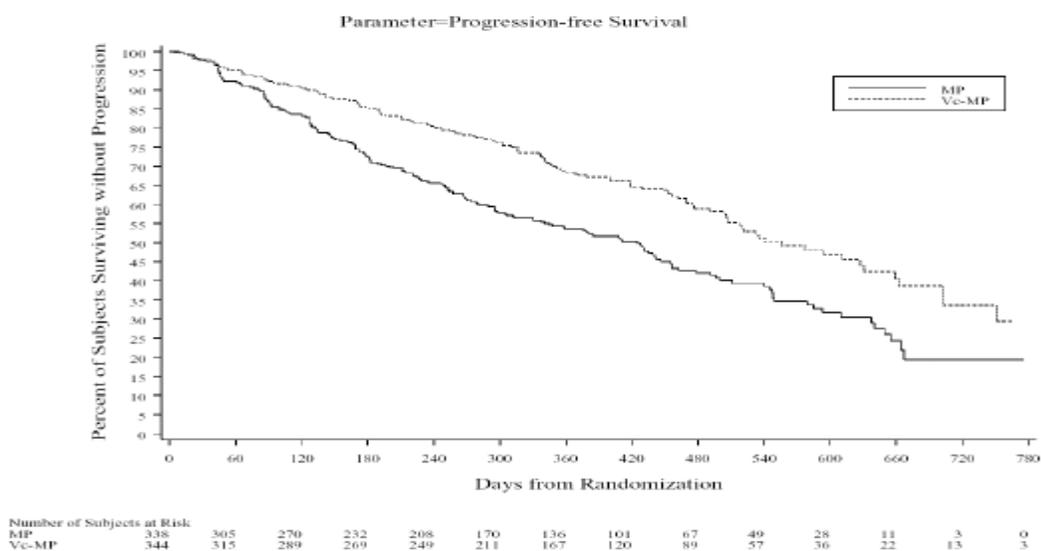
Secondary endpoints included PFS, OS, and response rate.

PFS:

At the time of the TTP analysis, there were 325 PFS events (progression or death from any cause): 135 on the Vc-MP arm and 190 on the MP arm. [For TTP, there were 99 events on Vc-MP and 148 on MP; thus, deaths added about 30% additional events to each study arm.] The median PFS was 18.3 months (556 days) in the Vc-MP treatment group and 14 months (425

days) in the MP treatment group. Approximately half (52.3%) of all patients were censored for the PFS analysis. The difference between the 2 treatment groups was highly significant, favoring the Vc-MP treatment group. The hazard ratio (Vc-MP vs. MP treatment group) was 0.609 (95% CI: 0.486, 0.763). The p-value was 0.00001 (stratified log-rank test). The subgroup analysis of PFS was very similar to that for TTP (data not shown).

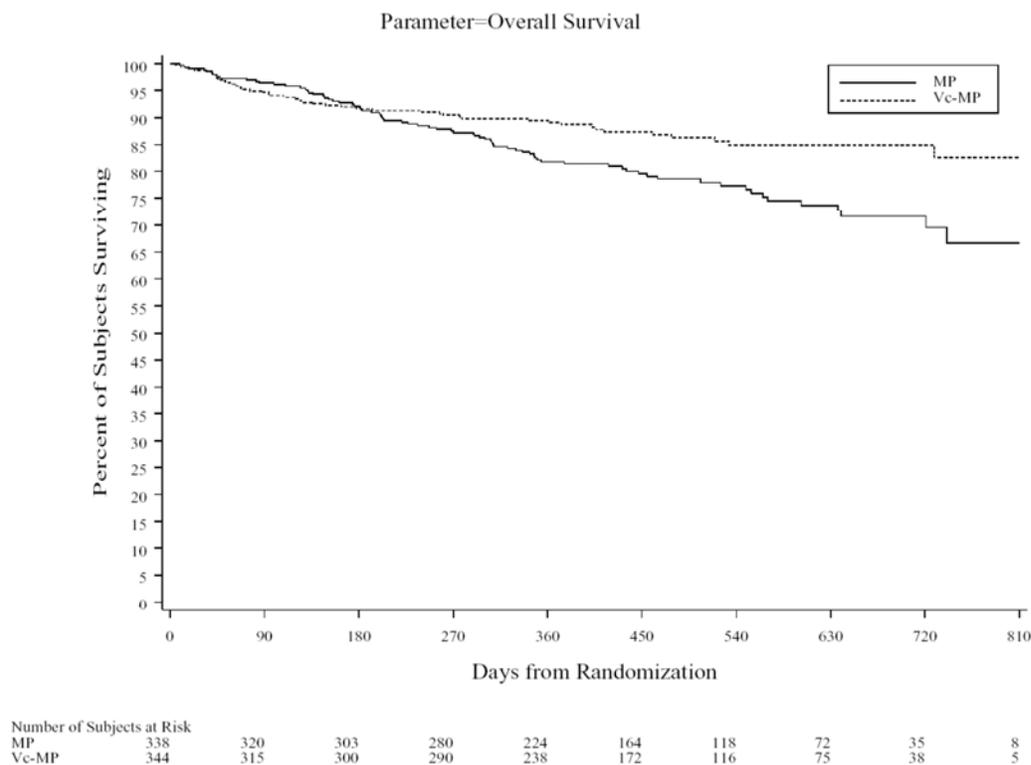
**Figure 5: PFS for the ITT population**



Reviewer comments: PFS is important for comparison with TTP as a safety analysis for possible chemotherapy toxicity, since deaths are censored in a TTP analysis. In this study, the PFS effect was very similar to the TTP result and supports the safety and efficacy of the therapy.

For OS, at the time of the data cutoff with a median follow-up time of 16.3 months (based on the Kaplan-Meier estimate), 121 patients died: 45 patients (13%) in the Vc-MP treatment group, and 76 patients (23%) in the MP treatment group. While the median survival had not been reached for either group, the hazard ratio for OS (Vc-MP vs. MP treatment group) was 0.607 (95% CI: 0.419, 0.880) and the p-value was 0.00782 (stratified log-rank test). By the time of the clinical cut-off for the third interim analysis, 68 patients (20%) in the Vc-MP treatment group and 121 (36%) in the MP treatment group had received subsequent therapy. In the Vc-MP treatment group, 8 of the 68 patients (12%) received subsequent therapy with Velcade while 54 of the 121 patients (45%) in the MP treatment group received subsequent therapy with Velcade.

**Figure 6: Applicant's Kaplan-Meier curves for OS, ITT population**



CSR page 149, module 5.3.5.1

The exploratory subgroup analyses for OS (not shown) were consistent with those for PFS and TTP, all favoring the Vc-MP arm. For the ISS categories, median survivals (Vc-MP) were 63 months for stage 1, 44 months for stage 2, and 29 months for stage 3, also providing support for the ISS prognostic staging system.

Response rate:

At the time of clinical cut-off, 249 patients in the Vc-MP treatment group and 234 in the MP treatment groups had completed at least 4 cycles, completing the twice weekly dosing regimen phase of the protocol. Forty-seven patients (14%) and 33 patients (10%), respectively, were still on treatment. One hundred two patients (30%) in the Vc-MP treatment group and 12 patients (4%) in the MP treatment group had a CR. The difference between the 2 treatment groups was highly significant. The Mantel-Haenszel odds ratio was 11.2 (95% CI: 6.1, 20.6), and the p-value was less than  $10^{-10}$  by the stratified Cochran-Mantel-Haenszel Chi-square test.

The ORR rate (CR+PR by EBMT criteria) was 71% (238 CR+PR responses) in the Vc-MP treatment group and 35% (115 CR+PR responses) in the MP treatment group. The difference between the 2 treatment groups was highly significant. The Mantel-Haenszel odds ratio was 4.5 (95% CI: 3.2, 6.2). The p-value for the OR rate was  $< 10^{-10}$  by the stratified Cochran-Mantel-Haenszel Chi-square test. In the Vc-MP treatment group, the CR rate was 39% for Asian patients and 28% for White patients. The CR rate was 41% in North America and other regions and 27%

in the EU/Australia regions. Response rates were similar and consistently in favor of Vc-MP for all albumin groups, beta<sub>2</sub>-microglobulin groups and for all ISS categories.

Reviewer comments: Some studies have suggested that achievement of CR in myeloma is associated with prolonged TTP and survival. If patients can safely tolerate a sufficient dose and duration of therapy to achieve a CR, achieving a durable CR may be a surrogate for additional clinical benefit.

### 6.1.6 Other Endpoints

Time to first response also was significantly shorter for the Vc-MP group (median 1.4 months versus 4.2 months) logrank  $p < 10^{-10}$ . Response for patients receiving Vc-MP continued to improve with continuing therapy. In particular, 29 (28%) of the 102 CRs in the Vc-MP treatment group achieved a CR as their best response only after the first 24 weeks of treatment (i.e., improved their response level to CR while on treatment Cycles 5 to 9).

Duration of response:

The median duration of response, conditional on achieving a response, was 19.9 months (606 days) in the Vc-MP treatment group and 13.1 months (400 days) in the MP treatment group by the Kaplan-Meier method. Duration of response was censored for the 237 patients (Vc-MP: 163 patients, MP: 74 patients) who responded and who subsequently had not progressed or relapsed from CR. For patients whose best response was a CR, the median duration of response was 24 months (729 days) for Vc-MP and 12.8 months (389 days), for the MP treatment groups. For patients whose best response was a PR, the median duration of response was 15.2 months (464 days) and 13.1 months (400 days), for the Vc-MP and MP treatment groups, respectively.

### 6.1.7 Subpopulations

See above sections for exploratory subset analyses for each endpoint. The applicant also analyzed additional indicators of clinical effect including time to subsequent therapy; incidence of hypercalcemia, renal function impairment, anemia, and normal immunoglobulin reconstitution. For each outcome, the Vc-MP treatment group had either a significantly better outcome or a trend towards improved outcome (see section 6.3.4, CSR; data not shown).

The applicant was queried on the subgroup of 23 patients under age 65 who were considered as not eligible for SCT. For each, eligibility was approved by the study medical monitor at the time of screening for entry. Reasons included:

- seven patients (300135, 300640, 300662, 300679, 300927, 301035, 301430) had a co-morbid cardiac disorder (4 patients with coronary heart disease, 2 patients with heart failure, and 1 subject with sequelae of myocardial infarction)
- seven patients (300684, 300721, 300902, 300936, 301442, 301902, 301559) had a co-morbid vascular disorder (2 patients with cerebrovascular accident residuals, 2 patients with obliterative peripheral atherosclerosis)

- one patient with upper gastrointestinal hemorrhage, and 2 patients with a history of hypertensive crisis)
- three patients had a co-morbid respiratory system disorder (2 patients with chronic obstructive pulmonary disease [300101, 301710] and 1 subject [300711] with bronchial asthma), 2 patients (300926, 301544) had a co-morbid metabolic disorder (both had morbid obesity)
- two patients (300317, 300944) had a co-morbid general system disorder (both experienced general physical deterioration)
- one patient (300913) had a co-morbid psychiatric disorder (depression)

Reviewer comments: The ineligibility of the 23 patients for SCT appears reasonable. Entry of these patients is unlikely to have biased any results.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Only one dose, the current label dose, was studied. The Velcade regimen (dose and schedule) used in this study in combination with MP is effective with acceptable safety based on the evidence provided.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Tolerance is not expected. Persistence of efficacy is estimated by the interval off therapy achieved by responding patients as discussed in the efficacy analyses.

### 6.1.10 Additional Efficacy Issues/Analyses

Four patients received HDT/SCT as subsequent therapy (2 in the Vc-MP treatment group and 2 in the MP treatment group). For these 4, the investigators indicated that the protocol treatment improved the patients' performance status sufficiently to permit subsequent SCT.

The incidence of skeletal events during study was low in both treatment groups: 26 patients (8%) in the Vc-MP treatment group and 23 patients (7%) in the MP treatment group. Fifteen patients (4%) in the Vc-MP treatment group and 9 patients (3%) in the MP treatment group had surgery or irradiation to bone reported. In most cases (14 in the Vc-MP treatment group and 8 in the MP treatment group) these events occurred within the first 2 cycles. During the study, overall, there was higher use of bisphosphonates in the MP treatment group (277 patients, 82%) than in the Vc-MP treatment group (249 patients, 73%). At baseline, 32% of the MP group and 34% of the Vc-MP group were receiving bisphosphonates. Lytic lesions were present in 66% of patients in both groups at baseline. Similar numbers of patients were found to have 1-3, 4-10, and >10 lytic bone lesions at baseline. Despite more bisphosphonate use, there was a greater frequency of progression of bone disease in patients receiving MP. Of note, 11% and 3% of patients in the MP and Vc-MP arms, respectively, discontinued treatment due to bone lesion-related disease progression as documented by algorithm (see CSR Table 29). When assessed by investigators, these rates increased to 15% and 7%, respectively.

There were fewer RBC transfusions in the Vc-MP treatment group than in the MP treatment group (26% vs. 35% of patients) and there was less use of erythropoiesis-stimulating agents (ESAs) (34% vs. 42%).

Reviewer comments: This reduction in transfusion and in use of ESAs in association with Vc-MP therapy is consistent with a positive treatment effect and thus lower incidence of higher-grade anemia in the Vc-MP treatment group compared with the MP treatment group. The skeletal event rate is low for both groups, although bisphosphonate use on-study occurred in the majority of patients for both groups. It is not possible to distinguish a benefit of chemotherapy versus the bisphosphonate effect in accounting for the relatively low rate of skeletal events on study.

The applicant provided historical results for the active control arm MP effect size. The reported median TTP among several studies was 18 months. The reported median OS was between 30 months and 36 months. PFS/EFS/TTP and OS data from seven recently reported studies in previously untreated patients that include an MP arm are presented below including data presented at the American Society of Hematology meeting in 2007. PFS/EFS/TTP ranged from 13.6 to 21.1 months while OS ranged from 27.7 to 49 months. Note that comparisons in PFS/EFS/TTP data between studies may be misleading since these endpoints are highly sensitive to differences in definitions, frequency of measurement, and methods of measurement.

Table 4: Recent Studies Including an MP Arm: PFS, EFS, TTP and OS Results

Study (Reference)	Age (yrs)	n	PFS/EFS/TTP (mos) for MP	OS (mos)
MD vs MP (Hernandez BJH 2004)	>70	96	EFS 15.9	29.4
MEL100 vs MP (Palumbo Blood 2004)	50-70	99	EFS 15.6	42.5
DEX regimens vs MP (Facon Blood 2006)	65-75	122	PFS 21.1	34
MPT vs MP (Palumbo Lancet 2006)	>65	126*	EFS 13.6	NR
MPT vs MEL100 vs MP (Facon Lancet 2007 )	65-75	196	PFS 17.8	33.2
MPT vs MP (Hulin ASH 2007)	>75	116	PFS 19 TTP 20.9	27.7
TD vs MP then IFN+/-T (Ludwig ASH 2007)	Median 72	143	PFS 20.7	49

Sponsor table Q4-1 from supplemental response

PFS = Progression-free survival      EFS = Event-free survival  
 TTP = Time to progression              OS = Overall survival  
 MD = melphalan dexamethasone      MP = melphalan prednisone

Clinical Review NDA 21-602 SE1  
Velcade (bortezomib)  
Robert Kane, MD

MEL100 = melphalan 100 mg/m<sup>2</sup>    TD = thalidomide dexamethasone  
DEX = dexamethasone  
MPT = melphalan prednisone thalidomide  
IFN+/-T = interferon alpha with or without thalidomide  
\*Excluded patients followed <6 months (n=38)

Reviewer comment:

The applicant's assumptions in planning the study and the control arm effect size were appropriate. This reviewer agrees that the results support the inference of superiority for Vc-MP over PM use for initial myeloma therapy.

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## **7 Review of Safety**

### **7.1 Methods**

#### **7.1.1 Clinical Studies Used to Evaluate Safety**

One clinical study and ongoing post-marketing surveillance are the data sources for review.

#### **7.1.2 Adequacy of Data**

In the study, 340 patients received the Vc-MP combination and provide an acceptable database for comparison with the 337 patients who received MP. The applicant evaluated 12 other studies involving Vc-MP for safety signals as well (see below).

#### **7.1.3 Pooling Data across Studies to Estimate and Compare Incidence**

No pooling was performed. In general, these results were similar to safety findings in other Velcade studies and consistent with an additive AE profile for Velcade plus MP compared to MP.

### **7.2 Adequacy of Safety Assessments**

#### **7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations**

Three hundred and forty-three patients in the Vc-MP treatment group and 337 patients in the MP treatment group are included in the safety analysis dataset. This dataset includes all randomized patients who had received at least 1 dose of any of the study drugs. Five study patients who were not treated were excluded from the safety analysis. Thus, the efficacy and safety populations are almost the same.

As of the cut-off date of 15 June 2007, the median number of cycles administered was 8 for the Vc-MP and 7 for the MP treatment groups. Forty-six percent of patients in the Vc-MP treatment group and 41% of patients in the MP treatment group received the full course of 9 treatment cycles. In the Vc-MP treatment group, the median dose intensity for Velcade in the first 4 cycles (twice-weekly regimen) was 8.3 mg/m<sup>2</sup>/cycle versus the target of 10.4 mg/m<sup>2</sup>/cycle, indicating a relative dose intensity of 80%. The median dose intensity for the next 5 cycles (weekly regimen) was 4.0 mg/m<sup>2</sup>/cycle compared with the maximum target of 5.2 mg/m<sup>2</sup>/cycle, indicating a relative dose intensity of 77%. The median dose intensity for melphalan and prednisone was similar in both treatment groups and was approximately 100%. The median dose intensity (mg/m<sup>2</sup>/cycle) of melphalan and prednisone for patients in the Vc-MP and MP treatment groups

over cycles 1 through 9 was 35.6 mg/m<sup>2</sup> (compared with the maximum target of 36.0 mg/m<sup>2</sup>) and 240.0 mg/m<sup>2</sup> (compared with the expected target of 240.0 mg/m<sup>2</sup>), respectively.

In Cycles 1 to 4, cycle delays of at least 5 days were reported in 81 patients (24%) and 88 patients (26%) in the Vc-MP and MP treatment groups, respectively. During cycles 1 to 4, 15% of patients in the Vc-MP treatment group had dose modifications of melphalan (11% dose reductions, 5% doses withheld). In the MP treatment group 13% of patients had dose modifications of melphalan in Cycles 1 to 4 (10% dose reductions, 4% doses withheld). During Cycles 5 to 9, 10% of patients in the Vc-MP treatment group had dose modifications of melphalan (8% dose reductions, 3% doses withheld), while 7% of patients in the MP treatment group had dose modifications of melphalan (6% dose reductions, 1% doses withheld).

The majority of patients in the Vc-MP treatment group had either no dose reduction (46%) or 1 dose reduction (36%) during the study, with only 18% of patients requiring 2 dose reductions. The protocol-specified treatment schedule planned for 52 administrations of Velcade during the 9 cycles of therapy for patients in the Vc-MP treatment group. The percentage of patients with at least one Velcade dose withheld during a cycle ranged from 36% to 46% during Cycles 1 to 4 and from 9% to 15% during Cycles 5 to 9.

### 7.2.2 Explorations for Dose Response

Only one dose schedule was used in the study. No dose-response exploration was performed. Most responses occurred by the end of the 4<sup>th</sup> cycle, but additional responses and higher "quality" of responses occurred later also.

### 7.2.3 Special Animal and/or In Vitro Testing

None

### 7.2.4 Routine Clinical Testing

Laboratory studies were performed every three weeks. Protein levels were measured at sites as well as centrally.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

A PK drug interaction study of Velcade and MP was performed (see pharmacology section).

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no similar class agents in late phase trials for comparison.

### 7.3 Major Safety Results

#### 7.3.1 Deaths

**Table 5: Deaths on study**

	MP (N=338)	Vc-MP (N=344)	Total (N=682)
	n (%)	n (%)	n (%)
<b>Deaths - All Causes</b>	76 (22)	45 (13)	121 (18)
Progressive disease	38 (11)	14 (4)	52 (8)
Adverse events	26 (8)	25 (7)	51 (7)
At least 1 related AE	8 (2)	6 (2)	14 (2)
AE(s) unrelated	18 (5)	19 (6)	37 (5)
Other	12 (4)	6 (2)	18 (3)
Deaths-All Causes With- in 30 Days of First Dose	4 (1)	4 (1)	8 (1)
Deaths-All Causes With- in 30 Days of last Dose	14 (4)	18 (5)	28 (4)

Reviewer table adapted from sponsor table 52, CSR page 206

Reviewer comment:

Overall during the study, there were fewer deaths on the Vc-MP treatment arm. Deaths considered as drug-related occurred equally on both arms (2%) and were mostly due to infection.

#### 7.3.2 Nonfatal Serious Adverse Events (SAEs)

The FDA requested the sponsor not to record disease progression as an AE for analysis. This may make comparisons to other data sets more complex. Serious adverse events were reported for 46% of patients who received Vc-MP, compared to 36% of patients who received MP; 28% and 15% of serious adverse events were considered by the investigator to be related to at least 1 of the study drugs in the Vc-MP and MP treatment groups, respectively.

#### 7.3.3 Dropouts and/or Discontinuations

The treatment regimen was planned for 54 weeks in the absence of limiting toxicity or patient refusal to continue. Study withdrawal occurred for withdrawal of consent or loss to follow-up. A patient completed the study if he/she met all 3 of the following criteria:

- completed 9 cycles (54 weeks) of study treatment or discontinued study treatment
- completed the End-of-Treatment Visit procedures and
- had either documented PD or relapse from IF-negative CR

**Table 6: Reasons for discontinuation**

	MP	Vc-MP	total
category	N = 338	N = 344	N = 682
Treatment discontinued	166 (49)	139 (40)	305 (45)
Overt disease progression	72 (21)	24 (7)	96 (14)
Subject choice	18 (5)	32 (9)	50 (7)
Adverse event	47 (14)	50 (15)	97 (14)
Related adverse event	35 (10)	37 (11)	72 (11)
Unrelated adverse event	12 (4)	13 (4)	25 (4)
Death	17 (5)	14 (4)	31 (5)
Other	12 (4)	19 (6)	31 (5)
Maintenance of confirmed IF-negative CR <sup>a</sup>	1 (<1)	9 (3)	10 (1)

Sponsor's table 7, CSR page 99

Reviewer comment: Overall, there were fewer discontinuations on the Vc-MP arm with more discontinuations for disease progression on the MP arm.

APPEARS THIS WAY ON ORIGINAL

### 7.3.4 Significant Adverse Events (AEs)

Per ICH guidelines for this section, there were no marked hematological or other lab abnormalities uniquely applicable to this section. Severe AEs and lab changes are noted in the other relevant sections of the safety review. Agent-specific toxicities are described below in 7.3.5

**Figure 7: Summary of serious and severe adverse events**

	MP (N=337)	Vc-MP (N=340)
	n (%)	n (%)
<b>Any TEAE</b>	326 (97)	338 (99)
At Least 1 Related	283 (84)	331 (97)
None Related	43 (13)	7 (2)
<b>Any Serious TEAE</b>	121 (36)	155 (46)
At Least 1 Related	51 (15)	96 (28)
None Related	70 (21)	59 (17)
<b>Maximum Severity of Any AE</b>	326 (97)	338 (99)
Grade 1	12 (4)	2 (1)
Grade 2	47 (14)	32 (9)
Grade 3	148 (44)	181 (53)
Grade 4	92 (27)	96 (28)
Grade 5	27 (8)	27 (8)
<b>Terminated Treatment Due to AEs<sup>a</sup></b>	47 (14)	50 (15)
At Least 1 Related	35 (10)	37 (11)
None Related	12 (4)	13 (4)

Sponsor table 47, CSR page 186

AE = adverse event; MP = melphalan-prednisone; TEAE = treatment emergent adverse event; Vc-MP = Velcade-melphalan-prednisone

Note: Percentages calculated with the number of patients in each group as denominator.

a For patients reported as having discontinued treatment due to an adverse event on the treatment termination CRF page

Reviewer comments:

On the Vc-MP arm, there were more events of serious AEs and more severe AEs. This likely reflects the additional toxicity of adding Velcade to the MP combination; however, patients on Vc-MP were on therapy a longer time as well.

### 7.3.5 Submission Specific Primary Safety Concerns

#### Infections:

The incidence of Grade  $\geq 3$  infections at any time during treatment was 19% (66 patients) in the Vc-MP treatment group and 18% (60 patients) in the MP treatment group. In the Vc-MP and MP treatment groups, respectively, the most common infections included pneumonia (16% vs. 11%), herpes zoster (13% vs. 4%), and bronchitis (13% vs. 8%). Respiratory tract infections were higher in MP-treated patients (5%) compared with Vc-MP-treated patients (1%).

The incidence of herpes zoster was higher in the Vc-MP treatment group (14%) compared with the MP treatment group (4%). The protocol contained a recommendation for antiviral prophylaxis for the Velcade group; 26% (90/340 patients) of patients in the Vc-MP treatment group compared with 4% (14/337 patients) received prophylactic antivirals. Of the 90 patients in the Vc-MP treatment group who received prophylactic antivirals, only 3 patients (3.3%) developed herpes zoster. Of the 250 patients in the Vc-MP treatment group who did not receive antiviral prophylaxis, 43 (17%) patients developed herpes zoster. Prophylactic use of antivirals may have reduced development of herpes zoster for Vc-MP-treated patients but there likely was a selection bias with regard to who received antivirals. In the MP treatment group, 2/14 patients (14%) who received prophylactic antivirals developed herpes zoster, while 12/323 patients (4%) without antiviral prophylaxis developed herpes zoster. Prophylactic antibacterial use prior to the start of treatment was similar in both treatment groups (14 patients [4%] and 15 patients [4%] in the Vc-MP and MP treatment groups, respectively).

#### Hematology:

The incidence of febrile neutropenia was low (2% in the Vc-MP treatment group and 4% in the MP treatment group). Leukopenia was similar for both groups (33% versus 30%). The incidence of anemia was lower in the Vc-MP group (43%) compared to the MP group (55%), even though there were fewer transfusions and less use of ESAs in the Vc-MP group. Grade  $\geq 3$  bleeding was observed in 3% of each treatment group.

#### Neurologic:

More Vc-MP patients had Nervous System adverse events (74% vs. 36%). Vc-MP-treated patients had more peripheral sensory neuropathy (44% vs. 5%), neuralgia (36% vs. 1%), and paresthesia (13% vs. 4%) than MP-treated patients. These events are not mutually exclusive and were often both reported for the same patient. The incidence of peripheral sensory neuropathy and neuralgia in the Nervous System Disorders SOC was higher in the Vc-MP treatment group (44% and 36%, respectively) compared with the MP treatment group (5% and 1%, respectively), consistent with the addition of Velcade to MP and with higher incidence of herpes zoster reactivation (post herpetic neuralgia sequelae). The incidence of paresthesia was also higher in the Vc-MP treatment group (13%) compared with the MP treatment group (4%). Peripheral neuropathies in the Vc-MP treatment group included peripheral sensory neuropathy (44%), peripheral motor neuropathy (6%), and neuropathy peripheral (3%). The majority (46%) of these peripheral neuropathies were considered related to study drug, were Grade 1 or 2 in the majority of patients (13% Grade  $\geq 3$ , <1% Grade 4), and were considered a serious adverse event in 1% of patients. Median cumulative dose of Velcade to first onset of peripheral neuropathy of any Grade was 32.6 mg/m<sup>2</sup>. Consistent with prior observations, reversibility of the peripheral neuropathy was documented (improvement in 74%, resolution in 56%).

**Circulatory and cardiac conditions:**

On the current study, there were 52 (15%) hypotension and orthostatic hypotension cases combined for the Vc-MP arm versus 11 (4%) on the MP arm. Hypotension can precipitate cardiovascular events. Treatment-emergent hypertension occurred in 13% on the Vc-MP arm versus 7% on the MP arm. Some of this hypertensive effect is likely due to the steroid (P), but the asymmetry in the effect is not explained.

In the Vc-MP treatment group, 11% of patients experienced a Cardiac Rhythm and Conduction Abnormality (most commonly palpitations and atrial fibrillation each in 3% of patients). In 4% of patients, these Cardiac Rhythm and Conduction Abnormalities were considered related to study drug, were Grade 3 or higher in 4% of patients, were considered serious adverse events in 4% of patients, and resulted in study drug discontinuation in 1% of patients. In the MP treatment group, 11% of patients experienced Cardiac Rhythm and Conduction Abnormalities including palpitations and atrial fibrillation in 3% each of patients. In 2% of patients, these Cardiac Rhythm and Conduction Abnormalities were considered related to study drug, were Grade 3 or higher in 3% of patients, were considered serious adverse events in 3% of patients, and resulted in study drug discontinuation in <1% of patients.

Seventeen patients (5%) in the Vc-MP treatment group and 11 patients (3%) in the MP treatment group experienced at least 1 heart failure event. Eleven of the 17 heart failure events reported in the Vc-MP treatment group were considered at least Grade 3 while 10 of the 11 heart failure events reported in the MP treatment group were considered at least Grade 3 toxicity. Note: 43 patients (13%) in the Vc-MP treatment group and 30 patients (9%) in the MP treatment group were reported with heart failure at baseline.

**Table 7: Time to heart failure events**

	MP (N=11)	Vc-MP (N=17)
<b>Any Heart Failure Event</b>		
N	11	17
Mean (SD) days	179.5 (138.85)	61.1 (81.35)
Median	217.0	39.0
Range	(4; 343)	(9; 355)
<b>Grade ≥ 3 Heart Failure Event</b>		
N	10	11
Mean (SD) days	167.8 (140.48)	43.3 (27.30)
Median	139.5	39.0
Range	(4; 343)	(9; 95)

Sponsor table 61, CSR page 228

Reviewer comments: The protocol excluded patients with uncontrolled or severe cardiovascular disease, including myocardial infarction within 6 months of enrollment, New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, clinically significant pericardial disease, or cardiac amyloidosis. Overall the differences in frequency of heart failure on study were similar. Time to onset appeared to be earlier on the Velcade arm.

For Vc-MP- and MP-treated patients without a history of hypotension, 47 (14%) patients and 11 (3%) patients respectively reported treatment-emergent hypotension events during the study. Four patients in MP treatment group and 6 patients in Vc-MP treatment group had a history or the presence of orthostatic hypotension at study entry. None of these in the MP treatment group and 2 of these 6 patients (33%) in the Vc-MP treatment group reported treatment-emergent hypotension.

Some cardiac ECHO data (for Velcade alone) was available in the randomized study of Velcade + Doxil versus Velcade (MMY-3001), reviewed for the sNDA for Doxil. In that study, a LVEF reduction was defined as an absolute decrease of  $\geq 15\%$  over baseline or a  $\geq 5\%$  decrease below the institutional lower limit of normal. Based on that definition, 25 (8%) patients in the Velcade alone arm and 42 (13%) patients in the Doxil + Velcade arm experienced a reduction in LVEF. In the study, the incidence of heart failure adverse events (ventricular dysfunction, cardiac failure, right ventricular failure, congestive cardiac failure, chronic cardiac failure, acute pulmonary edema and pulmonary edema) was similar (3% each) in the Doxil + Velcade group and the Velcade monotherapy group.

Other AEs rates can be summarized as follows:

Gastrointestinal Disorders	(Vc-MP: 77%, MP: 55%)
Nervous System Disorders	(Vc-MP: 74%, MP: 36%)
General Disorders	(Vc-MP: 70%, MP: 59%)
• Infections and Infestations	(Vc-MP: 69%, MP: 54%)
• Metabolism and Nutrition Disorders	(Vc-MP: 47%, MP: 37%)
• Skin and Subcutaneous Tissue Disorders	(Vc-MP: 41%, MP: 24%)
• Psychiatric Disorders	(Vc-MP: 33%, MP: 23%)
• Vascular Disorders	(Vc-MP: 33%, MP: 20%)

Reviewer comments: The addition of Velcade did not appear to increase substantially the cardiac AEs (a difference of 6 patients) compared to the MP arm. On the Vc-MP arm, 13 additional patients had entered the study with cardiac history. CHF of grade  $\geq 3$  occurred in equal numbers on each study arm. Hypotension is more common on the Vc-MP arm, and this AE is included in the label but should continue to be emphasized by the applicant in marketing materials. Psychiatric disorders were common on both arms, likely resulting from the prednisone, and the most common preferred term category was insomnia.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

**Table 8:** Most Commonly Reported Adverse Events ( $\geq 10\%$  in Vc-MP arm) with Grades 3 and  $\geq 4$  Intensity

	----- Vc-MP -----			----- MP -----		
	(N=340)			(N=337)		
<b>MedDRA System Organ Class</b>	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
Preferred Term	n (%)	3	$\geq 4$	n (%)	3	$\geq 4$
<b>Blood and Lymphatic System Disorders</b>						
Thrombocytopenia	178 ( 52)	68 ( 20)	59 ( 17)	159 ( 47)	55 ( 16)	47 ( 14)
Neutropenia	165 ( 49)	102 ( 30)	35 ( 10)	155 ( 46)	79 ( 23)	49 ( 15)
Anemia	147 ( 43)	53 ( 16)	9 ( 3)	187 ( 55)	66 ( 20)	26 ( 8)
Leukopenia	113 ( 33)	67 ( 20)	10 ( 3)	100 ( 30)	55 ( 16)	13 ( 4)
Lymphopenia	83 ( 24)	49 ( 14)	18 ( 5)	58 ( 17)	30 ( 9)	7 ( 2)
<b>Gastrointestinal Disorders</b>						
Nausea	164 ( 48)	14 ( 4)	0	94 ( 28)	1 (<1)	0
Diarrhea	157 ( 46)	23 ( 7)	2 ( 1)	58 ( 17)	2 ( 1)	0
Constipation	125 ( 37)	2 ( 1)	0	54 ( 16)	0	0
Vomiting	112 ( 33)	14 ( 4)	0	55 ( 16)	2 ( 1)	0
Abdominal Pain	49 ( 14)	7 ( 2)	0	22 ( 7)	1 (<1)	0
Abdominal Pain Upper	40 ( 12)	1 (<1)	0	29 ( 9)	0	0
Dyspepsia	39 ( 11)	0	0	23 ( 7)	0	0
<b>Nervous System Disorders</b>						
Peripheral Neuropathy	159 ( 47)	43 ( 13)	2 ( 1)	18 ( 5)	0	0
Neuralgia	121 ( 36)	28 ( 8)	2 ( 1)	5 ( 1)	1 (<1)	0
Dizziness	56 ( 16)	7 ( 2)	0	37 ( 11)	1 (<1)	0
Headache	49 ( 14)	2 ( 1)	0	35 ( 10)	4 ( 1)	0
Paresthesias	45 ( 13)	6 ( 2)	0	15 ( 4)	0	0
<b>General Disorders and Administration Site Conditions</b>						
Pyrexia	99 ( 29)	8 ( 2)	2 ( 1)	64 ( 19)	6 ( 2)	2 ( 1)
Fatigue	98 ( 29)	23 ( 7)	2 ( 1)	86 ( 26)	7 ( 2)	0
Asthenia	73 ( 21)	20 ( 6)	1 (<1)	60 ( 18)	9 ( 3)	0
Edema Peripheral	68 ( 20)	2 ( 1)	0	34 ( 10)	0	0
<b>Infections and Infestations</b>						
Pneumonia	56 ( 16)	16 ( 5)	13 ( 4)	36 ( 11)	13 ( 4)	9 ( 3)
Herpes Zoster	45 ( 13)	11 ( 3)	0	14 ( 4)	6 ( 2)	0
Bronchitis	44 ( 13)	4 ( 1)	0	27 ( 8)	4 ( 1)	0
Nasopharyngitis	39 ( 11)	1 (<1)	0	27 ( 8)	0	0
<b>Musculoskeletal and Connective Tissue Disorders</b>						
Back Pain	58 ( 17)	9 ( 3)	1 (<1)	62 ( 18)	11 ( 3)	1 (<1)
Pain In Extremity	47 ( 14)	8 ( 2)	0	32 ( 9)	3 ( 1)	1 (<1)
Bone Pain	37 ( 11)	7 ( 2)	1 (<1)	35 ( 10)	7 ( 2)	0
Arthralgia	36 ( 11)	4 ( 1)	0	50 ( 15)	2 ( 1)	1 (<1)
<b>Metabolism and Nutrition Disorders</b>						
Anorexia	77 ( 23)	9 ( 3)	1 (<1)	34 ( 10)	4 ( 1)	0
Hypokalemia	44 ( 13)	19 ( 6)	3 ( 1)	25 ( 7)	8 ( 2)	2 ( 1)
<b>Skin and Subcutaneous Tissue Disorders</b>						
Rash	66 ( 19)	2 ( 1)	0	24 ( 7)	1 (<1)	0
Pruritus	35 ( 10)	3 ( 1)	0	18 ( 5)	0	0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>						

Cough	71 ( 21)	0	0	45 ( 13)	2 ( 1)	0
Dyspnea	50 ( 15)	11 ( 3)	2 ( 1)	44 ( 13)	5 ( 1)	4 ( 1)
<b>Psychiatric Disorders</b>						
Insomnia	69 ( 20)	1 (<1)	0	43 ( 13)	0	0
<b>Vascular Disorders</b>						
Hypertension	45 ( 13)	8 ( 2)	1 (<1)	25 ( 7)	2 ( 1)	0
Hypotension	41 ( 12)	4 ( 1)	3 ( 1)	10 ( 3)	2 ( 1)	2 ( 1)

Applicant table 5, from the CSR and the revised label

Reviewer comments: Although cough and dyspnea are usually considered as nonspecific and multi-factorial, they may be useful signals in the context of this study as an indicator of pulmonary (and cardiac) adverse effects of Velcade. Compared to MP, Velcade only minimally increased neutropenia and thrombocytopenia. Anemia was more common on the MP arm. Nausea, vomiting, diarrhea, and constipation were more common with Velcade therapy, as was neuropathy.

#### 7.4.2 Laboratory Findings

During the entire study, the most frequently reported adverse events in any SOC in both treatment groups belonged to the Blood and Lymphatic SOC: anemia (Vc-MP: 43%, MP: 55%), thrombocytopenia (Vc-MP: 52%, MP: 47%), and neutropenia (Vc-MP: 49%, MP: 46%). This is expected in a study in a hematological malignancy treated with myelosuppressive chemotherapy (melphalan). The higher incidence of anemia was also reflected in a higher use of RBC transfusions (26% vs. 35%) and erythropoiesis-stimulating agents (30% vs. 39%) in the Vc-MP and MP treatment groups, respectively. The incidence of Grade 3 or 4 anemia was higher in the MP treatment group (33%) than in the Vc-MP treatment group (22%). The incidence of Grade 3 or 4 neutropenia and leukopenia was similar in the Vc-MP treatment group (55% and 58%, respectively) as in the MP treatment group (54% and 53%, respectively). Thrombocytopenia occurred slightly more often in the Vc-MP group (Vc-MP: 52%, MP: 47%). The additional thrombocytopenia in the Vc-MP treatment group did not lead to an increase in Grade  $\geq$  3 bleeding, observed in 3% of each treatment group.

Grade 2 or higher liver function abnormalities (transaminases, bilirubin) were uncommon (3% to 6%) in both treatment groups. Grade  $\geq$ 3 serum creatinine elevations were observed in 2% of patients in the Vc-MP treatment group and 4% of patients in the MP treatment group. Elevations in alkaline phosphatase (of any grade) were noted in 45% of patients in the Vc-MP treatment group and 35% of patients in the MP treatment group. Grade  $\geq$ 3 hypokalemia and hyponatremia were reported in 8% and 10% of patients in the Vc-MP treatment group and 5% and 9% of patients in the MP treatment group. Grade 4 hyperuricemia was reported in 4% of patients in the Vc-MP treatment group and 6% of patients in the MP treatment group.

Reviewer comments: A transient increase in bone alkaline phosphatase (approximately doubling by day 22) is a described phenomenon on Velcade therapy and is interpreted as an indication of osteoblastic activity and bone regeneration.

#### 7.4.3 Vital Signs

Vital signs were performed at clinic visits but results were not informative for safety.

#### 7.4.4 Electrocardiograms (ECGs)

Not assessed.

#### 7.4.5 Special Safety Studies

No special safety studies were performed.

#### 7.4.6 Immunogenicity

Not applicable

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

Only one dose was studied in this regimen based on the sponsor's prior drug development and preliminary PK findings. Dose reductions (14%) and withholding (4%) for melphalan and prednisone were infrequent and symmetrical in both treatment groups. Throughout the 52 planned administrations of Velcade per patient, dose reductions for Velcade due to adverse events occurred in 49% (in 36% for Nervous System disorders) and 78% of patients had at least 1 Velcade dose withheld (44% for Blood and Lymphatic disorders). Incidence of adverse events resulting in cycle delays was comparable (Vc-MP: 40%, MP: 42%) between the treatment groups, and were mainly due to insufficient hematological recovery (Vc-MP: 15%, MP: 27%).

#### 7.5.2 Time Dependency for Adverse Events

Neuropathy is a cumulative adverse reaction well described previously. Rash and thrombocytopenia are not cumulative but can require dose adjustment. The incidence of adverse events resulting in cycle delays was comparable (Vc-MP: 40%, MP: 42%) between the treatment groups, and was mainly due to delay in hematological recovery (Vc-MP: 15%, MP: 27%).

#### 7.5.3 Drug-Demographic Interactions

Of the 340 patients in the Vc-MP treatment group, 172 were male and 168 were female. Of the 337 patients in the MP treatment group, 166 were male and 171 were female. For both treatment groups, serious adverse events were reported for a greater percentage of males than females. In the Vc-MP treatment group, serious adverse events were reported for 49% of males and 42% of females; in the MP treatment group, for 41% of males and 31% of females. No apparent differences between males and females were evident for patients in either treatment group with regard to the overall incidence of adverse events within any SOC. For the Vc-MP treatment group, serious adverse events were reported in 58% of Asian patients and in 45% of white patients. The incidence of Grade 3 to 5 adverse events was 97% (32 of 33 patient) for Asian patients and 89% (267 of 300 patients) for white patients.

Adverse events leading to treatment termination were reported in 14% of Asian patients in the MP treatment group and in 15% of Asian patients in the Vc-MP treatment group (5 patients each). Adverse events leading to treatment termination were reported in 14% of white patients in the MP treatment group and in 15% of white patients in the Vc-MP treatment group.

Of the 340 patients in the Vc-MP treatment group, 234 were <75 years of age and 106 were ≥75 years of age. Of the 337 patients in the MP treatment group, 236 were <75 years of age and 101 were ≥75 years of age. The incidence of serious adverse events was greater among patients aged ≥75 years than those aged <75 years in both treatment groups. In the Vc-MP treatment group, serious adverse events were reported in 52% and 43% of patients aged ≥75 years and <75 years, respectively. In the MP treatment group, the incidence was 48% and 31%, respectively. In the Vc-MP treatment group, adverse events of maximum severity Grade 3, 4, or 5 were more common for patients aged <75 years (93%) than for those aged ≥75 years (82%). However, in the MP treatment group, the maximum severity of adverse events was Grade 3, 4, or 5 for a greater percentage of patients aged ≥75 years (86%) than patients aged <75 years (76%). The incidence of adverse events leading to treatment discontinuation was similar for both age groups in the Vc-MP treatment group (14% and 16%, respectively) and was higher for the ≥75-year-old patients in the MP treatment group (12% and 19%, respectively).

**Table 9: Comparison of AEs and SAEs by treatment group**

	----- MP -----			----- Vc-MP -----		
	Total - Age Group, n (%)			Total - Age Group, n (%)		
	(N=337) <75 ≥75			(N=340) <75 ≥75		
	n (%) (N=236)		(N=101)	n (%) (N=234)		(N=106)
<b>Any TEAE</b>	326 (97)	228 (97)	98 (97)	338 (99)	233 (>99)	105 (99)
At least 1 related	283 (84)	193 (82)	90 (89)	331 (97)	229 (98)	102 (96)
None related	43 (13)	35 (15)	8 (8)	7 (2)	4 (2)	3 (3)
<b>Any Serious TEAE</b>	121 (36)	73 (31)	48 (48)	155 (46)	100 (43)	55 (52)
At least 1 related	51 (15)	30 (13)	21 (21)	96 (28)	57 (24)	39 (37)
None related	70 (21)	43 (18)	27 (27)	59 (17)	43 (18)	16 (15)
<b>Maximum Severity of Any AE</b>	326 (97)	228 (97)	98 (97)	338 (99)	233 (>99)	105 (99)
Grade 1	12 (4)	11 (5)	1 (1)	2 (1)	1 (<1)	1 (1)
Grade 2	47 (14)	36 (15)	11 (11)	32 (9)	15 (6)	17 (16)
Grade 3	148 (44)	102 (43)	46 (46)	181 (53)	137 (59)	44 (42)
Grade 4	92 (27)	64 (27)	28 (28)	96 (28)	65 (28)	31 (29)
Grade 5	27 (8)	15 (6)	12 (12)	27 (8)	15 (6)	12 (11)
<b>Terminated Treatment Due to AEs<sup>a</sup></b>	47 (14)	28 (12)	19 (19)	50 (15)	33 (14)	17 (16)
At least 1 related	35 (10)	20 (8)	15 (15)	37 (11)	26 (11)	11 (10)
None related	12 (4)	8 (3)	4 (4)	13 (4)	7 (3)	6 (6)

Sponsor table 68, CSR page 243

Note: Percentages in 'Total' column for each group calculated with the number of patients in each group as denominator. Percentages of age group sub-groups calculated with number of patients per sub-group as denominator.

a: For patients indicated as having discontinued treatment due to an adverse event

#### 7.5.4 Drug-Disease Interactions

##### Baseline albumin:

Within the MP treatment group, SAEs were reported more frequently for patients with baseline albumin of <3.5 g/dL (40%) than for those with albumin  $\geq$ 3.5 g/dL (29%). This trend was not as pronounced in the Vc-MP treatment group (49% vs. 41%).

##### Baseline beta2-microglobulin:

In the Vc-MP treatment group, SAEs were reported for 33%, 47%, and 48% of patients, respectively, in the 3 beta2-microglobulin subgroups (<2.5 mg/L, 2.5 to 5.5 mg/L, >5.5 mg/L). In the MP treatment group, the incidence was 31%, 34%, and 41%, respectively, in the 3 subgroups. The incidence of adverse events leading to treatment termination also showed an increasing trend at higher baseline beta2-microglobulin levels. An adverse event led to treatment termination for 8%, 15%, and 16% of patients in the Vc-MP treatment group, and for 10%, 11%, and 20% of patients in the MP treatment group.

##### Baseline renal function:

Of the 340 patients in the Vc-MP treatment group, baseline creatinine clearance was  $\leq$ 30 mL/min for 19 patients, 31 to 60 mL/min for 162 patients, and >60 mL/min for 159 patients. Of the 337 patients in the MP treatment group, baseline creatinine clearance was  $\leq$ 30 mL/min for 15 patients, 31 to 60 mL/min for 168 patients, and >60 mL/min for 154 patients. For both treatment groups, adverse event data were comparable for patients with a baseline creatinine clearance of 31 to 60 mL/min and for patients with a creatinine clearance of >60 mL/min. In the Vc-MP treatment group, the incidence of SAEs were 42% and 47%, respectively, and the incidence of adverse events of maximum severity (Grade 3, 4, or 5) were 52% and 55%, 28% and 27%, and 8% and 8%, for patients with a baseline creatinine clearance of 31 to 60 mL/min and >60 mL/min, respectively. The incidence of adverse events leading to treatment discontinuation was also similar for patients with a baseline creatinine clearance of 31 to 60 mL/min and >60 mL/min in the Vc-MP treatment group (13% and 17%, respectively). In the small group of patients with a creatinine clearance  $\leq$ 30 mL/min, the incidence of adverse events leading to treatment termination and Grade 5 adverse events was similar to those observed in the 2 other subgroups (11% and 11%, respectively). However, the incidence of SAEs (63%) and Grade 4 adverse events (42%) was higher in this subgroup of creatinine clearance  $\leq$ 30 mL/min as compared to the 2 other subgroups. A similar trend was noted in the MP treatment group. Adverse event incidences were similar for patients with a baseline creatinine clearance of 31 to 60 mL/min and for patients with a baseline creatinine clearance of >60 mL/min. Incidence of adverse events of Grade 4 and 5 and incidence of adverse events leading to treatment termination were higher in patients with a creatinine clearance  $\leq$ 30 mL/min.

Reviewer comment: These findings may indicate a higher AE rate for the patients who at baseline were severely renal impaired. Of note, the rate was higher for both study arms which does not specifically implicate Velcade. Only 2 of the 19 had baseline serum creatinine values >

2 mg/dL, and they were permitted into the study by the monitor on the basis of renal myeloma involvement. None of the severely renal impaired participated in the PK Substudy.

### 7.5.5 Drug-Drug Interactions

See the clin-pharm section for the interaction study with MP.

## 7.6 Additional Safety Explorations

### 7.6.1 Human Carcinogenicity

No additional studies were submitted.

### 7.6.2 Human Reproduction and Pregnancy Data

No additional studies were submitted.

### 7.6.3 Pediatrics and Effect on Growth

Not applicable. Applicant has a pediatric waiver.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

None

## 8 Postmarketing Experience

The applicant searched their global safety database through September 15, 2007 for this submission for cases involving Velcade plus MP used as initial therapy for myeloma and excluding the present study. Three spontaneous safety reports of three patients and five clinical trials involving Vc-MP (total of 445 Vc-MP patients) were found; additional studies involved alternative dosing schedules or additional chemotherapy drugs also.

Spontaneous reports of SAEs (3 patients):

1. One case of pulmonary hypertension with associated chest discomfort and oxygen saturation decreased was reported. {Cases of pulmonary hypertension have been reported previously with Velcade and are noted in the current label}
2. One case of melena and hematemesis was reported. {Gastrointestinal adverse events and bleeding are known and are labeled toxicities associated with the use of Velcade}
3. One case of associated gait disturbance, pain in extremity, and paresthesia was reported

Clinical study reports of SAEs (101 patients):

The most commonly reported events were reported in the following SOCs:

- Infections & Infestations SOC (47 serious adverse events) with most common reports being cases of pneumonia (21 serious adverse events),
- General disorders and administration site conditions SOC (31 serious adverse events) with most common reports being cases of pyrexia (13 serious adverse events),
- Gastrointestinal SOC (23 serious adverse events) with most common reports being cases of diarrhea (6 serious adverse events),
- Blood and lymphatic system disorders (15 serious adverse events) with most common reports being cases of febrile neutropenia (6 serious adverse events) and cases of thrombocytopenia (6 serious adverse events),
- Cardiac disorders SOC (13 serious adverse events) with most common reports being cases of atrial fibrillation (5 serious adverse events),
- Nervous system disorders SOC (12 serious adverse events) with most common reports being neuropathy (3 serious adverse events),
- Respiratory, thoracic and mediastinal disorders SOC (11 adverse events) with most common reports being dyspnea (3 serious adverse events),
- Vascular disorders SOC (6 serious adverse events) with most common reports being hypotension (5 serious adverse events)

Cases identified by applicant with fatal outcomes and attribution:

1. Cardiac disorders SOC:

- arrhythmia (one fatal "not-related" case with associated syncope and hepatic enzymes incr.)
- cardiac arrest (one fatal "not-related" case with associated respiratory arrest).

2. Gastrointestinal SOC:

- one fatal related case of colitis ischemic and acute abdomen and
- one possibly related fatal case of paralytic ileus

3. General Disorders and administration site conditions SOC: multiorgan failure (2 cases including one fatal not related case with associated cardiac arrest and respiratory arrest and one fatal related case) and one case of sudden death probably related without any autopsy performed.

4. Nervous system disorders SOC: one fatal case- related polyneuropathy, muscular weakness, and neuropathy with associated not related respiratory infection.

5. Renal and urinary disorders SOC: renal failure (one fatal not related case with associated pulmonary hypertension).

6. Respiratory, thoracic and mediastinal disorders SOC: respiratory arrest (one fatal not related case with associated cardiac arrest and multiorgan failure) and pulmonary hypertension (one fatal not related case with associated renal failure).

7. In addition, 2 fatal cases of disease progression, one fatal case of pneumonia and one fatal case of lung neoplasm were reported, all cases considered as not related to study drugs.

Reviewer comments:

Overall, these adverse events are consistent with the known safety profile of Velcade.

Pneumonia, respiratory problems, and neuropathy are notably common but are also common in myeloma. Also, Velcade is known to cause nausea, vomiting, diarrhea, and asthenia which can

lead to dehydration and hypotension. On the current study, there were 52 (15%) hypotension and orthostatic hypotension cases combined for the Vc-MP arm versus 11 (4%) on the MP arm. Hypotension can precipitate cardiovascular events. Optimal hydration is essential to counteract these effects, but at the same time patients have been reported to develop CHF on Velcade therapy, so fluid balance is challenging. Treatment-emergent hypertension occurred in 13% on the Vc-MP arm versus 7% on the MP arm. Some of this effect is likely due to the steroid (P).

Reviewer comment: Hypertension was not a concern in the single-agent Velcade studies. Velcade is labeled for hypotension in highlights and the warnings and precautions section 5.5, as observed in nonclinical and single-agent clinical studies.

EMEA/CHMP REPORT:

On March 20, 2008, the European Medicines Agency (EMA) recommended that Velcade (bortezomib) should not be used in patients with certain severe pulmonary or heart problems (acute diffuse infiltrative pulmonary and pericardial disease). The EMA Committee for Medicinal Products for Human Use (CHMP) concluded during its March 2008 meeting that the benefits of Velcade are greater than its risks. However, "in patients with acute diffuse infiltrative pulmonary and pericardial disease," the CHMP recommended that Velcade not be used.

In addition, the committee recommended strengthening the existing warnings on pulmonary disorders, advised doctors to perform a chest X-ray before starting Velcade, and advised to consider individual benefit-risk profiles, before starting patients on treatment with Velcade. Finally, the CHMP also recommended that new information on cardiac and pulmonary side effects observed during the post-marketing phase be included in the product information.

In the CHMP Variation Assessment Report dated March 19, 2008, the cardiac deaths reported in the semi-annual periodic safety update reports (PSUR) are summarized here.

PSUR Version	Deaths due to Cardiac Events	Total Deaths	% Deaths due to Cardiac Events
2 (2004)	16	219	7.3
3	10	200	5.0
4	12	138	8.7
5	9	112	8.0
6	11	179	6.1
7 (2007)	9	198	4.5

Reviewer comments: The actual number of reported cardiac deaths was relatively constant during these interval reports although usage increased.

EMA provided their summary and analysis to FDA. The applicant also provided FDA with the information which had been submitted to EMA. OSE has been consulted to assist in this evaluation with the review division also and plans on-going monitoring for these events. The EMA summary of findings expresses concern about patients with existing pericardial or pulmonary conditions. However, in clinical trials, the principal risk to patients has been the

development of respiratory and cardiovascular adverse events on therapy, rather than aggravation of pre-existing pulmonary and pericardial conditions. The applicant was queried further and, in a teleconference, advised that they could not specifically explain the pericarditis concern in particular (see below in section 9.6).

To evaluate pulmonary complications further, the applicant performed a global search for cases of interstitial lung disease (ILD) and used a cutoff date of March 31, 2008. Among approximately 85,000 Velcade-treated patients, there are 193 separate case reports. Of the total, 59 reports are from the U.S., 54 are from Japan, 38 are from the EU, and the remainder from Australia, Korea, and Israel. Ethnicity was only documented for 40 of the 193 cases. An independent expert pulmonary panel reviewed the cases and concluded that no specific risk factors could be identified. The role of infectious processes contributing to the occurrence of pulmonary AEs on Velcade is likely since myeloma patients are often immunocompromised and become neutropenic on chemotherapy. In this study, pneumonia was slightly more common on the Vc-MP arm (16% vs. 11%); obtaining positive culture or serologic proof of bacterial or viral pneumonias is often difficult in this setting.

The diagnosis of the syndrome of acute diffuse infiltrative/interstitial pulmonary disease (ILD) is one of exclusion. Respiratory symptoms and disorders are common in patients with multiple myeloma due to the disease process and the therapy. In the applicant's study for this sNDA, there were 4 patients in the Vc-MP arm and 5 in the MP arm with "interstitial changes" on baseline chest radiograph. Three of the 4 Vc-MP patients completed all nine treatment cycles, and one patient discontinued for a non-pulmonary event. Two of the four did report grade 1 cough as their most severe pulmonary AE. Of these 4, two achieved a CR and two achieved a PR, suggesting that: (1) benefit exceeded a risk of pulmonary impairment and (2) baseline pulmonary interstitial abnormalities were not useful predictors of treatment-emergent pulmonary toxicity.

AE data in the phase 3 trial under review were reported using MedDRA System Organ Class (SOC) terms. In this system, respiratory-related AEs are derived from the primary MedDRA SOC of Respiratory, Thoracic and Mediastinal Disorders. To examine respiratory events further, a separate analysis of treatment-emergent respiratory conditions was performed by combining all respiratory-related AEs from the primary MedDRA SOC of Respiratory, Thoracic and Mediastinal Disorders with the respiratory events of infectious origin that were originally reported under their default primary SOC of Infections and Infestations. In the original analysis using the primary respiratory SOC, there were 123 (36%) patients in the MP arm and 133 (39%) patients in the Vc-MP arm with an AE in the Respiratory, Thoracic and Mediastinal Disorders SOC.

When lower respiratory AEs (from the Infections SOC) are added, the Respiratory-related AE rates increase to 165 (49%) patients in the MP arm and 190 (56%) patients in the Vc-MP arm. Rates of Grade 3 or greater Respiratory-related AEs are similar when the two arms are compared, with 45 (13%) patients in the MP arm and 54 (16%) patients in the Vc-MP arm experiencing a Grade 3 or greater AE. SAE rates also increase but remain similar when the two arms are compared, with 44 (13%) subject in the MP arm and 55 (16%) patients in the Vc-MP arm experiencing a Respiratory-related SAE. When both lower and upper respiratory AEs are combined, Respiratory-related AE rates increase to 180 (53%) patients in the MP arm and 204

(60%) patients in the Vc- MP arm. Rates of Grade 3 or greater Respiratory-related AEs also are similar, with 50 (15%) patients in the MP arm and 57 (17%) patients in the Vc-MP arm experiencing a Grade 3 or greater AE.

Reviewer comments: Overall, a slightly higher rate of respiratory AEs was observed on the Vc-MP arm using various classifications. The U.S. label for Velcade currently includes warnings and precautions for cardiac and pulmonary adverse reactions which include the events of concern to the EMEA.

The Division reviewed the evidence for the EMEA action internally and with the applicant. There is a discrepancy between the clinical safety information and the EMEA action. The EMEA has referred to a phase 2 study by the NCI Canada of mantle cell lymphoma in which 5 of the 29 enrolled patients had fluid retention problems. All 5 had fluid retention at baseline in the setting of extensive lymphoma with malignant pleural effusions, ascites, edema, and nephrotic syndrome in one. The case narratives are most consistent with these patients having very advanced disease and substantial fluid retention problems at baseline. In the NCIC Phase 2 study as published (Belch A et al., Annals of Oncology 2007; 18:116-121) and the CSR submitted with the Velcade mantle cell lymphoma sNDA (21-602 S010), 2 patients enrolled in the study were known to have pericardial effusions at baseline (patients CATW0001 and CAMP0001). Neither of these patients developed treatment emergent pericardial effusions. Among 155 patients with relapsed mantle cell lymphoma and treated with Velcade monotherapy in a study conducted by the applicant (M34103-053), only one case of fluid retention occurred, in the setting of acute renal failure, and this was considered as not related to Velcade by the investigator. In addition, no excess of fluid retention events have occurred in controlled trials in myeloma patients.

In addition to the cardiac and pulmonary findings discussed above, in this application there were 2 cases of pericardial effusion reported in the study, both on the Vc-MP arm. One patient developed a symptomatic pericardial effusion/pericarditis treated with prednisone and antibiotics. After resolution over 3 weeks, the patient received additional Vc-MP without re-occurrence during the following 2 months of therapy. The second patient developed symptomatic pericardial effusion/pericarditis after 3 months of therapy with Vc-MP. She had had a normal baseline cardiac ECHO. During an interval off of Velcade, she reported increasing neuropathy and Velcade was discontinued for the neuropathy. She was not re-challenged with Velcade.

Reviewer comments:

This reviewer can find no evidence to implicate a baseline pericardial condition as a risk factor for cardiac adverse events on Velcade treatment. Also, development of pericardial disease on Velcade is anecdotal. In the current label, pulmonary disorders are described in detail in section 5.5 and cardiac disorders are well described in section 5.4 of the warnings and precautions section. Evidence is insufficient to modify these label sections at present. See appendix section 9.6 for the full text of the sponsor's summary of pulmonary and cardiac AEs related to the EMEA assessment.

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Some additional explorations of pulmonary and cardiac function during Velcade therapy may be informative, but the clinical trial results do not show safety differences sufficient to require post-approval studies. The applicant may consider studying cardiac function further, as well as pulmonary function and lung mechanics during Velcade therapy to assess possible alterations.

This reviewer agrees with the study's safety results as reported. Labeling revisions are continuing during the sNDA review (see section 9.4 for additional description).

APPEARS THIS WAY ON ORIGINAL

## 9 Appendices

### 9.1 IMWG response criteria <sup>4</sup>

<i>Response subcategory</i>	<i>Response criteria</i> <sup>a</sup>
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and $\leq 5\%$ plasma cells in bone marrow <sup>b</sup>
sCR	CR as defined above plus Normal FLC ratio and absence of clonal cells in bone marrow <sup>b</sup> by immunohistochemistry or immunofluorescence <sup>c</sup>
VGPR	Serum and urine M-component detectable by immunofixation but not on electrophoresis or 90 or greater reduction in serum M-component plus urine M-component <100 mg per 24 h
PR	$\geq 50\%$ reduction of serum M-protein and reduction in 24-h urinary M-protein by > 90% or to <200 mg per 24 h
	If the serum and urine M-protein are unmeasurable, <sup>d</sup> a 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria <sup>2, 3</sup>
	If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, >50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was >30%
	In addition to the above listed criteria, if present at baseline, a >50% reduction in the size of soft tissue plasmacytomas is also required
SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

<sup>a</sup> All response categories require two consecutive assessments made at anytime before the institution of any new therapy; complete and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

<sup>b</sup> Confirmation with repeat bone marrow biopsy not needed.

<sup>c</sup> Presence/absence of clonal cells is based upon the  $k/\lambda$  ratio. An abnormal  $k/\lambda$  ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is  $k/\lambda$  of >4:1 or <1;2.

Reviewer comment: the primary response analysis was performed using the EBMT criteria as described in the previous clinical reviews of Velcade. The IMWG criteria for response were used for a secondary response assessment. Overall, it is similar to the EBMT criteria except for the additional designation of sCR as noted above.

## 9.2 Protocol definition of progression and relapse (EBMT)

Response	Criteria for Response <sup>1</sup>
Progressive Disease (PD) (for subjects not in CR)	Requires 1 or more of the following: <ul style="list-style-type: none"> <li>• &gt;25% increase<sup>4</sup> in the level of serum monoclonal paraprotein, which must also be an absolute increase of at least 5 g/L (500 mg/dL) and confirmed on a repeat investigation</li> <li>• &gt;25% increase<sup>4</sup> in 24-hour urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 h and confirmed on a repeat investigation</li> <li>• &gt;25% increase<sup>4</sup> in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%</li> <li>• Definite increase in the size of existing lytic bone lesions or soft tissue plasmacytomas<sup>5</sup></li> <li>• Development of new bone lesions or soft tissue plasmacytomas (not including compression fracture)</li> <li>• Development of hypercalcemia (corrected serum calcium &gt;11.5 mg/dL or 2.8 mmol/L not attributable to any other cause)<sup>6</sup></li> </ul>
Relapse from CR	Requires at least 1 of the following: <ul style="list-style-type: none"> <li>• Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis confirmed by at least 1 follow-up and excluding oligoclonal immune reconstitution</li> <li>• ≥5% plasma cells in the bone marrow aspirate or biopsy</li> <li>• Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (not including compression fracture)</li> <li>• Development of hypercalcemia (corrected serum calcium &gt;11.5 mg/dL or 2.8 mmol/L not attributable to any other cause)<sup>6</sup></li> </ul>

<sup>1</sup> Adapted from the criteria reported by Blade *et al.*, 1998.<sup>15</sup>

<sup>2</sup> According to Blade *et al.*, 1998<sup>15</sup>, if absence of the monoclonal protein is sustained for 6 weeks it is not necessary to repeat the bone marrow. In subjects with nonsecretory or oligosecretory myeloma the marrow examination (including 6 week follow-up examination) will be required.

<sup>3</sup> According to Blade *et al.*, 1998<sup>15</sup>, skeletal X-rays are not required for the definition of response, but if performed there must be no evidence of progression of bone disease (no increase in size or number of lytic bone lesions).

<sup>4</sup> The reference point for calculating any increase should be the lowest prior value documented at baseline or during the study unless the lowest prior value is considered to be spurious.

<sup>5</sup> A definite increase in size is defined as at least a 50% increase in the product of the greatest perpendicular dimensions.

<sup>6</sup> Other clinical data may be needed to assess the cause of the hypercalcemia before attributing it to myeloma disease progression.

### 9.3 Literature Review/References

The applicant provided a comprehensive literature review.

### 9.4 Labeling Recommendations

Labeling was converted to PLR format with the previous sNDA. The current label incorporates the first-line study and further AE descriptions for the combination with MP. The safety concerns in the highlights are comprehensive:

- "Women should avoid becoming pregnant while being treated with VELCADE. Pregnant women should be apprised of the potential harm to the fetus. (5.1)
- Peripheral neuropathy, including severe cases, may occur - manage with dose modification or discontinuation. (2.2, 2.4) Patients with preexisting severe neuropathy should be treated with Velcade only after careful risk-benefit assessment. (2.2, 2.4, 5.2)
- Hypotension can occur. Caution should be used when treating patients receiving antihypertensives, those with a history of syncope, and those who are dehydrated. (5.3)
- Patients with risk factors for, or existing heart disease, should be closely monitored. (5.4)
- Acute diffuse infiltrative pulmonary disease has been reported. (5.5)
- Nausea, diarrhea, constipation, and vomiting have occurred and may require use of antiemetic and antidiarrheal medications or fluid replacement. (5.7)
- Thrombocytopenia or neutropenia can occur; complete blood counts should be regularly monitored throughout treatment. (5.8)
- Tumor Lysis Syndrome (5.9), Reversible Posterior Leukoencephalopathy Syndrome (5.6), and acute hepatic failure (5.10) have been reported."

These concerns are expanded in the warnings and precautions also.

Herpes Virus Infection, Section 6.1, has been modified to reflect the current study use of antiviral prophylaxis and to update the clinical trial experience as follows:

(b) (4)

## **9.5 Advisory Committee Meeting**

No AC meeting was considered necessary for this evaluation.

## **9.6 Sponsor reply 4/24/08 to EMEA safety concerns**

Sponsor Information replies for Safety review Tcon held April 24, 2008

### **Agency Question 1:**

Please provide information regarding the safety concerns which arose in Study NCIC IND- 150. What were the specific pre-existing diagnoses, severity of co-morbid problems, treatment-associated changes, and the changes made to the protocol eligibility for this study or if more general eligibility changes are appropriate for VELCADE use.

### **Sponsor Response:**

The CSR for Study NCIC IND-150, A Phase II Study of PS-341 (NSC 681239) in Patients with Untreated or Relapsed Mantle Cell Lymphoma, was submitted as part of the VELCADE MCL sNDA 21-602 S011. Three of 29 (10%) patients enrolled in the NCI CTG IND-150 study died on study. Five (17%) patients, including the 3 who died, experienced serious fluid retention or edema. As a result of these events, subject accrual was temporarily suspended and the protocol was amended to exclude patients with pre-existing Grade 2 or greater edema, neuropathy or shortness of breath, or any intensity of ascites or pleural effusion. The amendment also added several procedures and assessments to monitor for subject safety, namely the inclusion of total protein and albumin to the blood chemistry panel, cardiac assessments, and 24-hour urine collection for protein determination. No cases of serious fluid retention or edema occurred after implementation of the protocol amendment (Amendment 3).

At baseline, all of these patients had pre-existing edema, pleural effusions or shortness of breath. SAEs in 4 patients occurred in the context of progressive disease. SAEs were considered unlikely or unrelated to VELCADE in 4 patients and possibly related to VELCADE in just 1 subject.

Narratives for the 5 patients experiencing serious fluid retention or edema are provided below. The SAEs are further discussed in Section 12.3 of the NCI CTG IND-150 study CSR. Three of the patients (CATW0001, CATW0002 and CAVA0001) had baseline dyspnea with peripheral edema. One subject (CATW0003) had baseline dyspnea without peripheral edema, ascites or pleural effusions. The fifth subject (CAVA0005) had peripheral edema with a history of coronary artery disease but no dyspnea at baseline. SAEs in all patients were associated with progressive disease. In patients CATW0001, CATW0003 and CAVA0001 all SAEs were considered unlikely to be related to VELCADE. In subject CATW0002, all SAEs were considered unrelated to VELCADE. SAEs in subject CAVA0005 were considered possibly related to VELCADE. In addition, in subject CATW0001 the pleural effusion was reported to be

malignant, and in subject CATW0003 pulmonary edema was found to be due to widely disseminated MCL at autopsy. The findings in all 4 patients with progressive disease are consistent with the aggressive, widely disseminated course that is typical of advanced mantle cell lymphoma.

Although no cases of serious fluid retention occurred after the changes in eligibility criteria, the study enrolled a small number of patients, and it is not known that the changes in eligibility criteria were the reason that additional cases of serious fluid retention did not occur. Importantly, only a single comparable case of serious fluid retention was observed in the Millennium-sponsored study of 155 patients (M34103-053) that supported the approval of VELCADE in patients with previously treated MCL. In that study subject 31-002 developed anasarca and pleural effusion in the setting of acute renal failure, and died due to respiratory failure. The anasarca, pleural effusion and respiratory failure were considered unlikely to be related to VELCADE. Study M34103-053 did not exclude patients with pre-existing edema, shortness of breath, ascites, or pleural effusion. Therefore, we believe that these are uncommon events that are most likely a consequence of advanced MCL and unlikely to be related to VELCADE, and that there is no evidence that excluding patients with pre-existing evidence of fluid retention will prevent these events from occurring.

**Subject ID Number CATW0001 (Serious adverse events unlikely related to study drug: peripheral edema, dyspepsia, nephrotic syndrome, hypoxia)** is a 74-year-old White male with Stage IV mantle cell lymphoma diagnosed 0.2 year prior to study entry, a BSA of m2, and a baseline ECOG score of 2 and IPI score of 4. The subject had received no prior chemotherapy for mantle cell lymphoma. His medical history included Grade 1 peripheral edema and nephrotic syndrome, depression and emphysema with Grade 3 shortness of breath.

The subject began treatment with VELCADE (1.3 mg/m<sup>2</sup>) on 19 November 2002 (Cycle 1 Day 1) and received 2 cycles for a total of 20.4 mg (8 doses). The subject's last dose of VELCADE was administered on 27 December 2002.

At baseline (15 November 2002), the subject had an ANC was 4.40 x 10<sup>9</sup>/L, a platelet count of at least 110 x 10<sup>9</sup>/L, a serum creatinine of 143 µmol/L, a total bilirubin of 5.00 µmol/L, an AST of 26 U/L, and a left ventricular ejection fraction of 45% or greater. During Cycles 1 and 2, Grade 3 dyspnea NOS was reported (no onset/resolution dates); these events were assessed by the investigator as not related to VELCADE treatment. On (b) (6) (Cycle 2 (b) (6)), (b) (6) days after the subject's last dose of VELCADE, the subject was admitted to the hospital for management of peripheral edema and nephrotic syndrome (albumin was 27 g/L and maximum creatinine was 340 µmol/L). While in the hospital the subject had a CT scan which showed new malignant bilateral pleural effusions and pulmonary edema causing Grade 3 hypoxia which began on 06 January 2003. While hospitalized, the subject's lowest albumin was 21 g/L and his highest creatinine was 340 µmol/L. The subject was taken off study due to progression. The investigator assessed the edema and hypoxia as unlikely related to VELCADE treatment.

**Subject ID Number CATW0002: Subject CATW0002 (Serious adverse events unrelated to study drug: fatigue and left leg peripheral edema. Death due to progressive disease)** was a 74-year-old White woman with Stage IV diffuse blastic mantle cell lymphoma diagnosed 0.3

year prior to study entry, a BSA of 1.78 m<sup>2</sup> and a baseline ECOG score of 0 and IPI score of 3. The subject had received no prior chemotherapy for mantle cell lymphoma. Her medical history included splenectomy in November 2002, fatigue, edema, and shortness of breath. At baseline, she had Grade 2 shortness of breath and was on coumadin for a previous deep vein thrombosis; however she did not have edema at baseline.

The subject began treatment with VELCADE (1.3 mg/m<sup>2</sup>) on 03 January 2003 (Cycle 1, Day 1) and received a total of 9.2 mg (4 doses). The subject's last dose of VELCADE was administered on 13 January 2003.

During Cycle 1, Grade 2 fatigue was reported (no onset/resolution dates); this event was assessed by the investigator as not related to VELCADE treatment. Grade 1 muscle weakness was reported beginning 04 January 2003; this event was assessed by the investigator as not related to VELCADE treatment. Also on 04 January 2003, the subject experienced edema NOS, which began as Grade 1 and progressed to Grade 3. On [REDACTED]<sup>(b) (6)</sup>, she was admitted to the hospital for symptomatic relief of progressive Grade 2 fatigue and a massive swollen leg (Grade 3). The subject refused any further treatment for mantle cell lymphoma. She died of progressive disease on [REDACTED]<sup>(b) (6)</sup>. The investigator assessed the death as due to disease progression and not related to VELCADE treatment.

**Subject ID Number CATW0003 (Serious adverse event unlikely related to study drug: Capillary leak syndrome with pulmonary congestion, bilateral arm and leg pain. Death due to capillary leak syndrome)** was a 57-year-old White male with Stage IV diffuse mantle cell lymphoma diagnosed 0.1 year prior to study entry, a BSA of 2.10 m<sup>2</sup>, and a baseline ECOG score of 2 and IPI score of 3. The subject had received no prior chemotherapy for mantle cell lymphoma. His medical history included hypertension and diverticulitis. The extent of his disease at study entry included lymphadenopathy and a massively enlarged spleen with Grade 1 abdominal bloating. At baseline, the subject also had Grade 2 dyspnea, mild anemia and thrombocytopenia, which were attributed to the hypersplenism.

The subject began treatment with VELCADE (1.3 mg/m<sup>2</sup>) on 14 January 2003 (Cycle 1 Day 1) and received 3.5 cycles for a total of 36.8 mg (14 doses). The subject's last dose of VELCADE was administered on 21 March 2003.

During Cycle 1, Grade 3 dyspnea NOS was reported (onset date not reported) which decreased in intensity to Grade 2 on 03 February 2003 and resolved on 09 February 2003 (C2D6); these events were assessed by the investigator as not related to VELCADE treatment. All other events reported during Cycle 1 through Cycle 3 were Grade 1 or Grade 2. A CT scan performed on 21 February 2003 (C2D18) revealed stable disease. At that time, there were no significant abnormalities in the mediastinum or pulmonary parenchyma. The subject began Cycle 4 of therapy on 18 March 2003 and received 2 of the 4 planned doses for that cycle. The subsequent 2 doses were held due to a low platelet count ( $43 \times 10^9/L$ ; Grade 3; on 25 March 2003). The subject presented to the emergency room on [REDACTED]<sup>(b) (6)</sup> (C4<sup>(b) (6)</sup>) with worsening bilateral arm pain and joint pain that began [REDACTED]<sup>(b) (6)</sup> days earlier on 22 March 2003. Vital signs included a heart rate of 125 beats/minute, blood pressure of 150/90 mmHg, and oxygen saturation of 87%. CBC

showed a WBC of  $114.5 \times 10^9/L$  with the differential revealing mostly large, immature lymphocytes; no blasts were seen. The subject felt better after receiving morphine and was discharged from the emergency room. Several hours later he died at home ( (b) (6) ). Preliminary autopsy findings showed massive congestion of the lungs, liver, and spleen associated with some right heart enlargement. No pulmonary embolus or infarct in the heart was noted, although there were infarcts in the spleen. The spleen was quite enlarged and was mostly blood with only a moderate amount of mantle cell nodules present. The subject was considered to possibly have acute capillary leak syndrome. Based on final evaluation, cause of death was reported as marked pulmonary edema due to advanced, widely disseminated lymphoma.

The investigator initially assessed the relationship of the event as possibly related to VELCADE; this was later changed to unlikely.

**Subject ID Number CAVA0001: Subject CAVA0001 (Serious adverse events unlikely related to study drug: Dyspnea, fatigue, melena, increased ascites, abdominal pain, anorexia. Death due to progressive disease)** was a 69-year-old White male with Stage IV diffuse mantle cell lymphoma diagnosed 1.2 years prior to study entry, a BSA of 2.09 m<sup>2</sup> and a baseline ECOG score of 2 and IPI score of 4. This subject had previously received 6 cycles of CHOP therapy. He was diabetic and had hypothyroidism as well as ascites, a pleural effusion and Grade 2 shortness of breath and abdominal pain at baseline. He had paracenteses for ascites prior to study entry. At screening (23 January 2003), the subject's platelet count was  $485 \times 10^9/L$ , serum creatinine was 102  $\mu\text{mol/L}$ , and serum potassium was 5.1 mmol/L (Grade 1 elevation).

The subject began treatment with VELCADE (1.3 mg/m<sup>2</sup>) on 28 January 2003 and received a total of 8.1 mg of VELCADE (3 doses). The subject's last dose of VELCADE was administered on 04 February 2003 (C1D8)

On (b) (6) (C1 (b) (6)); after receiving 3 doses of VELCADE), the subject was hospitalized for assessment of increased creatinine (her creatinine was 153  $\mu\text{mol/L}$  on that day, and had ranged from 131-171  $\mu\text{mol/L}$  on Days 2-8) and fatigue and for supportive care for disease progression (PD), which included increased ascites, shortness of breath, abdominal pain, and anorexia. On admission the subject had a distended abdomen due to increased ascites, Grade 3 fatigue, Grade 2 dyspnea, anorexia, abdominal pain, and constipation, Grade 1 nausea, leg edema, and skin rash. The subject received IV fluids. On (b) (6), his potassium was 5.3 mmol/L and creatinine was 144  $\mu\text{mol/L}$ . His pedal edema increased to Grade 2 and he developed Grade 1 scrotal edema on (b) (6). His shortness of breath worsened to Grade 3 and he developed melena (Grade 5) on (b) (6) (C1 (b) (6)). Serum creatinine remained elevated on (b) (6) (122  $\mu\text{mol/L}$ ) and returned to within normal limits (107  $\mu\text{mol/L}$ ) on the following day, and ranged from 92-100  $\mu\text{mol/L}$  between (b) (6) (b) (6)). The subject continued to deteriorate and died on (b) (6). His last known platelet count was  $248 \times 10^9/L$  ( (b) (6) , C1 (b) (6) ).

The primary cause of death was considered to be acute gastrointestinal bleed related to PD. In the opinion of the investigator, the subject's condition was unlikely related to VELCADE.

Increased ascites, dyspnea, abdominal pain and anorexia were all considered related to progressive disease.

**Subject ID Number CAVA0005 (Serious adverse events possibly related to study drug: fatigue, CHF/left ventricular failure with dyspnea and peripheral edema, hypoglycemia, increased creatinine and potassium)** is a 77-year-old White male with Stage IV diffuse mantle cell lymphoma diagnosed 1.7 years prior to study entry, a BSA of 2.31 m<sup>2</sup>, and a baseline ECOG score of 1 and IPI score of 2. Prior chemotherapy for mantle cell lymphoma included 2 regimens of cyclophosphamide from 30 July 2001 through 13 November 2001 and 17 July 2002 through 30 October 2002. His medical history included symptomatic coronary artery disease with coronary artery bypass graft performed in 1992, hypertension, hyperlipidemia, and type II diabetes (treated with glyburide) and edema (Grade 2 at baseline). At study entry, he had extensive disease throughout the abdomen and retroperitoneum with a large omental mass, retroperitoneal lymphadenopathy, and splenomegaly.

The subject began treatment with VELCADE (1.3 mg/m<sup>2</sup>) on 24 February 2003 (Cycle 1 Day 1) and received a total of 21 mg (7 doses). The subject's last dose of VELCADE was administered on 24 March 2003.

During Cycle 1, Grade 1 edema NOS and Grade 2 dyspnea NOS were reported (no onset/resolution dates). The edema was assessed by the investigator as not related to VELCADE treatment; the dyspnea was considered possibly related. The subject began Cycle 2 on 17 March 2003, at which time he reported increased fatigue and increased dyspnea with exertion. The subject also developed new peripheral edema extending up to his knees and was noted as having hypoglycemia. The subject was started on Lasix, and his dose of glyburide was decreased. On (b) (6) (C2 (b) (6) after receiving 6 doses of VELCADE), the subject was hospitalized with increasing fatigue (Grade 3), persistent edema up to the knees (Grade 1), dyspnea (Grade 2), elevated JVP, Grade 1 chest pain and hypoglycemia (creatinine 148 µmol/L; potassium 5.9 mmol/L). He was diagnosed with biventricular congestive heart failure and treated with diuretics. His glyburide was held. The subject was discontinued from VELCADE due to the toxicities. He was continued on diuretics and placed on a nitroglycerin patch, with resolution of symptoms. The subject was discharged from the hospital on (b) (4) with only mild edema and no further episodes of exertional dyspnea; these events were considered resolved on 10 April 2003. The subject's hypoglycemia resolved after cessation of VELCADE. The investigator assessed the fatigue, hypoglycemia, and left ventricular failure as possibly related to VELCADE treatment and edema and dyspnea as possibly related. Left ventricular failure was considered probably related to coronary artery disease.

References:

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- <sup>1</sup> Mateos M-V, Hernandez J-M, Hernandez M-T, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: results of a multicenter phase 1/2 study. *Blood* 2006; 108:2165–2172.
- <sup>2</sup> Harousseau J-L, Marit G, Caillot D, et al. VELCADE/dexamethasone (Vel/Dex) vs VAD as induction treatment prior to autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (MM): an interim analysis of the IFM 2005-01 Randomized Multicenter Phase III Trial [abstract]. *Blood* 2006; 108:56.
- <sup>3</sup> Philip R. Greipp, Jesus San Miguel, Brian G.M. Durie, John J. Crowley et al. International Staging System (ISS) for Multiple Myeloma. *J Clin Oncol* 2005; 23: 3412-3420.
- <sup>4</sup> Durie BGM et al. International uniform response criteria for multiple myeloma. *Leukemia* 2006; 20: 1467-1473.

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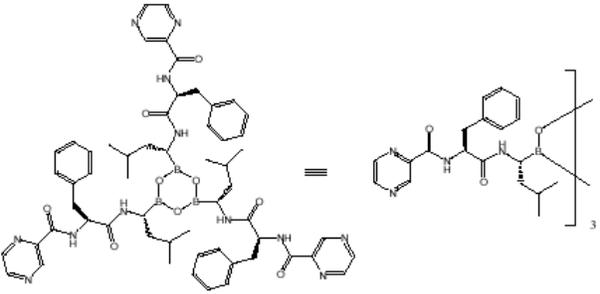
Ann Farrell  
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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-602/S-015**

**CHEMISTRY REVIEW(S)**

CHEMIST'S REVIEW		1. ORGANIZATION ONDQA/HFD-150		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	
				5. SUPPLEMENT (S) NUMBER(S) DATES(S) SE1-015 12/20/2007	
6. NAME OF DRUG VELCADE		7. NONPROPRIETARY NAME bortezomib for injection			
8. SUPPLEMENT PROVIDES FOR: new drug efficacy and safety information in drug packaging insert.				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 <sub>19</sub> H <sub>25</sub> BN <sub>4</sub> O <sub>4</sub> , 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 provided the drug efficacy and safety information to support the use of Velcade for Injection in patients with previously untreated multiple myeloma. The new efficacy information will be included into PI. No CMC related sections were changed from the approved packaging insert.  Millennium is claiming a categorical exclusion as allowed under 21 CFR 25.31(b) for substances entering the aquatic environment at concentrations of less than 1 part per billion.					
18. CONCLUSIONS AND RECOMMENDATIONS Approval is recommended.					
NAME Chengyi Liang, Ph.D.		SIGNATURE			DATE 6-19-2008
<b><u>DISTRIBUTION</u></b>	ORIGINAL NDA	DIVISION FILE	Reviewer: C.Y. Liang	CSO:	H. Patel Branch Chief

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Chengyi Liang  
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CHEMIST

Liang Zhou  
6/19/2008 10:41:00 AM  
CHEMIST  
for BC, Dr. H. Patel

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-602/S-015**

**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: **015**  
DATE RECEIVED BY CENTER: **20 December 2007**  
PRODUCT: **VELCADE®**  
INTENDED CLINICAL POPULATION: **Relapsed and refractory multiple myeloma**  
SPONSOR: **Millennium Pharmaceuticals, Inc.**  
DOCUMENTS REVIEWED: **Label**  
REVIEW DIVISION: **Division of Drug Oncology Products**  
PHARM/TOX REVIEWER: **Kimberly A. Benson, Ph.D.**  
PHARM/TOX SUPERVISOR: **S. Leigh Verbois, Ph.D.**  
DIVISION DIRECTOR: **Robert Justice, M.D.**  
PROJECT MANAGER: **Kim Robertson**

Date of review submission to Division File System (DFS): 24 June 2008

## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number:** 21-602

**Review number:** 3

**Sequence number/date/type of submission:** 015/20 December 2007/SE1

**Information to sponsor:** Yes ( ) No (X)

**Sponsor and/or agent:** Millennium Pharmaceuticals, Inc.

**Manufacturer for drug substance:** [REDACTED] (b) (4)

**Reviewer name:** Kimberly A. Benson, Ph.D.

**Division name:** Division of Drug Oncology Products

**Review completion date:** 20 June 2008

#### Drug:

Trade name: VELCADE®

Generic name: Bortezomib

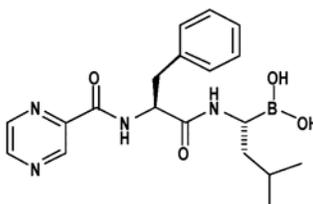
Code name: PS341

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

CAS registry number: 179324-69-7

Molecular formula/molecular weight: C<sub>19</sub>H<sub>25</sub>BN<sub>4</sub>O<sub>4</sub> / 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 (b) (4) mg mannitol.

**Route of administration:** Bolus IV injection

**Proposed use:** The recommended dose of VELCADE is 1.3 mg/m<sup>2</sup>/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

APPEARS THIS WAY ON ORIGINAL

A recent supplemental NDA for Velcade included several recommended changes to the label based on the current recommendations for the wording and location of the Pharmacology/Toxicology information regarding use during pregnancy and nursing mothers.

The following recommendations to the Sponsor's proposed labeling are given. The Sponsor's proposed wording is followed by the recommendation with a rationale for the recommended changes.

---

*The Sponsor proposed*

**5 WARNINGS AND PRECAUTIONS**

**5.1 Pregnancy Category D**

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

Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits at the highest dose tested (0.075 mg/kg; 0.5 mg/m<sup>2</sup> in the rat and 0.05 mg/kg; 0.6 mg/m<sup>2</sup> in the rabbit) when administered during organogenesis. These dosages are approximately half the clinical dose of 1.3 mg/m<sup>2</sup> based on body surface area.

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

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

*FDA recommends*

**5 WARNINGS AND PRECAUTIONS**

**5.1 Use in Pregnancy  
Pregnancy Category D**

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

*Rationale*

- Changed the title to Use in Pregnancy rather than Pregnancy Category D as the correct and more informative title is "Use in Pregnancy"

- Per the current design of the label, the Warnings and Precautions section should only have a succinct summary of the animal data that informs regarding the use of the drug during pregnancy. This paragraph should state that women should avoid getting pregnant while on the drug, and then what data are known that leads to that recommendation, i.e., the animal species used and what adverse findings were noted.
- Additionally, this paragraph should include a comparison of the animal dose to the clinical dose, by either AUC or on body surface area. This was added to the paragraph to show that the result in the rabbit was seen at a dose that was approximately half the clinical dose of 1.3 mg/m<sup>2</sup>, based on body surface area. This need for a comparison like this in this section was confirmed by the Maternal Health Team.

---

*The Sponsor proposed*

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

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

*FDA recommends*

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

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

Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits at the highest dose tested (0.075 mg/kg; 0.5 mg/m<sup>2</sup> in the rat and 0.05 mg/kg; 0.6 mg/m<sup>2</sup> in the rabbit) when administered during organogenesis. These dosages are approximately half the clinical dose of 1.3 mg/m<sup>2</sup> based on body surface area.

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

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

*Rationale*

- The detailed developmental non-clinical information that was once in the Warnings and Precautions section was moved to the Use in Special Populations section, per current practice based on input from the Maternal Health Team.

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Kimberly Benson  
6/24/2008 11:22:38 AM  
PHARMACOLOGIST

Leigh Verbois  
6/25/2008 04:10:57 PM  
PHARMACOLOGIST

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-602/S-015**

**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:** N021-602 / SE1-015  
**Drug Name:** VELCADE (bortezomib), 1.3 mg/m<sup>2</sup>/dose, for injection  
**Indication(s):** Treatment of patients with multiple myeloma  
**Applicant:** Millennium Pharmaceuticals, Inc.  
**Date(s):** Submission date: December 20, 2007  
PDUFA due date: June 17, 2008  
Review completion date: June 9, 2008

**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:** Kim Robertson

**Keywords:** one-study application, open-label, add-on design, time to progression, interim analysis

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## **1. EXECUTIVE SUMMARY**

This is a supplemental New Drug Application (sNDA) submission seeking indication for intravenous VELCADE<sup>®</sup> (bortezomib) as the treatment of patients with multiple myeloma (MM). This sNDA is comprised of one phase III pivotal study in patients with previously untreated MM. The proposed indication is to be supported based on superiority of VELCADE in combination with melphalan and prednisone (Vc-MP) over melphalan and prednisone (MP) with respect to time to progression (TTP).

### **1.1 Conclusions and Recommendations**

In this reviewer's opinion, the study results from the pivotal study MMY-3002 demonstrated the benefit of adding VELCADE to melphalan and prednisone as front-line therapy for multiple myeloma. A statistically significant improvement of 6 months in median time to disease progression was observed (hazard ratio [95% confidence interval]: 0.537 [0.413, 0.697], p-value = 0.000002), with improvement also observed in all secondary endpoints with the addition of VELCADE. Results of progression-free survival, which considered the influence of deaths on efficacy determination, showed an improvement of 4.3 months in median time with a hazard ratio of 0.609 (95% confidence interval: 0.486, 0.763) for the addition of VELCADE.

### **1.2 Brief Overview of Clinical Studies**

This sNDA contains data from one sponsor-conducted phase III pivotal study MMY-3002. Study MMY-3002 is a randomized, open-label clinical trial in multiple myeloma patients who were previously untreated and who were not candidates for high-dose chemotherapy with stem cell transplant. Eligible patients were randomized according to baseline beta2-microglobulin (<2.5 mg/L, 2.5 to 5.5 mg/L, >5.5 mg/L), baseline albumin (<3.5 g/dL, ≥3.5 g/dL [SI Units: <35 g/L, ≥35 g/L]), and region (North America, Europe including Australia, Other) to either VELCADE plus melphalan and prednisone (Vc-MP) treatment group or melphalan and prednisone (MP) treatment group at 1:1 ratio. Melphalan 9 mg/m<sup>2</sup> and prednisone 60 mg/m<sup>2</sup> were given once daily on Days 1 to 4 of each 6-week cycle. VELCADE injection 1.3 mg/m<sup>2</sup> was given twice weekly for four 6-week cycle followed by once weekly for five 6-week cycles to patients in the Vc-MP treatment group. For both groups, treatment continued for a maximum of 9 cycles (54 weeks) and was discontinued if progressive disease (PD) or unacceptable treatment-related toxicity occurred, or if a subject withdrew consent.

Study MMY-3002 enrolled a total of 682 patients (Vc-MP / MP: 344 / 338) from 151 centers worldwide to evaluate the add-on effect of VELCADE for treating multiple myeloma in a first-line setting based on time to progression (TTP) as the primary efficacy endpoint. Secondary efficacy endpoints include progression-free survival (PFS), overall survival (OS), response rates, duration of response, and time to first response.

Three interim analyses were planned in study MMY-3002 for safety and efficacy evaluations after 100 patients completed 1<sup>st</sup> treatment cycle, after approximately 120 observed progression events, and after approximately 260 observed progression events, respectively. The independent data monitoring committee (IDMC) notified the sponsor that the statistical boundary for the primary endpoint TTP was crossed based on data reviewed at the 3<sup>rd</sup> interim analysis. The sponsor terminated the study, and reported the study completed on the 3<sup>rd</sup> interim analysis data cut-off date of June 15, 2007.

### **1.3 Statistical Issues and Findings**

Review of this efficacy supplement is based on pivotal study MMY-3002 for evaluation of additional benefit from VELCADE in combination with melphalan and prednisone as a front-line therapy for the treatment of multiple myeloma. The primary efficacy endpoint for study MMY-3002 is time to disease progression (TTP), defined by the sponsor as the time from date of randomization to the date of progressive disease (PD) or to the date of death if PD was determined to be the cause of death.

Study MMY-3002 had a special protocol assessment under IND 56,515 in 2004. The Division agreed to the general aspects of the study design, but asked the applicant to revise the definition of TTP to censor all deaths at the time of the last complete myeloma assessment. The Division also suggested that progression-free survival (PFS) could be the primary endpoint where death from any cause would be classified as an event. The sponsor selected TTP as defined above as the primary endpoint, and added PFS as a secondary endpoint.

#### **Statistical Issues:**

This reviewer did not find major statistical issues that would preclude approval of VELCADE for the proposed indication based on review of the pivotal study MMY-3002. However, this reviewer recommends reporting different results from the ones appear in the clinical study report as follows:

1. Report TTP results without PD-related deaths as events. Although there were only a few PD-related deaths in sponsor's TTP analysis, the definition of time to disease progression should not include deaths per guidance for industry "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" published in May 2007.
2. Report response rates using all randomized patients. The sponsor had limited their response rate evaluation in a subset of randomized patients. For keeping the principle of randomization, any efficacy evaluations in a randomized trial should be based upon all randomized patients.

#### **Primary Findings:**

Table 1 summarizes the results on time to disease progression (TTP), defined as time from date of randomization to date of progressive disease with all deaths censored at the last disease assessment. As of the data cut-off date for study MMY-3002, 247 or 63.3% of the 390 targeted

events (Vc-MP/MP: 99 events / 148 events) have been observed. The median TTP was 631 days (20.7 months) in the Vc-MP treatment group compared with 456 days (15.0 months) in the MP treatment group. The hazard ratio for Vc-MP versus MP was 0.537 (95% CI: 0.413, 0.697). The p-value of 0.000002 from the stratified log-rank test indicates a highly significant difference in distribution of TTP between the two groups, compared to the O'Brien-Fleming stopping boundary of 0.0096 calculated based on observed 63.3% events at the time of the third interim analysis.

Table 1 also shows the results on progression-free survival (PFS). PFS is considered by the review Division to be an important and preferred efficacy endpoint because it does not only assess the treatment efficacy by looking at PD, but also account for the influence of deaths on the efficacy determination especially in the population considered in this application. Three hundred and twenty five (325) PD or death events were observed (Vc-MP / MP: 135 events / 190 events). The median PFS was 425 days (14.0 months) in the Vc-MP treatment group compared with 556 days (18.3 months) in the MP treatment group. The hazard ratio for Vc-MP versus MP was 0.609 (95% CI: 0.486, 0.763).

Results of key secondary endpoints as shown in Table 6 indicate that VELCADE has provided additional clinical benefit to the patients with respect to overall survival and overall response rate.

In addition, time to disease progression subgroup analyses as shown in section 4 support the addition of VELCADE for previously untreated multiple myeloma across subgroups.

**Table 1 - Summary of TTP and PFS Results (Study MMY-3002, ITT Population)**

N = 682	MP (n = 338)	Vc-MP (n = 344)
<b>TTP (days)</b>		
Number of events (%)	148 (43.8%)	99 (28.8%)
Median (95% CI) <sup>a</sup>	456 (429, 545)	631 (541, 751)
p-value <sup>b</sup> (compared to 0.0096 for 247 / 390 = 63.3% events)	0.000002	
HR (95% CI) <sup>c</sup>	0.537 (0.413, 0.697)	
<b>PFS (days)</b>		
Number of events (%)	190 (56.2%)	135 (39.2%)
Median (95% CI) <sup>a</sup>	425 (338, 456)	556 (506, 659)
HR (95% CI) <sup>c</sup>	0.609 (0.486, 0.763)	
p-value <sup>b, d</sup>	0.00001	

MP = melphalan + prednisone; Vc-MP=VELCADE + melphalan + prednisone

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

<sup>b</sup> p-value from the log-rank test, stratified by randomization factors

<sup>c</sup> Hazard ratio for Vc-MP over MP in TTP based on the Cox model adjusted for randomization factors

<sup>d</sup> O'Brien-Fleming stopping boundary was not calculated for PFS, since TTP is the protocol-specified primary efficacy endpoint

## 2. INTRODUCTION

### 2.1 Overview of the disease

Multiple myeloma is a malignant disease of plasma cells that accounts for 8% of all hematologic cancers (second only to non-Hodgkin's lymphoma) and which represents approximately 1% of all cancers. In Europe, the incidence is approximately 23,000 per year, with a prevalence of approximately 70,000. In the US, approximately 19,900 new cases of multiple myeloma are diagnosed and 10,790 patients die of the disease each year. Multiple myeloma usually manifests as 1 or more lytic bone lesions, monoclonal protein in the blood or urine, and disease in the bone marrow. Disease progression is often associated with worsening of symptoms and organ dysfunction characteristic of myeloma, such as anemia, bone lesion-related symptoms (including bone pain, bone fractures, and hypercalcemia), renal function impairment, and susceptibility to infections.

The current treatment recommendation is to have initial induction chemotherapy followed by 1 or 2 courses of high-dose chemotherapy with autologous stem cell transplant (HDT/SCT) support for patients ages 65 and younger. This approach has shown a significant survival advantage over conventional chemotherapy. In patients older than 65 years of age, the value of HDT/SCT is controversial and has not been formally established in prospective randomized studies. Given that the median age at diagnosis of multiple myeloma is between 65 and 70 years, the majorities of newly diagnosed patients are treated only with standard chemotherapy, with no consideration for HDT/SCT because of poor physical condition, co-morbidities, and increased toxicity. Combination chemotherapy with melphalan and prednisone (MP) has been the standard-of-care in front-line non-transplant multiple myeloma therapy since the 1960s, and remains the most widely accepted treatment option for patients ineligible for HDT/SCT.

*Reviewer comment:* Overview of the disease is summarized from sponsor's clinical overview section 1.2.

#### 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.

With results from Study JNJ-26866138-MMY-3002 (hereafter referred to as Study MMY-3002), the sponsor is seeking to extend the current labeling to the labeling of VELCADE in relapsed multiple myeloma patients to patients with previously untreated multiple myeloma. Study MMY-002 is designed to compare VELCADE plus melphalan and prednisone (Vc-MP) regimen with melphalan and prednisone (MP) regimen in patients with previously untreated multiple myeloma for additional benefit of VELCADE in this patient population.

### **2.1.2 Clinical Studies**

This sNDA contains data from one sponsor-conducted phase III pivotal study MMY-3002. Study MMY-3002 is a randomized, open-label clinical trial in multiple myeloma patients who were previously untreated and who were not candidates for high-dose chemotherapy with stem cell transplant. Eligible patients were randomized according to baseline beta2-microglobulin (<2.5 mg/L, 2.5 to 5.5 mg/L, >5.5 mg/L), baseline albumin (<3.5 g/dL, ≥3.5 g/dL [SI Units: <35 g/L, ≥35 g/L]), and region (North America, Europe including Australia, Other) to either VELCADE plus melphalan and prednisone (Vc-MP) treatment group or melphalan and prednisone (MP) treatment group at 1:1 ratio. Melphalan 9 mg/m<sup>2</sup> and prednisone 60 mg/m<sup>2</sup> were given once daily on Days 1 to 4 of each 6-week cycle. VELCADE injection 1.3 mg/m<sup>2</sup> was given twice weekly for four 6-week cycle followed by once weekly for five 6-week cycles to patients in the Vc-MP treatment group. For both groups, treatment continued for a maximum of 9 cycles (54 weeks) and was discontinued if progressive disease (PD) or unacceptable treatment-related toxicity occurred, or if a subject withdrew consent.

Study MMY-3002 enrolled a total of 682 patients (Vc-MP / MP: 344 / 338) from 151 centers worldwide to evaluate the add-on effect of VELCADE for treating multiple myeloma in a first-line setting based on time to progression (TTP) as the primary efficacy endpoint. Secondary efficacy endpoints include progression-free survival (PFS), overall survival (OS), response rates, duration of response, and time to first response.

Three interim analyses were planned in study MMY-3002 for safety and efficacy evaluations after 100 patients completed 1<sup>st</sup> treatment cycle, after approximately 120 observed progression events, and after approximately 260 observed progression events, respectively. The independent data monitoring committee (IDMC) notified the sponsor that the statistical boundary for the primary endpoint TTP was crossed based on data reviewed at the 3<sup>rd</sup> interim analysis. The sponsor terminated the study, and reported the study completed on the 3<sup>rd</sup> interim analysis data cut-off date of June 15, 2007.

### **2.1.3 Major Statistical Issues**

This reviewer did not find major statistical issues that would preclude approval of VELCADE for the proposed indication based on review of the pivotal study MMY-3002.

## **2.2 Data Sources**

Data used for this review are located on network with path “\\Cdsesub1\nonectd\N21602\S\_015\2007-12-20\m5\53-clin-study-reports\537-crf-ipl-crt\crt\datasets\mmy3002”.

### 3. STATISTICAL EVALUATION

#### 3.1 Evaluation of Efficacy

The sNDA is comprised of one pivotal study, Study MMY-3002, as the primary basis for efficacy evaluations.

##### 3.1.1 Pivotal Study MMY-3002

###### 3.1.1.1 Study Design

Study MMY-3002 is a randomized, open-label clinical trial in previously untreated multiple myeloma patients who are not candidates for high-dose chemotherapy with stem cell transplant. Eligible patients were randomized according to baseline beta2-microglobulin (<2.5 mg/L, 2.5 to 5.5 mg/L, >5.5 mg/L), baseline albumin (<3.5 g/dL, ≥3.5 g/dL [SI Units: <35 g/L, ≥35 g/L]), and region (North America, Europe including Australia, Other) to either the VELCADE plus melphalan and prednisone (Vc-MP) group or the melphalan and prednisone (MP) group at 1:1 ratio. Melphalan 9 mg/m<sup>2</sup> and prednisone 60 mg/m<sup>2</sup> were given once daily on Days 1 to 4 of each 6-week cycle. VELCADE injection 1.3 mg/m<sup>2</sup> was given twice weekly for four 6-week cycle followed by once weekly for five 6-week cycles to patients in the Vc-MP treatment group. For both groups, treatment continued for a maximum of 9 cycles (54 weeks) and was discontinued if progressive disease (PD) or unacceptable treatment-related toxicity occurred, or if a subject withdrew consent.

The study consisted of 3 phases: a pre-randomization (screening) phase, an open-label treatment phase, and a post-treatment follow-up phase. Throughout the open-label treatment and post-treatment follow-up phases, the investigator assessed the subject's response to therapy using the results of efficacy evaluations conducted at equivalent frequency (every 3 weeks in the first 54 weeks and every 8 weeks thereafter) in each treatment group and by applying protocol defined disease response criteria (the European Group for Blood and Marrow Transplant or EBMT criteria as presented in clinical study report Table 5). In the post-treatment follow-up phase, patients were followed until death or a maximum of 4.5 years after the last patient was randomized on the study.

*Reviewer comment:* The age restriction of 65 years or older was removed in protocol amendment 1 (Amendment INT-1, 14 October 2004), and patients less than 65 years of age with presence of important comorbid condition(s) likely to have a negative effect on tolerability of HDT/SCT were eligible for the study. This change in inclusion criteria was implemented before the study accrual. Detailed inclusion and exclusion criteria are described in clinical study report sections 3.2.2 and 3.2.3.

### 3.1.1.2 Study Objectives

The primary efficacy objective of this study was to determine whether the addition of VELCADE to standard MP therapy improved the time to disease progression (TTP) in patients with previously untreated multiple myeloma.

The secondary efficacy objectives of this study were to determine whether the addition of VELCADE to standard MP therapy in patients with previously untreated multiple myeloma improved the following: progression-free survival (PFS), overall survival (OS), complete response (CR) rate, objective response rate (CR + PR for complete or partial response), time to response, and duration of response.

### 3.1.1.3 Definition of Efficacy Endpoints

#### Primary endpoint

- **Time to disease progression (TTP):** TTP was measured from the date of randomization to the date of the first observation of progressive disease (PD) or relapse from IF-negative CR. The definition of PD and relapse from IF-negative CR and their documentation are described in the disease response criteria in clinical study report Table 5. Death related to PD was defined as an event if there was sufficient evidence for documentation of PD. TTP times for patients without an observed PD were censored at the last date known to be without PD or relapse.

*Reviewer comment:* Study MMY-3002 had a special protocol assessment under IND 56,515 in 2004. At that time, the Division asked the sponsor to revise the definition of TTP to censor all deaths at the time of the last complete myeloma assessment. The Division also suggested that progression-free survival (PFS) could be the primary endpoint where death from any cause would be classified as an event. The sponsor selected TTP as defined above as the primary endpoint, and added PFS as a secondary endpoint.

#### Secondary endpoints

- **Progression-free survival (PFS):** PFS was defined as the time between randomization and either PD, relapse, or death due to any cause, whichever occurred first. PFS times for those surviving patients without PD or relapse were censored at the last date known to be without PD or relapse.
- **Overall survival (OS):** OS was defined as the time between randomization and death. Deaths, regardless of the cause of death, were considered as events. OS times for patients who withdrew consent for the study were censored at the time of withdrawal. OS times for patients who completed the study and were still alive at the cut-off date of the final

analysis were censored at the cut-off date. OS times for patients who were lost to follow-up prior to the end of the study were censored at the time of last contact.

- **Response rates:** complete response (CR) rate, and objective response rate (ORR: complete response + partial response = CR + PR rate). The definition of each response is described in the disease response criteria in clinical study report section 3.10.4.2, Table 5.
- **Time to response:** Time to response was defined in patients with confirmed response as the time between randomization and the first documentation of response. Time to response for a patient without response was censored either at the time of lost to follow-up, PD, death, or at the end of the study treatment.
- **Duration of response:** Duration of response was defined in patients with confirmed response as the time between first documentation of response and PD or relapse. Duration of response for a responder without PD was censored at the last efficacy assessment for PD or relapse.

*Reviewer Comment:* Considering that many non-PD related deaths could occur in such population of elderly patients with co-morbidities, the review Division feels PFS is a more important efficacy endpoint than TTP because it does not only assess the impact of PD but also account for the influence of deaths on the efficacy determination

#### 3.1.1.4 Sample Size Justification

The study sample size of 680 patients for 390 PD events was determined based on the following assumptions:

- Hazard ratio (HR) of 1.33 for MP versus Vc-MP (or equivalently, median TTP to be 18 months and 24 months for the MP and Vc-MP treatment groups respectively)
- $\alpha=0.05$ , power=80%
- Study duration: 36 months (18 months accrual + 18 months follow-up)
- Dropout rate: 5%

#### 3.1.1.5 Interim Analysis

Three interim analyses (IA) were planned for safety and efficacy evaluation by an independent data monitoring committee (IDMC):

- 1st IA: 100 patients randomized, <15 PD events expected,  $\alpha < 0.00001$
- 2nd IA: 570 patients randomized, 120 PD events expected,  $\alpha = 0.0001$
- 3rd IA: 260 PD events or 1 year after the 2nd IA (whichever comes first),  $\alpha = 0.0121$
- Final analysis: 390 PD events,  $\alpha = 0.0463$

Reviewer's Comments:

1. The 3<sup>rd</sup> interim analysis was added in protocol amendment INT-3 (28 March 2006) to be conducted when approximately two thirds of the events (260 events) have been observed. The timing of the 3<sup>rd</sup> interim analysis was modified in protocol amendment INT-3/SS-1 (21 August 2006) on the basis of the IDMC's recommendation to occur when 260 events have been observed or 1 year after the second interim analysis, whichever comes first.
2. The actual alpha allocation for conducted interim analyses was calculated based on actual number of events observed at the time of analyses.

### **3.1.1.6 Analysis Populations**

The intent-to-treat (ITT) population of all randomized patients is the primary efficacy analysis population except for response rates, which were evaluated by the sponsor based on the response-evaluable population (see below for the definition of the response evaluable population).

Response-Evaluable (RE) population consists of randomized patients who have measurable disease at study entry, and receive at least one dose of the study medication.

Per-Protocol (PP) population is a subset of the ITT population defined as those patients who meet all inclusion and exclusion criteria, receive correct study drug according to randomization, and receive 8 doses of VELCADE and 4 doses of melphalan and prednisone in the first treatment cycle for those assigned to the Vc-MP treatment group, and 4 doses of melphalan and prednisone in the first treatment cycle for those assigned to the MP treatment group. The analyses using data for the PP population were considered secondary and sensitivity analyses.

Reviewer Comment: The RE population is a subset of the ITT population. Response rates should also be evaluated in the ITT population with patients not in the RE population been considered as non-responders. The ITT population should be the primary basis for making treatment comparison in keeping the randomization principle.

### **3.1.1.7 Statistical Methods**

#### Time to event endpoints (TTP, PFS, OS, time to response, and duration of response)

The Kaplan-Meier method was used to estimate the distribution of time to event endpoint for each treatment group. Except duration of response, for which no inferential statistics were performed, the treatment groups were compared based on a stratified log-rank test with randomization factors for stratification. Hazard ratio and its 95% confidence interval for the treatment comparison was estimated from a Cox model adjusted for the randomization factors.

## Response rates

Best confirmed response was determined by sponsor-developed computer algorithm per EBMT criteria based on lab data. Number and percentage of patients had CR and CR+PR were presented by treatment group. Stratified Cochran-Mantel-Haenszel test was used to test for treatment difference in response rates.

### **3.1.1.8 Efficacy Results and Conclusions**

#### **3.1.1.8.1 Disposition of Efficacy Analysis Populations**

The study was stopped and data were analyzed by the sponsor after the third interim analysis following the recommendation from IDMC. As of the data cut-off of 15 June 2007 for the third interim analysis, 682 patients (Vc-MP / MP: 344 / 338) from 151 centers in 22 countries were randomized into Study MMY-3002.

Break down by treatment group, Table 2 lists the size of efficacy analysis populations as defined in section 3.1.1.6. The two treatment groups have similar sizes for the analysis populations; except for the PP population, where the MP group had more patients who did not meet the inclusion/exclusion criteria (per sponsor's clinical report Table 9, 19 patients in MP group did not meet the inclusion/exclusion criteria versus 9 patients in the Vc-MP group). Both treatment groups had 7 patients who were not in the RE population, sponsor's clinical report Figure 1 indicates 4 randomized patients were not treated in the Vc-MP group and 1 randomized patient in the MP group was not treated.

**Table 2 - Disposition of Efficacy Analysis Populations**

Analysis population	Vc-MP	MP	Total
Intent-to-treat (ITT)	344	338	682
Response evaluable (RE)	337	331	668
Per-protocol (PP)	331	318	649

#### **3.1.1.8.2 Demographics and Other Patient Characteristics**

A total of 682 previously untreated multiple myeloma patients who were not candidates for high-dose chemotherapy with stem cell transplant were randomized into Study MMY-3002 as of data cut-off date 15 June 2007 for this submission.

Table 3 summarizes the distribution of demographics, stratification factors, and other baseline characteristics by treatment group for all randomized patients. The majorities of patients in this study were older than 65 with a median age of 71 years and a range of 48 to 91 years. Similar number of male and female patients participated in the study. The 87% of Caucasian participants

reflects the fact that 87% of study participants were treated in Europe and North America regions.

The two treatment groups appear to have similar distributions in the listed patient characteristics.

**Table 3 - Summary of Patient Demographic and Baseline Characteristics  
(Study MMY-3002, ITT population)**

Patient characteristics	Vc-MP (N = 344)	MP (N = 338)	Total (N = 682)
Age in yrs: <65/65-74/>=75, median(range)	4% / 65% / 31%, 71 (57, 90)	3% / 67% / 30%, 71 (48, 91)	3% / 66% / 30%, 71 (48, 91)
Gender, male/female	51% / 49%	49% / 51%	50% / 50%
Race: Caucasian/Asian/black/other	88% / 10% / 1% / 1%	87% / 11% / 2% / 0%	88% / 10% / 2% / <1%
Region: Europe/North America/Other	78% / 9% / 12%	78% / 9% / 13%	78% / 9% / 13%
Karnofsky performance status score <=70	35%	33%	34%
Hemoglobin <100 g/L	37%	36%	36%
Platelet count <75×10 <sup>9</sup> /L	< 1%	1%	1%
Type of myeloma: IgG/IgA/Light chain	64% / 24% / 8%	62% / 26% / 8%	63% / 25% / 8%
Median β <sub>2</sub> -microglobulin (mg/L)	4.2	4.3	4.3
Median albumin (g/L)	33.0	33.0	33.0
Creatinine clearance <=30 mL/min [n(%)]	20 (6%)	16 (5%)	36 (5%)

*Reviewer Comment:* The age limit of 65 years or older was removed from the inclusion criteria in protocol amendment INT-1 (14 October 2004), which was implemented prior to initiation of patient enrollment.

### 3.1.1.8.3 Efficacy Results

This section will show the efficacy results from Study MMY-3002 for comparing Vc-MP versus MP based on the primary endpoint time to disease progression (TTP), as well as results on key secondary endpoints including progression-free survival (PFS), overall survival (OS), and response rates.

#### 3.1.1.8.3.1 Primary Endpoint: Time to Disease Progression (TTP)

Disease progression and relapse were determined based on lab measurements per EBMT criteria. A SAS program was written by the sponsor to implement the criteria to determine the date for progression events. TTP was defined in the protocol as time from date of randomization to date of progressive disease (PD) or to date of death if death is PD-related.

Table 4 summarizes the results on TTP, as defined in the protocol, in the ITT population. As of the data cut-off date, 253 or 65% of the 390 targeted events (Vc-MP/MP: 101 events / 152 events) have been observed. The median TTP was 631 days (20.7 months) in the Vc-MP treatment group compared with 456 days (15.0 months) in the MP treatment group. The p-value of 0.000002 from the stratified log-rank test indicates a highly significant difference in

distribution of TTP between the two groups, compared to the O'Brien-Fleming stopping boundary of 0.0108 calculated based on observed 65% events at the time of the third interim analysis. The hazard ratio (HR) for Vc-MP versus MP, adjusted for randomization factors, was 0.540 (95% CI: 0.416, 0.699). Un-adjusted HR was almost identical to the adjusted HR (un-adjusted HR = 0.542, 95% CI: 0.421, 0.698).

**Table 4 - Summary of TTP Results (ITT population, PD-related Deaths as Events)**

N = 682	MP (n = 338)	Vc-MP (n = 344)
TTP (days)		
Number of events (%)	152 (45.0%)	101 (29.4%)
Median (95% CI) <sup>a</sup>	456 (428, 545)	631 (535, 751)
p-value <sup>b</sup> (compared to 0.0108 for 253 / 390 = 65% events)	0.000002	
HR (95% CI) <sup>c</sup>	0.540 (0.417, 0.699)	

MP = melphalan + prednisone; Vc-MP=VELCADE + melphalan + prednisone

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

<sup>b</sup> p-value from the log-rank test, stratified by randomization factors

<sup>c</sup> Hazard ratio for Vc-MP over MP in TTP based on the Cox model adjusted for randomization factors

*Reviewer Comment:* The TTP results appeared in clinical study report include PD-related deaths from 6 patients (patient id: 300436, 301006, 301083, 301091, 301226, and 301517) as TTP events. Per guidance for industry “Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics”, the definition of time to disease progression should not include deaths. Table 5 shows the TTP results with all deaths censored at the last disease assessment. The results are very similar to the ones presented in Table 4. Figure 1 displays the distribution of TTP by treatment group with only PD as events.

**Table 5 - Summary of TTP Results (ITT population, Deaths Censored)**

N = 682	MP (n = 338)	Vc-MP (n = 344)
TTP (days)		
Number of events (%)	148 (43.8%)	99 (28.8%)
Median (95% CI) <sup>a</sup>	456 (429, 545)	631 (541, 751)
p-value <sup>b</sup> (compared to 0.0096 for 247 / 390 = 63.3% events)	0.000002	
HR (95% CI) <sup>c</sup>	0.537 (0.413, 0.697)	

MP = melphalan + prednisone; Vc-MP=VELCADE + melphalan + prednisone

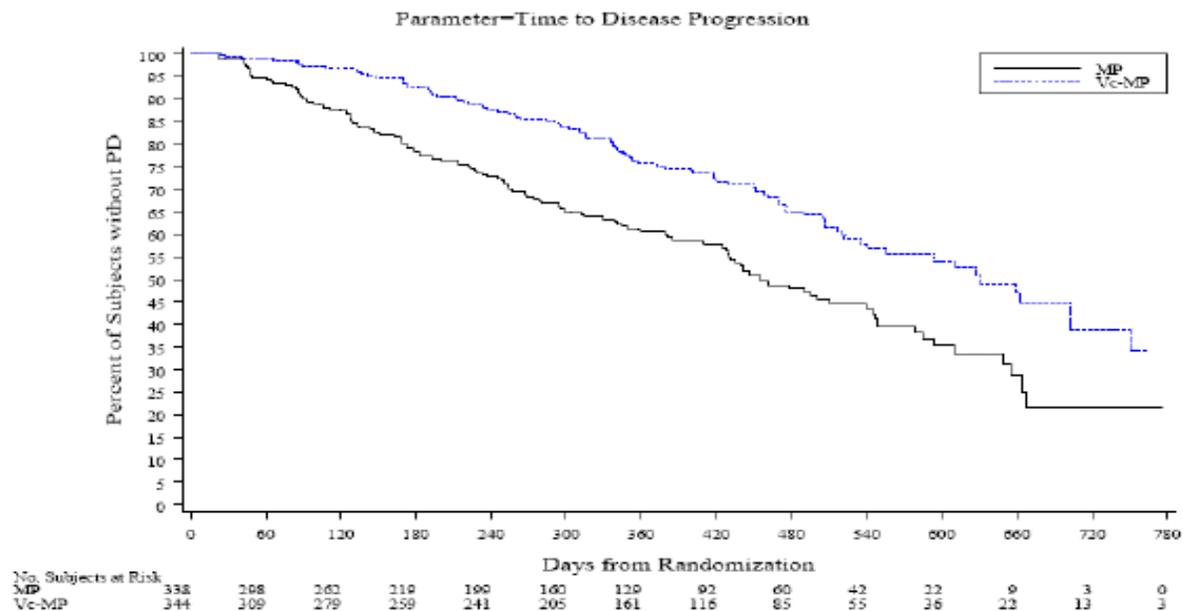
<sup>a</sup> Kaplan-Meier estimate

<sup>b</sup> p-value from the log-rank test, stratified by randomization factors

<sup>c</sup> Hazard ratio for Vc-MP over MP in TTP based on the Cox model adjusted for randomization factors

Note: All deaths are censored at the last disease assessment.

**Figure 1 – Time to Disease Progression (ITT Population, Deaths Censored)**



Note: All deaths are censored at the last disease assessment.

**3.1.1.8.3.2 Key Secondary Endpoints: PFS, OS, and Response Rates**

The key secondary efficacy endpoints of the study include progression-free survival (PFS), overall survival (OS), and response rates as defined in section 3.1.1.3. As shown in Table 6, VELCADE appears to provide additional clinical benefit with respect to PFS and OS with hazard ratios less than one. For response rates, the sponsor reported the complete response and overall response rates to be 4% and 35% for the MP group, and 30% and 71% for the Vc-MP group using response evaluable (RE) population of patients who had measurable disease at study entry and received at least one dose of study medication. When calculated using the ITT population with all randomized patients, the response rates are similar because majority of the randomized patients are response evaluable. The Vc-MP treated group achieved a higher overall response rate with a longer duration of response compared to the MP treated group.

**Table 6 - Results of PFS, OS, Response Rates, and Duration of Response**

Secondary endpoints	MP		Vc-MP	
<b>PFS (days), event / N (%)</b>	190 / 338 (56.2%)		135 / 344 (39.2%)	
Median (95% CI) <sup>a</sup>	425 (338, 456)		556 (506, 659)	
HR (95% CI) <sup>b</sup>	0.609 (0.486, 0.763)			
<b>OS (days), event / N (%)</b>	76 / 338 (22.5%)		45 / 344 (13.1%)	
Median (95% CI) <sup>a</sup>	Not reached		Not reached	
HR (95% CI) <sup>b</sup>	0.607 (0.419, 0.880)			
<b>Best response, n (%)</b>	RE pop. (n = 331)	ITT pop. (n = 338)	RE pop. (n = 337)	ITT pop. (n = 344)
CR	12 (4%)	12 (4%)	102 (30%)	102 (30%)
Median duration <sup>c</sup> : CR	12.8 mo		24.0 mo	
CR+PR	115 (35%)	115 (34%)	238 (71%)	238 (69%)
Median duration <sup>c</sup> : CR+PR	13.1 mo		19.9 mo	

MP = melphalan + prednisone; Vc-MP=VELCADE + melphalan + prednisone

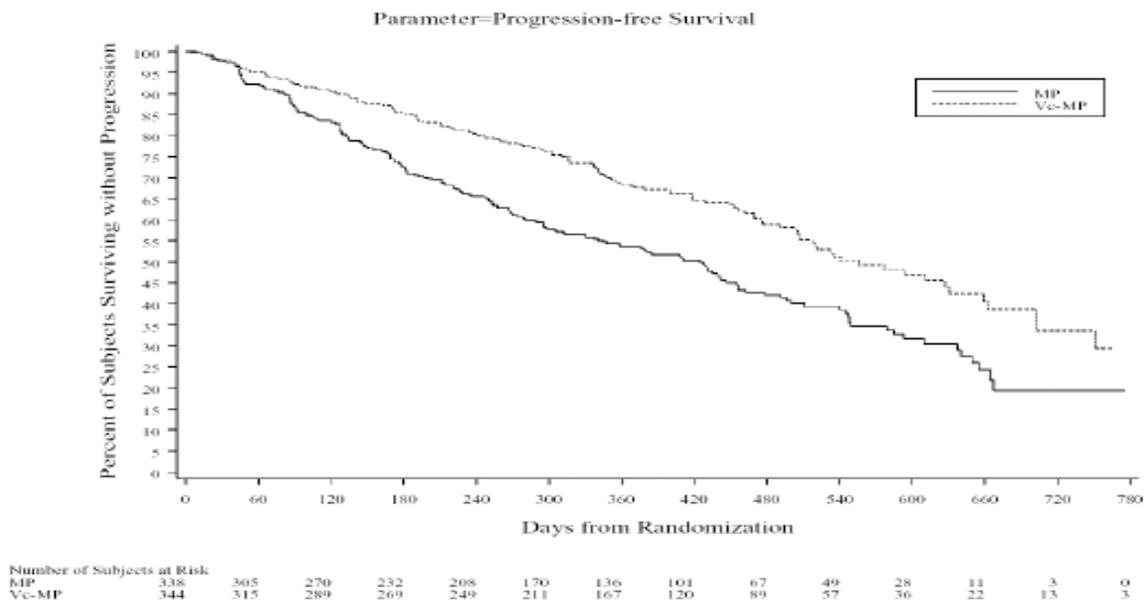
RE = response evaluable; ITT = intent-to-treat

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

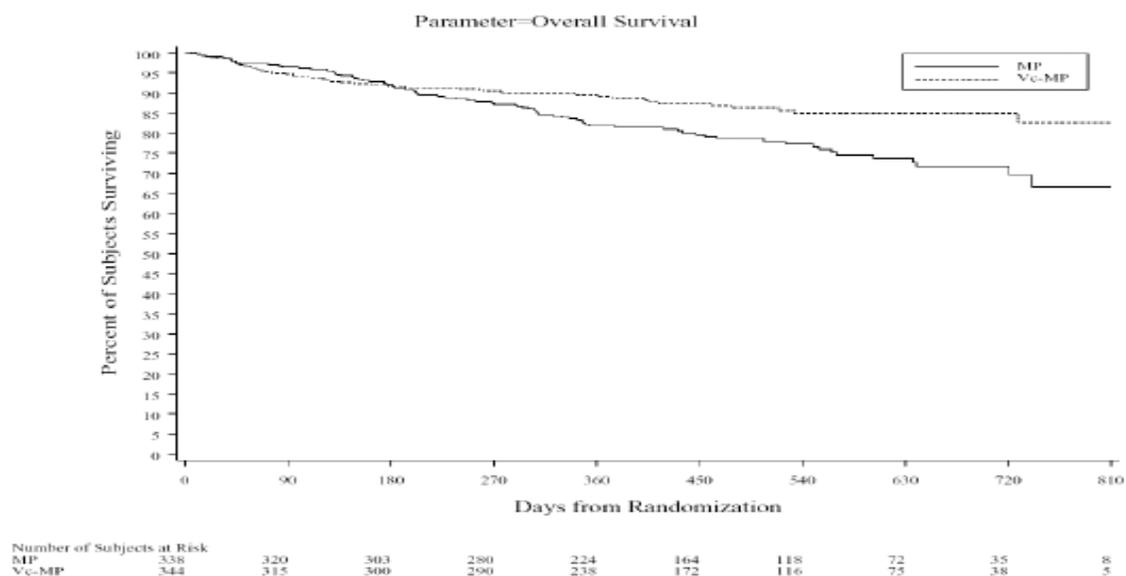
<sup>b</sup> Hazard ratio for Vc-MP over MP based on the Cox model adjusted for randomization factors

<sup>c</sup> Duration of response calculated in responders only

**Figure 2 – Progression Free Survival (ITT Population)**



**Figure 3 - Overall Survival (ITT Population)**



**Reviewer Comments:**

1. PFS was added as a secondary endpoint in protocol amendment INT-1 (14 October 2004) following the Division’s recommendation to include an analysis of PFS as a sensitivity analysis for TTP if the sponsor decided to select TTP as the primary endpoint (Per Division’s comment: Alternatively, PFS could be the primary endpoint).
2. There were 78 deaths contributed to the difference between results of TTP and PFS (TTP number of events = 247, PFS number of events = 325, a difference of 78 events for deaths observed). Considering that many deaths could occur in such population of elderly patients with co-morbidities, PFS may be a more important efficacy endpoint than TTP because it does not only assess the impact of PD but also account for the influence of deaths on the efficacy determination.

**3.1.1.8.4 Conclusions for Efficacy**

In this reviewer’s opinion, the study results from the pivotal study MMY-3002 demonstrated the benefit of adding VELCADE to melphalan and prednisone as front-line therapy for multiple myeloma. A statistically significant improvement of 6 months in median time to disease progression was observed (hazard ratio [95% confidence interval]: 0.537 [0.413, 0.697], p-value = 0.000002), with improvement also observed in all secondary endpoints with the addition of VELCADE. Results of progression-free survival, which considered the influence of deaths on efficacy determination, showed an improvement of 4.3 months in median time with a hazard ratio of 0.609 (95% confidence interval: 0.486, 0.763) for the addition of VELCADE.

**3.2 Evaluation of Safety**

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

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

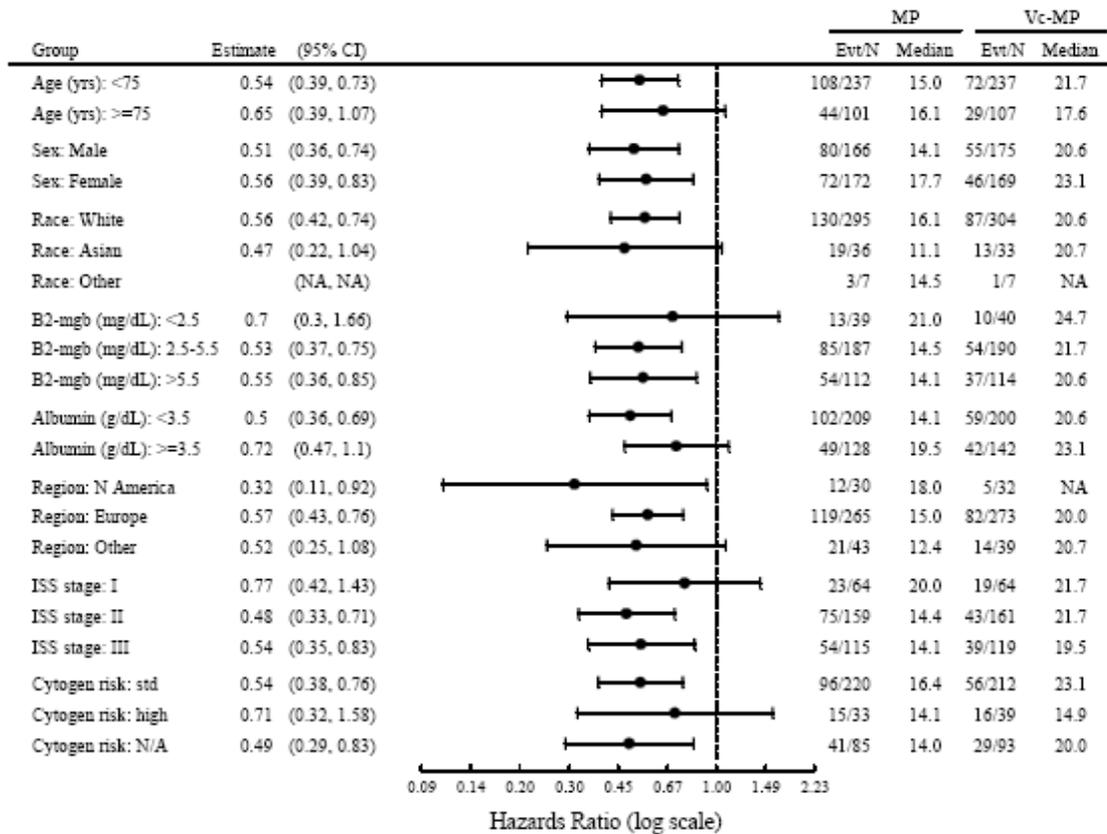
### 4.1 Gender, Race and Age

TTP results (as determined by sponsor’s computer algorithm) relative to demographics (age, sex, race) are displayed in Figure 4. The hazard ratios of Vc-MP versus MP are comparable to the one estimated based on the whole ITT population, therefore these results suggest a benefit of adding VELCADE to melphalan and prednisone as a front-line therapy for treating multiple myeloma across demographic subgroups.

### 4.2 Other Special/Subgroup Populations

Also displayed in Figure 4 are TTP results relative to baseline stratification factors (beta2-microglobulin, albumin, region), and disease characteristics (ISS staging and bone marrow cytogenetic abnormalities). These analyses are consistent with the results seen in overall study population, and support the addition of VELCADE to melphalan and prednisone as a front-line therapy for treating multiple myeloma across subgroups.

**Figure 4 - Time to Disease Progression Subgroup Analyses  
(Study MMY-3002, ITT Population)**



Note: Estimate = estimated HR; median is expressed in months

## **5. SUMMARY AND CONCLUSIONS**

### **5.1 Statistical Issues and Collective Evidence**

This reviewer did not find major statistical issues that would preclude approval of VELCADE for the proposed indication based on review of the pivotal study MMY-3002. However, this reviewer recommends reporting different results from the ones appear in the clinical study report as follows:

1. Report TTP results without PD-related deaths as events. Although there were only a few PD-related deaths in sponsor's TTP analysis, the definition of time to disease progression should not include deaths per guidance for industry "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" published in May 2007.
2. Report response rates using all randomized patients. The sponsor had limited their response rate evaluation in a subset of randomized patients. For keeping the principle of randomization, any efficacy evaluations in a randomized trial should be based upon all randomized patients.

### **5.2 Conclusions and Recommendations**

In this reviewer's opinion, the study results from the pivotal study MMY-3002 demonstrated the benefit of adding VELCADE to melphalan and prednisone as front-line therapy for multiple myeloma. A statistically significant improvement of 6 months in median time to disease progression was observed (hazard ratio [95% confidence interval]: 0.537 [0.413, 0.697], p-value = 0.000002), with improvement also observed in all secondary endpoints with the addition of VELCADE. Results of progression-free survival, which considered the influence of deaths on efficacy determination, showed an improvement of 4.3 months in median time with a hazard ratio of 0.609 (95% confidence interval: 0.486, 0.763) for the addition of VELCADE.

## **SIGNATURES/DISTRIBUTION LIST**

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Date: June 9, 2008

Concurring Reviewers: Rajeshwari Sridhara, Ph.D.  
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Aloka Chakravarty  
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<b>NDA # / Indication</b>	<b>Drug Name / formulation</b>	<b>Applicant</b>	<b>Submission Date</b>	<b>NDA Type</b>
21-602 (S015) / Treatment of patients with multiple myeloma (MM)	Velcade (bortezomib) / IV	Millennium Pharmaceuticals	December 20, 2007	supplemental

On **initial** overview of the NDA application for fileability: This sNDA submission is fileable. Submitted documents and data sets are organized in a manner to allow substantive review to begin.

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comments</b>
1	Is Index sufficient to locate necessary reports, tables, data, etc.?	X		
2	Are study reports including original protocols, subsequent amendments, etc. complete and available?	X		
3	Were safety and efficacy for gender, racial, and geriatric subgroups investigated (if applicable)?	X		
4	Are data sets in EDR accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets)?	X		
5	Were ISS and ISE submitted?	X		
6	Designs utilized appropriate for the indications requested	X		The Phase III trial used to support this application was evaluated under a SPA (see additional comments #1).
7	Endpoints and methods of analysis spelled out in the protocols	X		
8	Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	X		The phase III trial had 3 planned interim analyses – one to assess safety only, and two to assess efficacy along with safety data. The study was halted after completion of the third interim analysis (see additional comments #2).
9	Appropriate references included for novel statistical methodology (if present)	X		
10	Sufficient data listings and intermediate analysis tables to permit a statistical review	X		
11	Intent-to-treat analyses	X		
12	Effects of dropouts on primary analyses investigated	X		Reasons for censoring, including lost to follow-up, were tabulated by treatment group for TTP analyses

**Additional Comments:**

1. The Phase III open-label trial of VELCADE-Melphalan-Prednisone (Vc-MP) versus Melphalan-Prednisone (MP) in subjects with previously untreated MM had a SPA under IND 56,515 in 2004.
2. The pre-specified O'Brien-Fleming boundary for superiority of Vc-MP over MP was crossed at the third interim analysis based on time to progression. However, the IDMC had indicated significant safety concerns in their meeting report (see IDMC meeting report dated September 13, 2007).

Comment to the sponsor following the filling meeting (agreed upon by the review team):

Please point out where in the application the information on the three conducted interim analyses can be found. If this information was not provided, please provide a separate report with details on interim analyses including purpose, timing, calculated statistical boundaries, and analysis results along with corresponding IDMC meeting reports

Chia-Wen Ko	January 16, 2008
Reviewing Statistician	Date
Raji Sridhara	January 16, 2008
Supervisor/Team Leader	Date

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-602/S-015**

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

## CLINICAL PHARMACOLOGY REVIEW

**NDA:** 21-602/SE1-015, N-000/4F, N-000  
**BRAND NAME:** VELCADE  
**GENERIC NAME:** Bortezomib (PS-341)  
**DOSAGE FORM:** 3.5 mg Bortezomib in Vials  
**INDICATIONS:** First-Line Multiple Myeloma  
**SUBMISSION DATES:** 20-Dec-2007, 30-March-2007, 04-Jun-2007, 12-Feb-2007  
**SUBMISSION TYPES:** NDA-Supplement and NDA-Amendments  
**APPLICANT:** Millennium Pharmaceuticals, Inc.  
**DDOP DIVISION:** Division of Drug Oncology Products  
**OCP DIVISION:** Division of Clinical Pharmacology 5  
**OCP REVIEWER:** Sophia Abraham, Ph.D.  
**OCP TEAM LEADER:** Brian Booth, Ph.D.  
**PHARMACOGENOMIC REVIEWER:** Silvana Borges, M.D.

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## 1. EXECUTIVE SUMMARY

The Applicant seeks approval of a supplemental New Drug Application (sNDA) for the use of VELCADE (bortezomib) in combination with melphalan plus prednisone for the treatment of patients with previously untreated multiple myeloma.

VELCADE was approved on 12-May-2003 as a single agent for the treatment of patients with relapsed or refractory multiple myeloma. The approved dose is 1.3 mg/m<sup>2</sup> administered as a

bolus intravenous injection twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period.

In support of this sNDA, the Applicant submitted a pivotal Phase 3 study (Study MMY-3002) of VELCADE at the approved dosage in combination with melphalan plus prednisone (Vc-MP) compared to melphalan plus prednisone alone (MP) in 682 patients with previously untreated multiple myeloma. The primary clinical endpoint was Time to Progression (TTP). The results of this study demonstrated that the triple combination therapy of Vc-MP was superior to the double combination therapy of MP. The median TTP was 21 months in the Vc-MP treatment group compared with 15 months in the MP treatment group. In overall, the safety profile of the Vc-MP treatment group was comparable to that reported for VELCADE single-agent.

The effect of co-administration of melphalan and prednisone on the pharmacokinetics (PK) of VELCADE was evaluated in 20 patients as a part of the pivotal Phase 3 Study MMY-3002 (Study MMY-3002-PK). The co-administration of melphalan and prednisone increased the exposure (geometric mean  $AUC_{0-\infty}$ ) of VELCADE by 15% which may be associated with higher toxicity than with VELCADE alone administration. The effect of VELCADE on the PK of melphalan and prednisone has not been examined in this study. A pharmacogenomic analysis was performed in this study to explore the impact of genetic variations of metabolic CYP isozymes, CYP2C19, 2D6, 3A4, and 3A5, on the PK of VELCADE alone versus VELCADE in the presence of MP. No definitive conclusion could be derived from this analysis.

A final clinical study report was submitted for Study 059 (Submissions of 30-March-2007 and 04-Jun-2007) to address the post-marketing Commitment # 11 of the approvable letter of 12-May-2003. Study 059 evaluated the effect of co-administration of ketoconazole (a potent CYP3A4 inhibitor) on the PK of VELCADE in patients with advanced solid tumors. The co-administration of ketoconazole increased the exposure of VELCADE by 35% in 12 evaluable patients.

A final clinical study report was also submitted for Study CAN-1001 to assess the effect of co-administration of omeprazole (a potent CYP2C19 inhibitor) on the pharmacokinetics of VELCADE in patients with advanced solid tumors, non-Hodgkin's lymphoma, or multiple myeloma. (Submission of 12-Feb-2007). No difference was observed in the exposure of VELCADE when it was co-administered with omeprazole in 17 evaluable patients.

**The current package insert for VELCADE was revised to include the results from the above mentioned studies.**

## **1.1 RECOMMENDATIONS**

- The supplemental NDA 21-602/S-015 submitted for the use of VELCADE in combination with melphalan plus prednisone for the treatment of patients with previously untreated multiple myeloma is acceptable from the clinical pharmacology perspective.

- The Applicant has fulfilled the post-marketing Commitment #11 according to the approvable letter of 12-May-2003 for VELCADE (NDA amendment submitted on 30-Mar-2007 and 04-Jun-2007, N-000/4F).
- The final study report submitted for Study CAN-1001 on 12-Feb-2007 is acceptable from the clinical pharmacology perspective.
- The Applicant should incorporate the Clinical Pharmacology Labeling Recommendations as outlined under Section 3 of this review (pp. 23).

**In addition, we have the following Pharmacogenomic Recommendations:**

- Provide more information about conditions for blood collection, time elapsed between blood collection and DNA extraction and DNA extraction methods
- What is the rationale for not testing for the CYP2D6\*10 and \*41 alleles?
- Provide a listing of the nucleotide(s) identified at each defining polymorphic position for all CYP2C19, CYP2D6, CYP3A4, and CYP3A5 alleles tested
- Provide a summary of the genotyping procedures (e.g. type of assay, method validation, quality control, etc.)
- Given that only 12 patients had PK and genotype data, how is the genotype data from study 26866138-MMY-3002 (n=367) going to be utilized? Additional PK data to be collected? Evaluation of genotype on clinical outcome?

Please forward the above Recommendations and the Clinical Pharmacology Labeling Recommendations (Section 3 of this review, pp. 24) to the Applicant.

**1.2 PHASE 4 COMMITMENTS**

[None]

**1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS**

VELCADE was shown to be primarily metabolized via CYP3A4, 2C19, and 1A2 in human liver microsomes (Original NDA). According to the Medical Reviewer of this NDA, there is no obvious relationship between VELCADE dose and toxicities when the dose was increased from 1.0 to 1.3 mg/m<sup>2</sup>.

**Effect of Melphalan and Prednisone:**

The effect of co-administration of melphalan and prednisone on the exposure of VELCADE was evaluated in 20 evaluable patients as a part of the pivotal Phase 3 Study MMY-3002 (Study MMY-3002-PK). Patients received VELCADE alone (1.3 mg/m<sup>2</sup>) intravenously (i.v.) **twice weekly** for four 6-week cycles, followed by VELCADE (1.3 mg/m<sup>2</sup>) i.v. **once weekly** for five 6-week cycles, in combination with melphalan (9 mg/m<sup>2</sup>) and prednisone (60 mg/m<sup>2</sup>), both given orally once daily on Days 1 to 4 of each 6-week cycle. All patients received 2 cycles of study treatments. The pharmacokinetics (PK) of VELCADE were determined on Day 25 of Cycle 1 during VELCADE alone therapy and on Day 4 of Cycle 2 during VELCADE plus melphalan and prednisone therapy. The results of this study showed that the exposure (geometric mean AUC<sub>0-∞</sub>) of VELCADE was increased by 15% (p=0.221) when VELCADE was co-administered with melphalan and prednisone in 20 patients. It is not known whether

melphalan or prednisone inhibits CYP3A4, the principal enzyme involved in VELCADE metabolism. As the overall safety profile of VELCADE when given with melphalan and prednisone was comparable to that reported for VELCADE single-agent, the 15% increase in VELCADE exposure in the presence of melphalan and prednisone may not be clinically significant.

The effect of VELCADE on the PK of melphalan and prednisone has not been examined in this study. VELCADE is a poor inhibitor of CYP 1A2, 2C9, 2D6, and 3A4 with  $IC_{50}$  values of  $> 11.5 \mu\text{g/ml}$  (Mean steady state  $C_{\text{max}} = 0.088 \mu\text{g/ml}$  at the  $1.3 \text{ mg/m}^2$  approved dose, the estimated  $[I]/ki$  ratio=0.015) (Original NDA). Melphalan is eliminated from plasma primarily by chemical hydrolysis and there is no evidence of cytochrome P450-mediated metabolism. Prednisone is metabolized by the liver to the active metabolite prednisolone through the  $11\beta$ -hydroxydehydrogenase enzyme, which is not part of the CYP system. Once formed, however, prednisolone is metabolized by the CYP3A4-mediated  $6\beta$ -hydroxylase enzyme. Thus, it is unlikely that VELCADE inhibits the metabolic clearance of either melphalan or prednisone.

#### **Effect of Ketoconazole:**

One of the post-marketing Commitments (Commitment #11) of the approvable letter of 12-May-2003 was requesting the sponsor to conduct a study to examine the potential for drug-drug interactions between VELCADE and potent CYP3A4 inhibitors. To address this Commitment, the Applicant submitted a final study report for Study 059 which evaluated the effect of co-administration of ketoconazole (a potent CYP3A4 inhibitor) on the pharmacokinetic (PK) profile of VELCADE in patients with advanced solid tumors. In this study, 12 evaluable patients were randomized to receive either VELCADE alone or VELCADE with ketoconazole in Cycle 1 and were crossed over to receive the other treatment in Cycle 2. VELCADE was administered at a dose of  $1.0 \text{ mg/m}^2$  as an intravenous bolus on Days 1, 4, 8, and 11 followed by a 10-day rest period (21-day cycle) of Cycles 1 and 2. Ketoconazole was administered orally at a dose of 400 mg on Days 6, 7, 8, and 9 of Cycles 1 and 2. The results of the study indicated that the exposure of VELCADE was increased by 35% ( $p=0.071$ ) when it was co-administered with ketoconazole to 12 patients. Patients taking ketoconazole concomitantly with VELCADE should be monitored for toxicities.

#### **Effect of Omeprazole:**

The effect of omeprazole (a potent CYP2C19 inhibitor) on the pharmacokinetics of VELCADE was assessed in Study CAN-1001. In this study, 17 evaluable patients were randomized to receive either VELCADE alone or VELCADE with omeprazole in Cycle 1 and were crossed over to receive the other treatment in Cycle 2. VELCADE was administered at a dose of  $1.3 \text{ mg/m}^2$  as an intravenous bolus on Days 1, 4, 8, and 11 followed by a 10-day rest period (21-day cycle) of cycle 1 and 2. Omeprazole was administered orally at a dose of 40 mg on the morning of Days 6, 7, 8, 9, and 10 of Cycles 1 and 2 (another dose was also given on the evening of Day 8). The results of the study indicated co-administration of omeprazole had no effect on the exposure to VELCADE in 17 cancer patients ( $p > 0.05$ ).

### **Pharmacogenomic Analysis:**

Additionally, in Study MMY-3002, the Applicant performed a pharmacogenomic analysis to explore the impact of genetic variations of metabolic CYP isozymes, CYP2C19, 2D6, 3A4, and 3A5, on the PK of VELCADE alone versus VELCADE in the presence of MP. DNA samples from 367 patients who participated in Study MMY-3002 were available for analysis. The PK data for this analysis was only available from 12 out of the 367 patients. Therefore, no definitive conclusion could be derived on the impact of CYP2C19, 2D6, 3A4, and 3A5 genetic polymorphisms on the PK of VELCADE alone or in the presence of MP from this study (see attached review, Appendix 2, pp. 52).

## **2 QUESTION BASED REVIEW**

**The following questions were addressed based on the information submitted in support of the Supplement and Amendments to NDA 21-602:**

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

In support of the effectiveness and safety of VELCADE in the first-line treatment of patients with multiple myeloma, the Applicant submitted a pivotal Phase 3 study (Study MMY-3002). The primary objective of this study was to determine whether the addition of VELCADE to a standard therapy of melphalan and prednisone (Vc-MP) improved the TTP (time to progression) compared to the standard therapy of melphalan and prednisone (MP) alone in patients with previously untreated multiple myeloma.

Study MMY-3002 was a Phase 3, randomized, open-label, multi-center study in 682 patients with previously untreated multiple myeloma and who were not candidates for HDT/SCT (high-dose chemotherapy with stem cell transplant). Patients were randomized to receive either of the following treatment groups:

- **Vc-MP Group (N=344):** Patients received VELCADE alone 1.3 mg/m<sup>2</sup> intravenously (i.v.) twice weekly [Weeks 1, 2, 4, and 5] for four 6-week cycles. Patients then received VELCADE 1.3 mg/m<sup>2</sup> i.v. once weekly [Weeks 1, 2, 4, and 5] for five 6-week cycles in combination with melphalan 9 mg/m<sup>2</sup> and prednisone 60 mg/m<sup>2</sup> both given orally once daily on Days 1 to 4 of each 6-week cycle.
- **MP Group (N=338):** Patients received melphalan 9 mg/m<sup>2</sup> and prednisone 60 mg/m<sup>2</sup> both given orally once daily on Days 1 to 4 of each 6-week cycle.

For both groups, treatment continued for a maximum of 9 cycles (54 weeks) and was discontinued if disease progression or unacceptable treatment-related toxicity occurred, or if a subject withdrew consent. Follow-up for survival was continued until each patient died or for a maximum of 4.5 years after the last patient's randomization to treatment. The primary efficacy endpoint was TTP, defined as the interval between the date of randomization and the date of the first observation of either disease progression (DP), including death due to DP, or relapse from IF (immunofixation), or negative CR (complete response). The efficacy results of this study are shown in Table 1.

**TABLE 1: FDA Summary of Time to Disease Progression (TTP)**

Descriptive	Melphalan-Prednisone (MP)	VELCADE-melphalan-prednisone (Vc-MP)
Number assessed	338	344
Number of censored (%)	186 (55%)	243 (71%)
Number of events (%)	152 (45%)	101 (29%)
Median TTP (95% CI) (Months)	15.2 (14.3, 18.2)	21.03 (17.8, 25.03)
P-value*	0.000002	
Hazard ratio (95% CI)**	0.54 (0.42, 0.70)	
* Log-rank test adjusted for stratification factors: beta-2-microglobulin, albumin, and region.		
** Hazard ratio estimate is based on a Cox regression model.		

The median TTP was significantly higher in the Vc-MP treatment group (21 months) than in the MP treatment group (15 months). The difference between the two treatment groups was highly significant demonstrating a 46% decrease in the risk of disease progression for patients on the Vc-MP treatment group.

### Safety:

**TABLE 2: Incidence of Most Common (at Least 10% in Any Group) Treatment-Emergent Adverse Events (TEAE)**

System Organ Class	Previously Untreated		Previously Treated
	Vc-MP	MP	VELCADE
	(N=340)	(N=337)	(N=1033)
<b>Blood and lymphatic system disorders</b>			
Anaemia	147 (43)	187 (55)	344 (33)
Leukopenia	113 (33)	100 (30)	75 (7)
Lymphopenia	83 (24)	58 (17)	51 (5)
Neutropenia	165 (49)	155 (46)	201 (19)
Thrombocytopenia	178 (52)	159 (47)	408 (39)
<b>Gastrointestinal disorders</b>			
Abdominal pain	49 (14)	22 (7)	152 (15)
Abdominal pain upper	40 (12)	29 (9)	89 (9)
Constipation	125 (37)	54 (16)	432 (42)
Diarrhoea	157 (46)	58 (17)	570 (55)
Dyspepsia	39 (11)	23 (7)	83 (8)
Nausea	164 (48)	94 (28)	593 (57)
Vomiting	112 (33)	55 (16)	359 (35)
<b>Nervous system disorders</b>			
Dizziness	56 (16)	37 (11)	164 (16)
Headache	49 (14)	35 (10)	241 (23)
Neuralgia	121 (36)	5 (1)	77 (7)
Neuropathy peripheral	11 (3)	1 (<1)	281 (27)
Paraesthesia	45 (13)	15 (4)	154 (15)
Peripheral sensory neuropathy	151 (44)	16 (5)	87 (8)

In overall, the safety profile of VELCADE in combination with melphalan and prednisone was comparable to that of VELCADE single-agent. The most frequently reported adverse events for the Vc-MP treatment group were thrombocytopenia (52%), neutropenia (49%), nausea (48%), diarrhea (46%), peripheral sensory neuropathy (44%), constipation (37%), neuralgia (36%), and leukopenia (33%). In comparison, in VELCADE single-agent treatment group, the incidence of gastrointestinal toxicities (nausea, diarrhea, and constipation) was comparable to that reported for the Vc-MP treatment group. However, the incidence of thrombocytopenia, neutropenia, peripheral sensory neuropathy, neuralgia, and leukopenia in Vc-MP treatment group was higher than that reported for VELCADE single-agent treatment group.

The incidence of thrombocytopenia, neutropenia, and leukopenia in the MP treatment group was comparable to that reported for the Vc-MP treatment group. The incidence of gastrointestinal toxicities and neuropathy in the MP treatment group (diarrhea, constipation, and peripheral sensory neuropathy) was lower than that reported for the Vc-MP treatment group.

- **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?**

The primary efficacy endpoint of this study is TTP. The choice of this endpoint was based on the following rationale:

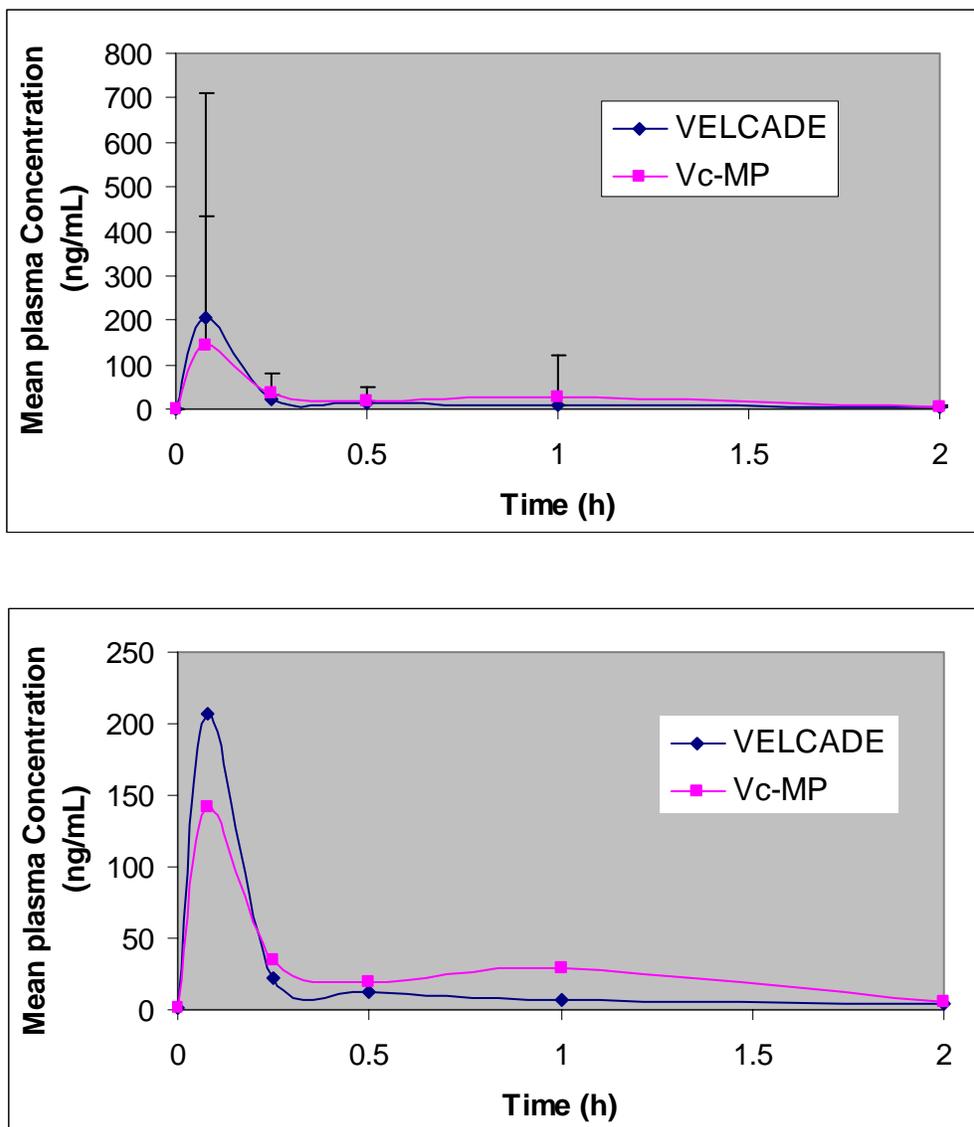
- TTP is a meaningful endpoint in a patient population with multiple myeloma for whom currently available treatment options are not curative and can only delay disease progression.
  - TTP was preferred as the primary endpoint instead of progression-free survival (PFS) as PFS does not constitute a composite endpoint. In an elderly patient population with many co-morbidities, there is potential risk that death events may be caused by unrelated co-morbidities and may confound the PFS analysis.
  - TTP is an acceptable endpoint in multiple myeloma where it is expected that subsequent treatment may have an effect on overall survival (OS), and may importantly interfere with the detection of a relevant treatment effect on OS.
- 
- **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?**

The label specifies that VELCADE is to be co-administered with melphalan plus prednisone for the treatment of patients with previously untreated multiple myeloma.

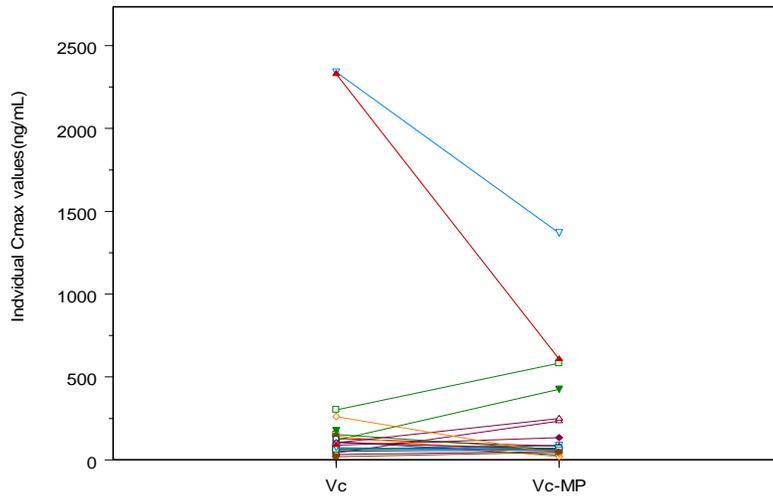
The pharmacokinetics (PK) of VELCADE were determined in 21 patients as a part of the pivotal Phase 3 Study MMY-3002 (Study MMy-3002). The primary objective of this sub-study was to determine whether the co-administration of melphalan plus prednisone (MP) with VELCADE (Vc-MP) had any effect on the PK of VELCADE. Patients received VELCADE alone (1.3 mg/m<sup>2</sup>) intravenously (i.v.) twice weekly for four 6-week cycles, followed by VELCADE (1.3 mg/m<sup>2</sup>) i.v. once weekly for five 6-week cycles, in combination with melphalan (9 mg/m<sup>2</sup>) and prednisone (60 mg/m<sup>2</sup>), both given orally once daily on Days 1 to 4 of

each 6-week cycle. All patients received 2 cycles of study treatments. Blood samples for the determination of VELCADE PK were collected pre-dose and up to 24 hours after dosing on Day 25 of Cycle 1 (VELCADE alone therapy) and on Day 4 of Cycle 2 (combination therapy). Pharmacogenomic (PGx) analyses were performed to determine the variations in drug metabolizing genes and their relationship to the pharmacokinetic parameters (see the attached PGx review, Appendix 2, pp. 54). The PK results are shown in Figures 1-4 and Tables 3 and 4.

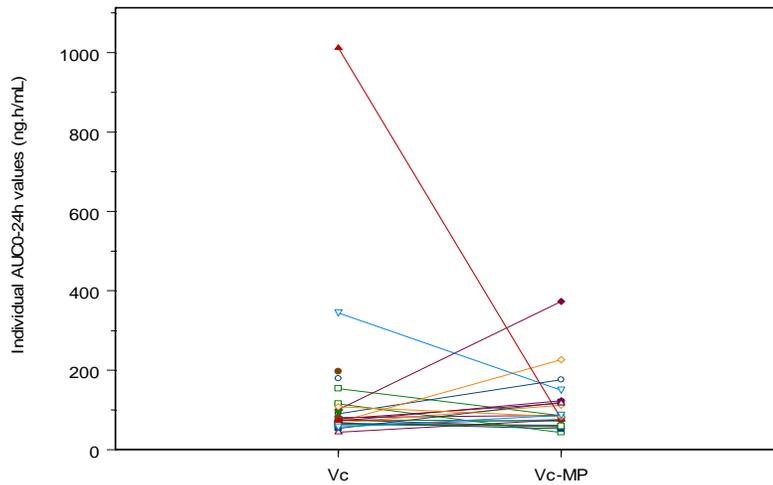
**FIGURE 1. Mean (SD) Plasma Concentration-Time Profile of VELCADE within 2 hours after Administration of VELCADE ( $1.3 \text{ mg/m}^2$ ) with and without Melphalan and Prednisone in 21 Evaluable Patients**



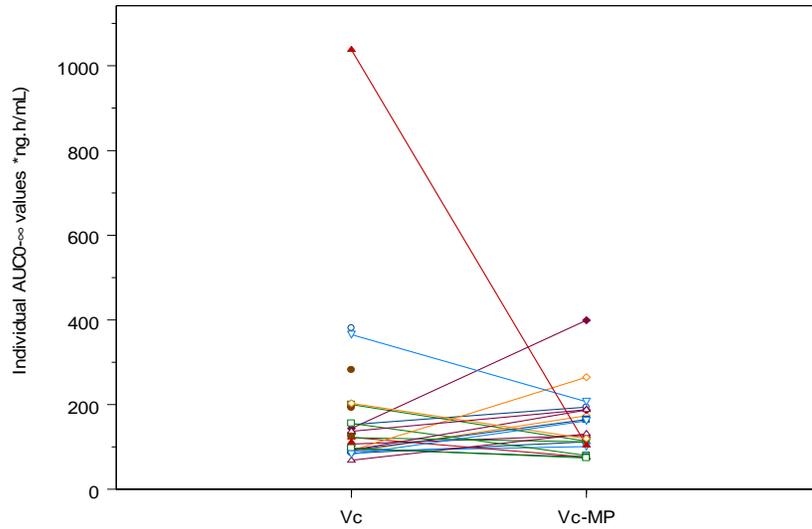
**FIGURE 2: Comparison of Individual  $C_{max}$  of VELCADE With or Without Co-Administration with Melphalan+Prednisone in 21 Evaluable Patients**



**FIGURE 3. Comparison of Individual Exposure ( $AUC_{0-24h}$ ) of VELCADE With or Without Co-Administration with Melphalan+Prednisone in 21 Evaluable Patients**



**FIGURE 4. Comparison of Individual Exposure ( $AUC_{0-\infty}$ ) of VELCADE With or Without Co-Administration with Melphalan+Prednisone in 21 Evaluable Patients**



As seen in Figure 3, apart from the outliers, there was no substantial difference in daily exposure ( $AUC_{0-24h}$ ) to VELCADE after MP administration when compared to VELCADE alone. A similar observation was made for  $AUC_{0-\infty}$ .

The variability was high for both AUCs (71% for  $AUC_{0-24h}$  and 52% for  $AUC_{0-\infty}$  for VELCADE alone and for VELCADE + MP treatments, respectively). As noted in the graphs, one patient appeared to drive the high variability in  $C_{max}$  and AUC values. This patient had extremely high  $C_{max}$  (2340 ng/mL) and was excluded from data analysis (N=20 evaluable patients).

**TABLE 3. Arithmetic Mean±SD (CV%) VELCADE PK Parameters Following i.v. Administration of VELCADE (1.3 mg/m<sup>2</sup>) Alone and in Combination with Melphalan and Prednisone (Vc-MP)**

PK Parameter	Treatment	
	Vc Alone (N=20)	Vc-MP (N=20)
C <sub>max</sub> (ng/ml)	207±505 (244%)	165±300 (182%)
*T <sub>max</sub> (h)	0.08 (0.08-0.5)	0.08 (0.08-1.0)
AUC <sub>0-24h</sub> (ng h/ml)	88.4±62.7 (71%)	108±76.2 (71%)
AUC <sub>0-∞</sub> (ng h/ml)	126±65.1 (52%)	148±77.1 (52%)
t <sub>1/2</sub> (h)	18.9±4.1 (22%)	18.3±4.5 (25%)
CL (L/h/ m <sup>2</sup> )	11.7±3.6 (31%)	10.5±4.5 (43%)
V <sub>ss</sub> (L/m <sup>2</sup> )	312±90 (29%)	271±117 (43%)

\*Median (range)

The co-administration of melphalan and prednisone increased the systemic exposure (arithmetic mean AUC<sub>0-∞</sub>) of VELCADE by 17%. Mean plasma clearance, elimination half-life, and steady state of distribution values were comparable between the treatment arms.

**TABLE 4. Geometric Mean Ratios and 90% Confidence Intervals (CI) of the PK Parameters of VELCADE Alone or in Combination with Melphalan and Prednisone (Vc-MP) for the Patients who completed both Arms of the study**

PK Parameter	Geometric Mean		Ratio	90% CI	P-value
	Vc Alone (N=20)	Vc-MP (N=20)			
C <sub>max</sub> (ng/mL)	95.5	86.7	0.91	62.3-133%	0.665
AUC <sub>0-24h</sub> (ng.h/ml)	78.8	92.9	1.18	95.4-146%	0.215
AUC <sub>0-∞</sub> (ng*h/mL)	116	134	1.15	94.9-140%	0.221

The least square geometric ratio of AUC<sub>0-∞</sub> for VELCADE with melphalan and prednisone relative to VELCADE alone was 1.15, representing a 15% increase in VELCADE systemic exposure in the presence of melphalan and prednisone.

In conclusion, the systemic exposure (geometric mean AUC<sub>0-∞</sub>) of VELCADE was increased by 15% when VELCADE was co-administered with melphalan and prednisone. The clinical relevance of this increase in exposure is not known. The effect of VELCADE on the PK of melphalan and prednisone has not been examined in this study.

- **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?**

#### **Effect of Ketoconazole:**

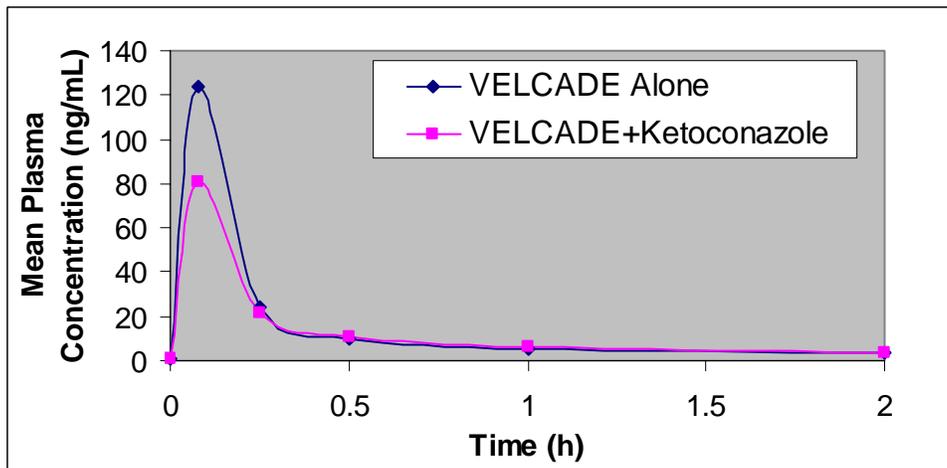
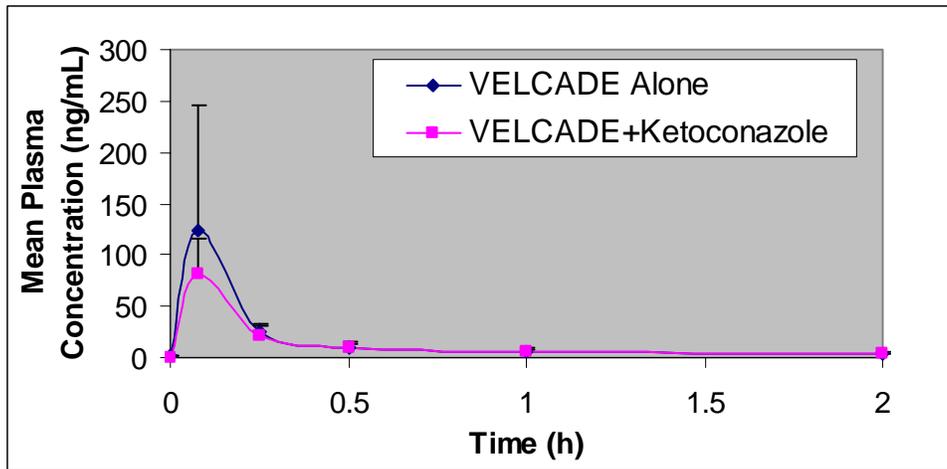
One of the post-marketing Commitments of the approvable letter of 12-May-2003 for VELCADE was as follows:

***“Commitment #11: “Conduct a PK and PK/PD (pharmacokinetics/pharmacodynamics) study to examine the potential drug-drug interactions between bortezomib and a drug that is a cytochrome P450 3A4 inhibitor (e.g., antifungal agents or antibiotics that are potent inhibitors of CYP3A4). You should also collect the adverse reactions noted in the study and evaluate any relationship between plasma levels and adverse reactions.”***

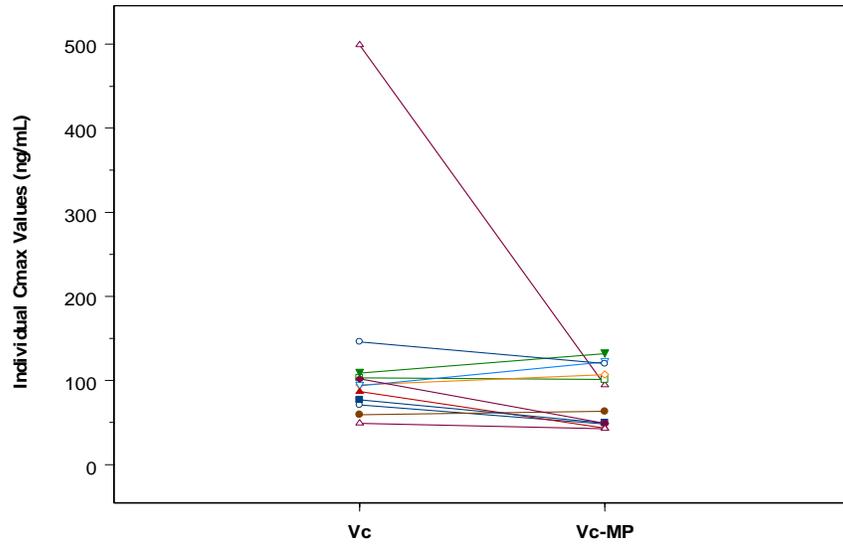
To address the above Commitment, the Applicant submitted Study 059. The objective of this study was to evaluate the effect of co-administration of ketoconazole (a potent CYP3A4 inhibitor) on the pharmacokinetic (PK) profile of VELCADE in patients with advanced solid tumors. This was an open-label, multi-center, open-label, randomized, multiple-dose, two-way crossover study in 12 patients. Patients were randomized to receive either VELCADE alone or VELCADE with ketoconazole in Cycle 1 and were crossed over to receive the other treatment in Cycle 2. VELCADE was administered at a dose of 1.0 mg/m<sup>2</sup> as an intravenous bolus on Days 1, 4, 8, and 11 followed by a 10-day rest period (21-day cycle) of Cycle 1 and 2. Ketoconazole was administered orally at a dose of 400 mg on Days 6, 7, 8, and 9 of Cycles 1 and 2. The dose of VELCADE dose chosen for this study was 1.0 mg/m<sup>2</sup> instead of the approved dose of 1.3 mg/m<sup>2</sup> because of the concern that co-administration of ketoconazole could potentially increase exposure to bortezomib with a consequent increase in bortezomib-related toxicity. In the sNDA 21-602/S-010 submission of 28-Dec-2005, AUC increased in less than proportional increase in dose from 1.0 to 1.3 mg/m<sup>2</sup>.

Blood samples for the determination of VELCADE pharmacokinetics were collected pre-dose and up to 72 hours after dosing on Day 8 of each of Cycles 1 and 2. Additional blood samples were collected to assess the 20S proteasome inhibition activity of VELCADE before and at select time points after the Day 8 VELCADE administrations (Cycles 1 and 2). The potential for drug-drug interactions between VELCADE and ketoconazole was assessed based the point estimates and 90% confidence interval for the ratio of natural log-transformed AUC means for VELCADE+ ketoconazole/VELCADE alone). The results are shown in Figures 5-8 and Tables 5-7.

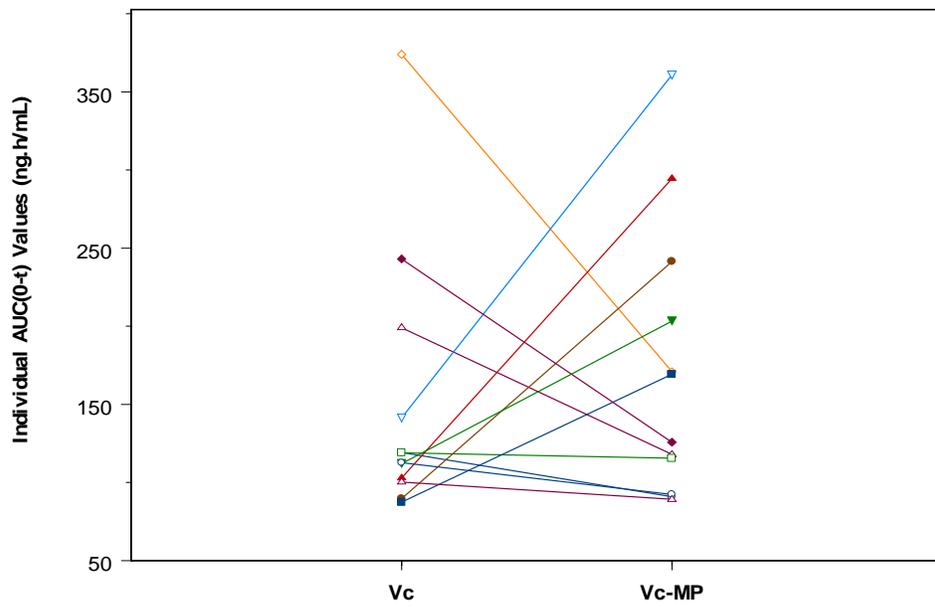
**FIGURE 5. Mean (SD) Plasma Concentration-Time Profiles of VELCADE within 2 hours after Administration of VELCADE (1.0 mg/m<sup>2</sup>) with and without Ketoconazole (400 mg) on Day 8 of Cycles 1 and 2 in 12 Patients (with or without error bars)**



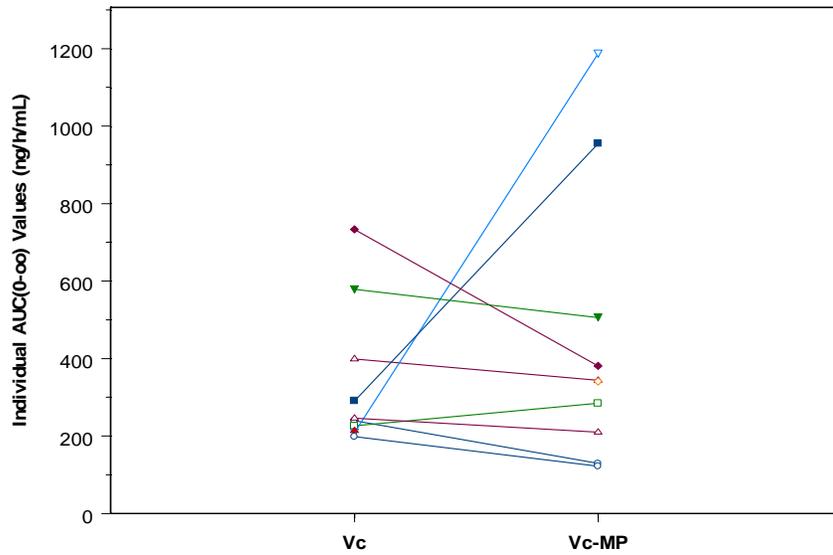
**FIGURE 6: Comparison of Individual  $C_{max}$  of VELCADE With or Without Co-Administration with Ketoconazole in 12 Patients**



**FIGURE 7: Comparison of Individual  $AUC_{0-t}$  of VELCADE With or Without Co-Administration with Ketoconazole in 12 Patients**



**FIGURE 8: Comparison of Individual  $AUC_{0-\infty}$  of VELCADE With or Without Co-Administration with Ketoconazole in 12 Patients**



In Figure 6, in the above figure, except for one patient, who had a relatively high  $C_{max}$  value after VELCADE alone treatment, all other  $C_{max}$  values were comparable between the two treatments (VELCADE alone or VELCADE+ketoconazole).

For Figure 7, five patients had higher  $AUC_{0-t}$  values for VELCADE when it was co-administered with ketoconazole than VELVADE alone treatment while values for other three patients were vice versa. The rest of the patients ( $n=4$ ) had comparable AUC values between the two treatments.

For Figure 9, only two patients had higher  $AUC_{0-\infty}$  values for VELCADE when it was co-administered with ketoconazole than VELVADE alone treatment while one patient was vice versa. Six patients had comparable VELCADE  $AUC_{0-\infty}$  values whether it was administered alone or with ketoconazole. Three patients had no estimated  $AUC_{0-\infty}$  values.

**TABLE 5. Arithmetic Mean±SD Pharmacokinetic Parameters of VELCADE (1.0 mg/m<sup>2</sup> i.v. Twice Weekly) on Day 8 of Cycles 1 and 2 with and without Oral Ketoconazole (400 mg QD for 4 Days)**

PK Parameter	Treatment	
	VELCADE Alone (N=12)	VELCADE+Ketoconazole (N=12)
C <sub>max</sub> (ng/ml)	124±121 (97%)	81±35 (43%)
*T <sub>max</sub> (h)	0.083 (0.07-0.08)	0.083 (0.08-0.083)
AUC <sub>0-t</sub> (ng h/ml)	150±84.3 (56%)	173±88 (51%)
AUC <sub>0-∞</sub> (ng h/ml)	334±183 (55%)	446±353 (79%)
t <sub>1/2</sub> (h)	120±79 (65%)	106±835 (78%)
CL (L/h/m <sup>2</sup> )	7.9±2.7 (34%)	7.1±3.0 (43%)
V <sub>ss</sub> (L/m <sup>2</sup> )	1135±2002 (88%)	1039±850 (82%)

\*Median (range)

**TABLE 6. Statistical Analyses Summary of the Effect of Ketoconazole on VELCADE Exposure**

PK Parameter	N	Geometric Mean		Ratio	90% CI	P-value
		VELCADE Alone	VELCADE+ Ketoconazole			
AUC <sub>0-t</sub> (ng.h/ml)	12	127	172	1.35	103-177%	0.071
AUC <sub>0-∞t</sub> (ng h/ml)	9	324	420	1.30	85-197%	0.178

(CI=confidence interval determined using the Two one-sided t-Test)

Because the estimation of AUC<sub>0-∞</sub> was unreliable, the percent extrapolated area under curve ratio (AUC<sub>t-∞</sub>/AUC<sub>0-∞</sub>) was more than 50%. Thus, AUC<sub>0-t</sub> was selected as the primary exposure parameter. However, this may not be accurate as these values greatly varied among individual patients (see Figure 7).

As seen in Table 6, the ratio of the least-square mean AUC<sub>0-t</sub> for VELCADE plus ketoconazole relative to VELCADE alone was 1.35, representing a 35% increase in VELCADE exposure in the presence of ketoconazole. The 90% confidence interval for the geometric mean AUC<sub>0-t</sub> ratio was 103-177% (p=0.071), which is outside the 80-125% criteria specified in the FDA guidance for evaluating drug-drug interaction.

**Table 7. Mean±SD Percent inhibition of 20S Proteasome Activity in Whole Blood on Day 8**

	Cycle 1	Cycle 2
<b>PD Parameter</b>	<b>VELCADE Alone (N=4)</b>	
*T <sub>max</sub> (h)	0.54 (0.08-1.0)	0.083 (.07-1.1)
Observed maximum inhibition (%)	62.3±5.3	55.3±12.0
AUE <sub>0-48h</sub> (% h)	1027±1156	865±547
	<b>VELCADE + Ketoconazole (N=8)</b>	
*T <sub>max</sub> (h)	0.25 (0.08-4.0)	0.083 (0.08-72)
Observed maximum inhibition (%)	60.6±12.9	56.8±5.1
AUE <sub>0-48h</sub> (% h)	1504±526	1073±716

\*Median (range)

The percent change in proteasome inhibition activity from baseline was determined only in 4 patients treated with VELCADE alone and in 8 patients treated with VELCADE plus ketoconazole during Cycles 1 and 2. As seen in Table 7, during both Cycles 1 and 2, the mean observed maximum inhibition of proteasome activity (from baseline) of VELCADE was comparable whether VELCADE was administered with or without ketoconazole. However, the mean area under the effect-time curve from time 0 to 48 hours (AUE<sub>0-48h</sub>) increased by 46% and 24% during Cycle 1 and Cycle 2, respectively, when VELCADE was given in combination with ketoconazole.

In conclusion, the results of this study demonstrated that the exposure of VELCADE was increased by 35% when VELCADE was co-administered with ketoconazole (a potent CYP3A4 inhibitor) to 12 patients with advanced solid tumors. The mean area under the effect-time curve from time 0 to 48 hours (AUE<sub>0-48h</sub>) of 20S proteasome inhibition activity of VELCADE was increased by 46% and 24% during Cycle 1 (N=4) and Cycle 2 (N=8), respectively, when VELCADE was given in combination with ketoconazole.

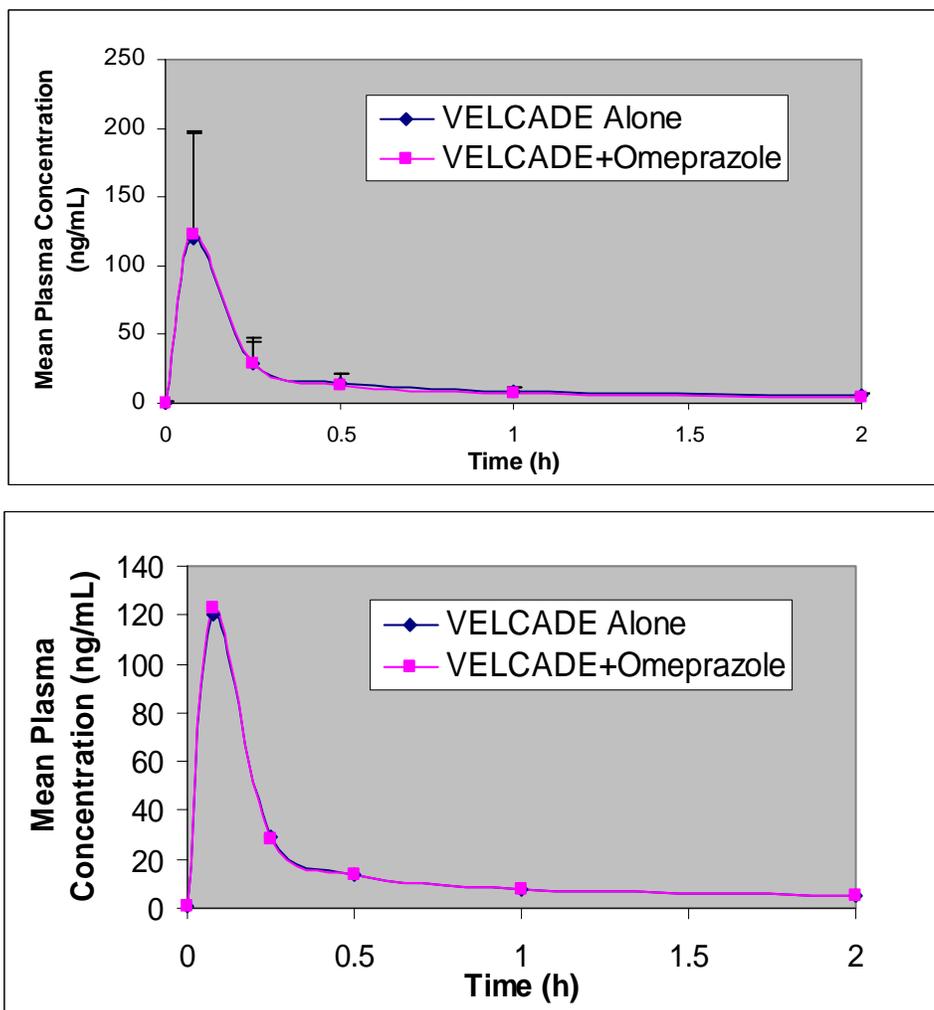
### **Effect of Omeprazole:**

The Applicant conducted a study to evaluate the effect of co-administration of omeprazole (a potent CYP2C19 inhibitor) on the pharmacokinetics of VELCADE in patients with advanced solid tumors, non-Hodgkin's lymphoma, or multiple myeloma.

This was an open-label, randomized, multi-center, 2-way crossover study in 17 evaluable patients. Patients were randomized to receive either VELCADE alone or VELCADE with omeprazole in Cycle 1 and were crossed over to receive the other treatment in Cycle 2. VELCADE was administered at a dose of 1.3 mg/m<sup>2</sup> as an i.v. bolus on Days 1, 4, 8, and 11 during Cycles 1 and 2. Omeprazole was administered orally at a dose of 40 mg in the morning of Days 6, 7, 8, 9, and 10 and in the evening of Day 8 during Cycle 1 and Cycle 2 (the approved clinical dosage of omeprazole is 20-40 mg PO once daily 1 hour before meals for up to 4-8 weeks). Blood samples for the determination of VELCADE pharmacokinetics were collected on Day 8 of Cycles 1 and 2 pre-dose and up to 72 hours after VELCADE dosing. Additional blood samples were collected to assess the 20S proteasome inhibition activity of VELCADE

before and at select time points after the Day 8 VELCADE administrations (Cycles 1 and 2). The potential for drug-drug interactions between VELCADE and omeprazole was assessed based the point estimates and 90% confidence interval for the ratio of natural log-transformed AUC means for VELCADE+omeprazole/VELCADE alone). The results are shown in Figure 9 and Tables 8-10.

**FIGURE 9. Mean (SD) Plasma Concentration-Time Profiles of VELCADE within 2 hours after Administration of VELCADE (1.3 mg/m<sup>2</sup>) with and without Omeprazole (40 mg) on Day 8 of Cycles 1 and 2 in 17 Patients (with or without error bars)**



**TABLE 8. Arithmetic Mean±SD Pharmacokinetic Parameters of VELCADE (1.3 mg/m<sup>2</sup> i.v. Twice Weekly) on Day 8 of Cycles 1 and 2 with and without Oral Omeprazole (40 mg QD for 5 Days, except on Day 8: BID)**

PK Parameter	Treatment	
	VELCADE Alone (N=17)	VELCADE+Omeprazole (N=17)
C <sub>max</sub> (ng/ml)	120±77.6 (65%)	123±74 (60%)
*T <sub>max</sub> (h)	0.08 (0.08-0.08)	0.08 (0.08-0.08)
AUC <sub>0-72</sub> (ng h/ml)	129±70.0 (54%)	135±63.3 (47%)
AUC <sub>0-∞</sub> (ng h/ml)	196±119 (61%)	211±109 (52%)
t <sub>1/2</sub> (h)	48.7±18.4 (38%)	49.8±19.9 (40%)
CL (L/h/m <sup>2</sup> )	12.8±7.5 (59%)	12.3±7.7 (62%)
V <sub>ss</sub> (L/m <sup>2</sup> )	645±277 (43%)	603±376 (62%)

\*Median (range)

**TABLE 9. Summary of the Statistical Analyses of the Effect of Omeprazole on VELCADE Exposure**

PK Parameter	N	Geometric Mean		Ratio	90% CI	p-value
		VELCADE Alone	VELCADE+Omeprazole			
C <sub>max</sub> (ng/mL)	17	99.7	104	104%	79-138%	0.372
AUC <sub>0-27h</sub> (ng.h/ml)	17	115	118	103%	90-117%	0.301
AUC <sub>0-∞</sub> (ng.h/mL)	16	171	175	102%	87-120%	0.412

(CI=confidence interval)

No significant difference was observed in the exposure of VELCADE when omeprazole was co-administered with VELCADE ( $p > 0.05$ ). The 90% confidence intervals of geometric mean AUC ratios were within the criteria of 80-125% for both AUC<sub>0-72h</sub> and AUC<sub>0-∞</sub> for VELCADE when it was administered in combination with omeprazole.

**TABLE 10. Mean±SD Percent inhibition of 20S Proteasome Activity in Whole Blood on Day 8**

Parameter	VELCADE (N=15)	VELCADE + Omeprazole (N=15)
*T <sub>max</sub> (h)	0.08 (0.0-11)	0.08 (0.08-72)
Observed maximum inhibition (%)	85.8±7.3	93.7±23.7
AUE <sub>0-48h</sub> (%.h)	2794±903	2678±851
AUE <sub>0-72h</sub> (%.h)	4052±1408	3910±1450

Median (range)

The mean observed maximum percent inhibition of 20S proteasome activity (relative to baseline) of VELCADE was comparable between the two treatments. Similarly, the means area

under the effect-time curve from time 0 to 48 hours and from time 0 to 72 hours ( $AUE_{0-48h}$  and  $AUC_{0-27h}$ ) of 20S proteasome inhibition activity for VELCADE were comparable when VELCADE was given alone or in combination with omeprazole.

In conclusion, the results of this study demonstrated that no difference was observed in the exposure of VELCADE when it was administered in combination with omeprazole (a potent CYP2C19 inhibitor) to 17 cancer patients.

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

## **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?
- 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?
- 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?

### **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?
- 2.2.5.2 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?

### **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]

## 2.6 Analytical Section

### 2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology 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?

A validated liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) method was used to analyze plasma samples for Bortezomib (PS341) from Studies MMY-3002-PK, 059, and CAN-1001. 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 following concentration ranges:**

<u>Study MMY-3002-PK:</u>	0.1-25 ng/ml
<u>Study 059:</u>	0.1-25 ng/ml
<u>Study CAN-1001:</u>	0.5-50 ng/mL

Samples containing PS-341 at a concentration greater than the upper limit of the calibration curve were analyzed after dilution with control matrix.

#### 2.6.4.2 What is the lower limit of quantification (LLOQ)?

**The LLOQ was:**

<u>Study MMY-3002-PK:</u>	0.1 ng/ml
<u>Study 059:</u>	0.1 ng/mL
<u>Study CAN-1001:</u>	0.5-50 ng/mL

### 2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

#### Study MMY-3002-PK:

The intra-assay and inter-assay precision ranged from 3.6-3.8% at all tested Quality Control (QC) Sample concentrations (0.3, 2.0, 10, and 20 ng/mL). The intra-assay and inter-assay accuracy ranged from -2.5% to 0.3% at all QC concentration at the tested QC Sample concentrations (0.3, 2.0, 10, and 20 ng/mL).

#### Study 059:

The intra-assay and inter-assay precision ranged from 2.2-13.1% at all tested Quality Control (QC) Sample concentrations (0.1, 0.3, 2.0, 10, and 20 ng/mL). The intra-assay and inter-assay accuracy ranged from -3.5% to 12% at all QC concentration at the tested QC Sample concentrations (0.1, 0.3, 2.0, 10 and 20 ng/mL).

#### Study CAN-1001:

The intra-assay and inter-assay precision ranged from 0.8-9.3% at all tested Quality Control (QC) Sample concentrations (1.5, 10, and 40 ng/mL). The intra-assay and inter-assay accuracy ranged from -13.8% to 18% at all QC concentration at the tested QC Sample concentrations (1.5, 10, and 40 ng/mL).

## 3. Clinical Pharmacology Labeling Recommendations

The following sentence was removed from under the Highlights

(b) (4)

## 7 DRUG INTERACTIONS

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

**7.2 Melphalan-Prednisone:** Co-administration of melphalan-prednisone increased the exposure of bortezomib. However, **This increase is unlikely to be clinically relevant.**

**7.3 Omeprazole:** Co-administration of omeprazole, a potent inhibitor of CYP2C19, had no effect on the exposure of bortezomib.

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

## 12.3 Pharmacokinetics

Following intravenous administration of 1 mg/m<sup>2</sup> and 1.3 mg/m<sup>2</sup> doses to 24 patients with multiple myeloma (n=12, per each dose level), the mean maximum plasma concentrations of bortezomib (C<sub>max</sub>) after the first dose (Day 1) were 57 and 112 ng/mL, respectively. In subsequent doses, when administered twice weekly, the mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1 mg/m<sup>2</sup> dose and 89 to 120 ng/mL for the 1.3 mg/m<sup>2</sup> dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours after the 1 mg/m<sup>2</sup> dose and 76 to 108 hours after the 1.3mg/m<sup>2</sup> dose. The mean total body clearances was 102 and 112 L/h following the first dose for doses of 1 mg/m<sup>2</sup> and 1.3 mg/m<sup>2</sup>, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1 and 1.3 mg/m<sup>2</sup>, respectively.

**Distribution:** The mean distribution volume of bortezomib ranged from approximately 498 to 1884 L/m<sup>2</sup> following single- or repeat-dose administration of 1 mg/m<sup>2</sup> or 1.3mg/m<sup>2</sup> to patients 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.

**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 mg/m<sup>2</sup> and 1.3 mg/m<sup>2</sup> showed that both dose-normalized AUC and C<sub>max</sub> tend to be less in younger patients. Patients < 65 years of age (n=26) had about 25% lower mean dose-normalized AUC and C<sub>max</sub> than those ≥ 65 years of age (n=13).

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

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

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

**Renal Impairment:** A pharmacokinetic study was conducted in patients with various degrees of renal impairment who were classified according to their creatinine clearance values (CrCl) into the following groups: Normal (CrCl ≥60 mL/min/1.73 m<sup>2</sup>, N=12), Mild (CrCl=40-59 mL/min/1.73 m<sup>2</sup>, N=10), Moderate (CrCl=20-39 mL/min/1.73 m<sup>2</sup>, N=9), and Severe (CrCl < 20 mL/min/1.73 m<sup>2</sup>, N=3). A group of dialysis patients who were dosed after dialysis was also included in the study (N=8). Patients were administered intravenous doses of 0.7 to 1.3 mg/m<sup>2</sup> of bortezomib twice weekly. Exposure of bortezomib (dose-normalized AUC and C<sub>max</sub>) was comparable among all the groups. [See **Specific Populations (8.6)**]

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

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

**Effect of Melphalan-Prednisone:** Co-administration of melphalan-prednisone on VELCADE showed a <sup>(b)</sup><sub>(4)</sub>% increase in mean bortezomib AUC, based on data from 21 patients. This increase is unlikely to be clinically relevant.

**Effect of Omeprazole:** Co-administration of omeprazole, a potent inhibitor of CYP2C19, had no significant effect on the pharmacokinetics of bortezomib, based on data from 17 patients.

**Cytochrome P450:** Bortezomib is a poor inhibitor of human liver microsome cytochrome P450 1A2, 2C9, 2D6, and 3A4, with IC<sub>50</sub> values of >30µM (>11.5µg/mL). Bortezomib may inhibit 2C19 activity (IC<sub>50</sub> = 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. [see **Drug Interactions (7.4)**]

## 4.2 Pharmacogenomic Review

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**NDA (Serial Number):** 21-602/SE1-015

**Sponsor:** Millennium Pharms

**Drug:** VELCADE (bortezomib)

**Formulation:** Vials for injection

**Proposed Indication:** Multiple Myeloma

**Review Due Date:** 3/14/2008

**Requested Genomic Review:** Sophia Abraham

**Material Submitted:** Pharmacogenomic evaluation of CYP enzymes on the metabolism of the drug (Phase 3 Study 26866138-MMY-3002)

**Genomic Reviewer:** Silvana Borges, M.D.

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### **Background:**

#### **Sponsor:**

VELCADE is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. It is cytotoxic to a variety of cancer cell types in vitro and causes a delay in tumor growth in vivo in nonclinical tumor models, including multiple myeloma. Specifically, VELCADE is efficacious in multiple myeloma via its inhibition of nuclear factor  $\kappa$ B (NF- $\kappa$ B) activation, its attenuation of interleukin-6 (IL-6)-mediated cell growth, a direct apoptotic effect, and possibly antiangiogenic and other effects.

VELCADE is eliminated through extensive oxidative metabolism by the CYP450 superfamily of enzymes. It is thought that the Phase 2 drug metabolism does not significantly contribute to VELCADE disposition. More than 30 metabolites have thus far been identified but the primary route of VELCADE metabolism (>90%) is mediated by deboronation. The latter reaction is catalyzed by CYP2D6 and CYP3A4 in model systems in vitro. Preliminary in vitro studies suggest that CYP2C19 can potentially make an additional contribution to VELCADE metabolism. Study MMY-3002 was a randomized, open-label, multicenter study to compare the efficacy and safety of VELCADE and melphalan (Vc-MP) therapy against melphalan (MP) therapy in subjects with previously untreated multiple myeloma who were not candidates for HDT/SCT.

The primary objective of the PK portion of the MMY-3002 study was to assess the impact of melphalan and prednisone on the clinical PK of VELCADE. Additionally, pharmacogenomic investigation of the variability of the PK of VELCADE alone versus VELCADE in the presence of MP in relationship to CYP2C19, CYP2D6, CYP3A4, and CYP3A5 gene variations was also planned.

#### **Comments from reviewer:**

The sponsor conducted a genetic analysis of individuals participating in the study 26866138-MMY-3002. Out of 682 randomized patients, 367 DNA samples were available for analysis. PK data was available only from 12 of those 367 patients. Therefore, the effect of CYP2C19, CYP2D6, CYP3A4, and CYP3A5 genetic variation on the PK of VELCADE and VELCADE-MP can be evaluated in a small sample of patients (n=12).

However, the sponsor genotyped all 367 patients. It is not clear whether the sponsor plans to utilize the genotype data in the remaining samples to evaluate for instance the impact of CYP2C19, CYP2D6, CYP3A4, and CYP3A5 genetic variation on the efficacy of the drug.

Regarding the quality of the genotypic data:

**Collection of DNA.** There is no sufficient information about the conditions of blood collection, storage of the blood samples before DNA extraction and DNA extraction procedures. DNA in a blood sample is susceptible to degradation unless properly stored. Although DNA is quite stable, the time elapsed between blood collection and DNA extraction also influences the DNA quality.

**CYP2C19, CYP2D6, CYP3A4, and CYP3A5 genotyping.** Being CYP2D6 a highly polymorphic enzyme, with more than 70 alleles and allelic variants described, it is always a challenge to select a small number of alleles that allows efficient testing and yet considers the CYP2D6 allelic frequencies in different ethnic groups. There is no full

agreement in the scientific community to what the list of recommended alleles is for each ethnic group and that list is also different according to the type and goals of the studies. In this case, the sponsor studied 5 alleles (\*3, \*4, \*5, \*6, gene duplication). Although this selection is appropriate to identify poor and ultrarapid metabolizers in Caucasians, it is not adequate to evaluate the most frequent slow metabolizing group (CYP2D6\*10/\*10) among Asians, who constitute 10% of the patient population of this study. In addition, CYP2D6\*41 is common among Caucasians and homozygotes for this variant (CYP2D6\*41/\*41) show a very low metabolic capacity, similar in many cases to poor metabolizers. In the case of CYP2C19, CYP3A4, and CYP3A5, the allele selection was adequate for the ethnic distribution of the studied patients. However, the sponsor has not provided information neither about the defining nucleotide polymorphisms for the identification of each allele (e.g. 681G>A for CYP2C19\*2; 1846G>A for CYP2D6\*4) nor about the genotyping procedures (e.g. type of assay, method validation, quality control, etc.).

**Genotyping Results:** It is not possible to evaluate the genotype assignment for each sample without the information about the defining nucleotide polymorphisms that the sponsor used to identify each allele.

**Phenotype Prediction:** The sponsor designed a table to predict the CYP2C19, CYP2D6, and CYP3A5 phenotype for each allelic combination. Although it is still controversial whether such prediction could be made, the prediction approach presented by the sponsor is reasonable and similar to the prediction table provided in the package insert of the only FDA approved CYP2D6/CYP2C19 test. In the case of CYP3A4/5 the impact of genetic polymorphisms on the enzyme activity is less clear. We agree with the sponsor's approach of classifying CYP3A5\*1 carriers as high CYP3A5 expressers and CYP3A5\*3 homozygotes as low CYP3A5 expressers, as well as of not assigning predicted phenotypes to carriers of CYP3A4 variants.

Regarding the impact of CYP2C19, CYP2D6, CYP3A4, and CYP3A5 genotype-PK association, the sponsor concluded that "No meaningful relationships were apparent between polymorphisms in the genes (CYP2C19, CYP2D6, CYP3A4, and CYP3A5) and both PK endpoints (AUC<sub>24h</sub> and C<sub>max</sub>) of subjects who received VELCADE alone or in the presence of MP. However, the impact of the genetic variation in this study could not be clearly ascertained by formal statistical testing due to the small sample size". We agree with the sponsor that no definite conclusion can be derived on the impact of CYP2C19, CYP2D6, CYP3A4, and CYP3A5 genetic polymorphisms on the PK of VELCADE alone or in the presence of MP from this study. For that purpose, these results should be regarded as exploratory. It is also important to consider that the sponsor obtained DNA samples from the additional 355 participants. It is not clear how those genetic data are going to be utilized in the analysis of the study [26866138-MMY-3002](#).

#### **Conclusions and Recommendations:**

- No definite conclusion can be derived on the impact of CYP2C19, CYP2D6, CYP3A4, and CYP3A5 genetic polymorphisms on the PK of VELCADE alone or in the presence of MP from this study.

About the genotyping analysis, these are the recommendations:

- Provide more information about conditions for blood collection, time elapsed between blood collection and DNA extraction and DNA extraction methods
- What is the rationale for not testing for the CYP2D6\*10 and \*41 alleles?
- Provide a listing of the nucleotide(s) identified at each defining polymorphic position for all CYP2C19, CYP2D6, CYP3A4, and CYP3A5 alleles tested
- Provide a summary of the genotyping procedures (e.g. type of assay, method validation, quality control, etc.)
- Given that only 12 patients had PK and genotype data, how is the genotype data from study 26866138-MMY-3002 (n=367) going to be utilized? Additional PK data to be collected? Evaluation of genotype on clinical outcome?

### 4.3 Filing Memo

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<b>I. <u>General Information About the Submission</u></b>				
	Information		Information	
<b>NDA Number</b>	21-602		<b>Brand Name</b>	Velcade
<b>OCP Division (1-5)</b>	DPE 5		<b>Generic Name</b>	Bortezomib
<b>Medical Division</b>	DODP		<b>Drug Class</b>	Dipeptidyl boronic acid
<b>OCP Reviewer</b>	Sophia Abraham, Ph.D.		<b>Indication(s)</b>	1 <sup>st</sup> -line multiple myeloma
<b>OCP Team Leader</b>	Brian Booth, Ph.D.		<b>Dosage Form</b>	3.5 mg single-dose vials
			<b>Dosing Regimen</b>	1.3 mg/m <sup>2</sup> twice weekly
<b>Date of Submission</b>	21-Dec-2007		<b>Route of Administration</b>	intravenously
<b>Estimated Due Date of OCPB Review</b>	01-Mar-2008		<b>Sponsor</b>	Millennium Pharmaceuticals
<b>PDUFA Due Date</b>	21-Jun-2008		<b>Priority Classification</b>	
<b>Division Due Date</b>	21-Mar-2008			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
<b>Table of Contents present and sufficient to locate reports, tables, data, etc.</b>	X			
<b>Tabular Listing of All Human Studies</b>	X			
<b>HPK Summary</b>				
<b>Labeling</b>	X			
<b>Reference Bioanalytical and Analytical Methods</b>				
<b>I. Clinical Pharmacology</b>				
<b>Mass balance:</b>				
<b>Isozyme characterization:</b>				
<b>Blood/plasma ratio:</b>				
<b>Plasma protein binding:</b>				
<b>Pharmacokinetics (e.g., Phase I)</b>				
-				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
<b>In-vitro:</b>				

<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>				
<b>Filability and QBR comments</b>				
	<b>“X” if yes</b>	<b>Comments</b>		
<b>Application filable ?</b>	<b>X</b>			
<b>Comments sent to firm ?</b>				
<b>QBR questions (key issues to be considered)</b>				
<b>Other comments or information not included above</b>				
<b>Primary reviewer Signature and Date</b>	<b>Sophia Abraham</b>			

<b>Secondary reviewer Signature and Date</b>	

**CC: NDA 21-602, DCP5 (Electronic Entry), DDOP (Brent-Steele), DCP 5 (Rahman, Booth, Abraham), CDR (Biopharm)**

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/s/

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Sophia Abraham  
5/15/2008 01:48:01 PM  
BIOPHARMACEUTICS

Silvana Borges  
5/15/2008 02:52:57 PM  
BIOPHARMACEUTICS

Brian Booth  
5/19/2008 12:39:59 PM  
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-602/S-015**

**OTHER REVIEW(S)**



**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**

Date: June 13, 2008

To: Robert Justice, MD, Director  
Division of Drug Oncology Products

Thru: Kellie Taylor, PharmD, MPH, Team Leader  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention

From: Jinhee J. Lee, PharmD, Safety Evaluator  
Division of Medication Error Prevention

Subject: Labeling Review

Drug Name: Velcade (Bortezomib for Injection)  
3.5 mg

Application Type/Number: NDA 21-602

Applicant: Millennium Pharmaceuticals, Inc.

OSE RCM #: 2008-166

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## **EXECUTIVE SUMMARY**

The Division of Medication Error Prevention's analysis of the revised package insert and patient labeling noted needed improvements to ensure proper use of the product and avoid medication errors. Such improvements include the removal of abbreviations and symbols, including a cautionary statement about the preparation of Velcade, and the removal of redundant statements that could lead to medication errors. A search of the Adverse Event Reporting System (AERS) database identified postmarketing reports of medication errors associated with Velcade which will be addressed in a separate review.

For full recommendations, we refer you to section 5 of this review.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

This memorandum is in response to a January 24, 2008 request from the Division of Oncology Products, to review the applicant's revised package insert and patient labeling. The applicant has submitted a supplemental NDA to expand the existing indication to first-line treatment for multiple myeloma. The Division of Medication Error Prevention reviewed the applicant's proposed package insert labeling (the PLR version) and patient labeling contained in the supplemental NDA submission submitted December 11, 2007.

### **1.2 REGULATORY HISTORY**

Velcade was approved on May 13, 2003 with the indication for treatment of patients with multiple myeloma or mantle cell lymphoma who have received at least 1 prior therapy. The applicant has now submitted a supplemental application to expand the multiple myeloma indication to first-line treatment. Postmarketing data for Velcade relating to the container labels and carton labeling will be included in a separate review forthcoming.

### **1.3 PRODUCT INFORMATION**

Velcade (bortezomib) for Injection is an antineoplastic agent available for intravenous use only. Velcade is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells.

Velcade was previously indicated for the 2<sup>nd</sup> line treatment for multiple myeloma and mantle cell lymphoma. However, the applicant now proposes to expand the multiple myeloma indication to first-line treatment.

The recommended dose of Velcade is 1.3 mg/m<sup>2</sup> administered as a 3 to 5 second bolus intravenous injection

- Previously Untreated Multiple Myeloma: in combination with oral melphalan (9 mg/m<sup>2</sup>) and oral prednisone (60 mg/m<sup>2</sup>) for nine 6-week treatment cycles. In Cycles 1-4, Velcade is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, Velcade is administered once weekly (days 1, 8, 22 and 29).
- Relapsed Multiple Myeloma and Mantle Cell Lymphoma (MCL): twice weekly for 2 weeks (Days 1, 4, 8, and 11) every 21 days. For extended therapy of more than 8 cycles, Velcade may be administered on the standard schedule or once weekly for 4 weeks (Days 1, 8, 15 and 22) every 35 days.

Dose adjustment may be used to manage adverse events that occur during treatment.

Velcade is supplied as a single use vial containing 3.5 mg of bortezomib.

## 2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error and Prevention medication error staff conducting a label, labeling, and/or packaging risk assessment (see section 3 Results). The primary focus for the assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.<sup>1</sup>

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton and container labels communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.<sup>2</sup>

Because the Division of Medication Error Prevention staff analyze reported misuse of drugs, the Division of Medication Error Prevention staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. The Division of Medication Error Prevention uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

### 2.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

Because Velcade has been marketed since 2003, we conducted a search of the Adverse Event Reporting System (AERS) database to identify any medication errors associated with the use of Velcade. The MedDRA Higher Level Terms (HLT) “Maladministration”, “Medication Errors NEC”, “Medication Errors Due to Accidental Exposures”, “Medication Monitoring Errors”, and the Preferred Terms (PT) “Overdose”, “Accidental Overdose”, “Multiple Drug Overdose”, “Multiple Drug Overdose Accidental”, “Pharmaceutical Product Complaint”, and verbatim substance name “Velcade%”, “Bortezo%”, tradename “Velcade” and active ingredient “bortezomib” were used as search criteria on April 25, 2008.

The cases were manually reviewed to determine if medication errors occurred. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

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<sup>1</sup> National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

<sup>2</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

## 2.2 INSERT LABELING

For this product, the applicant submitted on December 20, 2007, the following insert labeling for the Division of Medication Error Prevention review

- Prescribing Information – package insert (no image)
- Patient Information (no image)

## 3 RESULTS

### 3.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

The FDA Adverse Event Reporting System (AERS) search conducted on April 25, 2008 yielded a total of forty-five cases. Out of the 45 cases for Velcade, seven were found to be duplicates, eight were medication error cases involving another drug as the primary suspect, and two cases primarily involved an adverse drug event. Thus, this search strategy retrieved 28 cases involving Velcade medication errors.

Although it was difficult to determine why some of the medication error cases occurred because much of the detail relating to the cause of the error was omitted from the narratives, a few of the reporters identified the container label as being problematic. It does not appear that the insert labeling attributed to any of the reported medication errors. Thus, we will provide our results and discussion of our findings in a postmarketing review forthcoming (OSE #2007-1769).

### 3.2 INSERT LABELING

The Division of Medication Error Prevention notes that the changes are consistent with the expanded indication, however, we note that the applicant uses abbreviations for Velcade, Melphalan, and Prednisone in the insert (Section 2.1, Table 1).

We also note that the Velcade dose is listed as “1.3 mg/m<sup>2</sup>/dose administered...” in some parts of the DOSAGE and ADMINISTRATION section.

We note the use of the symbol, “μ”, when describing the units, microliter.

We further note that the cautionary statement, “Caution should be used in calculating the dose to prevent overdose”, should also include caution about the preparation of Velcade.

### 3.3 PATIENT LABELING

We do not have any comments.

## 4 DISCUSSION

Our assessment noted the insert labeling includes a table (Table 1) that utilizes abbreviations “Vc”, “M”, and “P” for Velcade, Melphalan, and Prednisone, respectively. Post-marketing evidence demonstrates that abbreviations can often be misinterpreted and should not be used. Moreover, in June 2006, FDA launched a campaign in conjunction with Institute for Safe Medication Practices (ISMP) to prevent the use of error prone abbreviations. As part of this campaign, FDA agreed not to approve abbreviations in their labeling. When the Agency approves these abbreviations in labels and labeling, these habits are carried over to prescribing.

The word “dose” immediately follows m<sup>2</sup> in some parts of the DOSAGE and ADMINISTRATION section, however, we believe including this word is redundant.

The symbol, “μ”, appears throughout the text when describing the units, microliter. Our postmarketing surveillance demonstrates that this symbol, when used in conjunction with the letter, “l”, to describe microliter, has often been confused as milliliter.

Additionally, the applicant includes a statement that cautions users about dose calculations. We believe it is prudent to also include a statement about the preparation of Velcade. In a forthcoming post-marketing review, we identified several cases relating to the incorrect preparation of Velcade.

## **5 CONCLUSIONS AND RECOMMENDATIONS**

The approval of the expanded indication does not appear to increase the risk of medication errors. However, the Division of Medication Errors Prevention recommends that modifications be made to the labeling in the Dosage and Administration section, particularly in Table 1 and section 2.5.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Sandra Griffith, OSE Project Manager, at 301-796-2445.

### **5.1 COMMENTS TO THE DIVISION**

Based upon our assessment of the labeling, we have identified areas of needed improvement. We have provided recommendations in section 5.2 below and request this information be forwarded to the applicant.

### **5.2 COMMENTS TO THE APPLICANT**

Based upon our assessment of the labeling, the Division of Medication Error Prevention identified the following areas of need improvement.

1. Revise Table 1 in section 2.1 so that abbreviations are no longer a part of the table. We recommend inserting the complete drug name to avoid confusion.
2. Remove the word “dose” immediately following m<sup>2</sup> throughout the text.
3. Replace the symbol, “μ”, with “microliter” throughout the text.
4. Revise the statement “Caution should be used in calculating the dose to prevent overdose” in section 2.5, to read “Caution should be used in calculating the dose *and preparing* the dose to prevent overdose.

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/s/

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Kellie Taylor  
6/13/2008 06:17:24 PM  
DRUG SAFETY OFFICE REVIEWER  
signing on behalf of primary reviewer J. Jahng Lee  
and Team Leader K. Taylor

Carol Holquist  
6/16/2008 08:22:02 AM  
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: March 27, 2008

To: Robert Justice, M.D., Director  
Division of Drug Oncology Products

Through: Jodi Duckhorn, M.A., Team Leader  
Patient Labeling and Education Team  
Division of Risk Management (DRISK)

From: Sharon R. Mills, BSN, RN, CCRP  
Patient Product Information Specialist  
Patient Education and Labeling Team  
Division of Risk Management (DRISK)

Subject: Memo to File Regarding Patient Labeling Consult

Drug Name(s): Velcade (bortezomib) for Injection

Application Type/Number: NDA 21-602

Submission Number: S-015

Applicant/sponsor: Millenium Pharmaceuticals, Inc.

OSE RCM #: 2008-172

## **1 INTRODUCTION**

Millenium Pharmaceuticals, Inc. submitted a supplemental NDA, sNDA 21-602/S-015 based on a Phase 3 clinical trial which was evaluated under special protocol assessment, proposing a new indication for use in patients with previously untreated multiple myeloma: “Velcade® (bortezomib) for Injection is indicated for the treatment of patients with multiple myeloma.”

The Patient Education and Labeling Team has been requested to review the patient labeling contained in this supplemental NDA. This memo is written in response to that request. OSE previously reviewed the Patient Information for S-006 on March 24, 2005, and S-013 on June 19, 2007.

## **2 MATERIAL REVIEWED**

- Velcade Professional Information submitted December 20, 2007
- Velcade Professional Information submitted March 19, 2008
- Velcade Professional Information as revised by the Review Division, dated March 26, 2008
- Velcade currently approved Professional Information, dated October 10, 2007

## **3 DISCUSSION**

Velcade is an antineoplastic agent that is administered by bolus intravenous injection and per section 5 of the Professional Information, “...should be administered under the supervision of a physician experienced in the use of antineoplastics.”

The sponsor has provided Patient Information in section 17 of the Patient Counseling Information section of the Professional Information and has not noted any changes to this section. The purpose of patient information (PPI) leaflets is to enhance appropriate use and provide important risk information about medications. The language submitted by the sponsor has a Flesch Kinkaid grade level of 9.3, and a Flesch Reading Ease score of 55.1. To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8<sup>th</sup> grade reading level).

## **4 CONCLUSIONS AND RECOMMENDATIONS**

- Refer to our prior reviews dated March 24, 2005 and June 19, 2007.
- Section 17 of the PI Patient Counseling Information “must contain information necessary for patients to use the drug safely and effectively...” “Any FDA-approved patient labeling must be referenced in this section and the full text of such patient labeling must be reprinted immediately following this section or, alternatively, accompany the prescription drug labeling.” See 21 CFR 208.57 (c) (18). This section is intended for use by healthcare providers in providing counseling to patients. As currently presented, the Patient Information constitutes section 17, it is not a subsection following the main part of section 17. We suggest consulting the SEALD team in reference to section 17 of the PI.
- Since Velcade is an intravenous medication, it is unlikely that patients will receive a patient information leaflet. The sponsor should clarify the following:

- Does the sponsor intend to distribute the Patient Information to patients? If the purpose of the Patient Information is to provide general information about the product that the patient can take home with them, the sponsor must then reference the FDA-approved patient labeling in section 17. We recommend that the sponsor revise the Patient Information using the question-and-answer format specified in the Medication Guide Regulations (21 CFR 208.20), that we recommend for all FDA-approved patient labeling. Alternative formats are discouraged without supportive data for their communication effectiveness from studies such as label comprehension studies.

If the sponsor does not intend for the Patient Information to be distributed to patients, the Patient Information submitted by the sponsor should be more appropriately directed to physicians to incorporate in their patient counseling. We recommend the following:

- Delete the header “Patient Information”.
- In the first paragraph of Section 17 Patient Counseling Information, remove references to “Patient Information.”
- Re-word the language in each paragraph currently under the “Patient Information” header so that they are directed to physicians for patient counseling purposes. (b) (4)  
[REDACTED] it is the physician’s responsibility to provide patients with appropriate counseling about their medicine.
- In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We recommend that the sponsor format the PPI document using one of the three recommended fonts.
- The Patient Information is not written in consumer friendly language. The readability scores provided in the **Discussion** section above continue to exceed those recommended for optimum comprehension.
- Any changes to the Patient Information labeling should also be changed in any materials that appear on the company’s website.

We would be glad to review revised Patient Information based on the above recommendations.

Please let us know if you have any questions.

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Sharon Mills  
3/28/2008 03:00:46 PM  
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn  
3/28/2008 03:04:17 PM  
CSO

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-602/S-015**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 21-602

SUPPL # 015

HFD # 150

Trade Name VELCADE for Injection

Generic Name Bortezomib

Applicant Name Millennium Pharmaceuticals, Inc.

Approval Date, If Known June 20, 2008

### **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 patients with multiple myeloma.

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

The sponsor did not request any measure of exclusivity time at all.

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:

Study number: 26866138-MMY-3002; A Phase 3, 2-arm, open-label add-on design study to treat patients with multiple myeloma.

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"):

Study number: 26866138-MMY-3002; A Phase 3, 2-arm, open-label add-on design study to treat patients with multiple myeloma.

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       ! NO   
! Explain:

Investigation #2  
IND #              YES       ! NO   
! 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: Kim J. Robertson  
Title: Consumer Safety Officer  
Date: June 17, 2008

Name of Office/Division Director signing form: Ann T. Farrell, M.D.  
Title: Division Deputy Director, Division of Drug Oncology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

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Ann Farrell  
6/17/2008 01:24:05 PM

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-602 Supplement Type (e.g. SE5): SE1 Supplement Number: 015

Stamp Date: December 20, 2007 PDUFA Goal Date: June 17, 2008

HFD-150 Trade and generic names/dosage form: Velcade (bortezomib) for Injection

Applicant: Millennium Pharmaceuticals, Inc. Therapeutic Class: Antineoplastic Agent

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? \*

- Yes. Please proceed to the next question.  
 No. PREA does not apply. Skip to signature block.

\* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) *previously approved* (please complete this section for supplements only):

Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

Treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy.

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Treatment of patients with previously untreated multiple myeloma

Is this an orphan indication?

Yes. PREA does not apply. Skip to signature block.

No. Please proceed to the next question.

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 (fill in applicable criteria below):

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 (fill in applicable criteria below):

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 (fill in applicable criteria below):

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.*

NDA 21-602 S-015

Page 3

**This page was completed by:**

*{See appended electronic signature page}*

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**Tammie Brent, RN, MSN**  
**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

**(Revised: 10/10/2006)**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: \_\_\_\_\_

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

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 (fill in applicable criteria below)::

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 (fill in applicable criteria below)::

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 (fill in applicable criteria below):

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

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 10/10/2006)

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/s/

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Tammie Brent-Steele  
4/22/2008 03:10:31 PM

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-602 Supplement Type (e.g. SE5): SE1 Supplement Number: 015

Stamp Date: December 20, 2007 PDUFA Goal Date: June 17, 2008

HFD-150 Trade and generic names/dosage form: Velcade (bortezomib) for Injection

Applicant: Millennium Pharmaceuticals, Inc. Therapeutic Class: Antineoplastic Agent

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? \*

- Yes. Please proceed to the next question.  
 No. PREA does not apply. Skip to signature block.

\* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) *previously approved* (please complete this section for supplements only):

Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

Treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy.

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Treatment of patients with previously untreated multiple myeloma

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.  
 No. Please proceed to the next question.

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 (fill in applicable criteria below):

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 (fill in applicable criteria below):

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 (fill in applicable criteria below):

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.*

NDA ##-###

Page 3

**This page was completed by:**

*{See appended electronic signature page}*

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**Tammie Brent, RN, MSN  
Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH  
STAFF at 301-796-0700**

**(Revised: 10/10/2006)**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: \_\_\_\_\_

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

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 (fill in applicable criteria below)::

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 (fill in applicable criteria below)::

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 (fill in applicable criteria below):

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

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 10/10/2006)

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/s/

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Tammie Brent-Steele  
1/25/2008 01:48:46 PM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-602\S-015  
Millennium Pharmaceuticals, Inc.  
Attention: Tanya Lewis, MS  
Sr. 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 and your request for 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, 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

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/s/

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Robert Justice  
2/11/2008 06:29:56 PM



## FILING COMMUNICATION

NDA 21-602/S-015

Millennium Pharmaceuticals, Inc.  
Attention: Tanya Lewis, M.S.  
Sr. Director, Regulatory Affairs  
40 Landsdowne Street  
Cambridge, MA 01239

Dear Ms. Lewis:

Please refer to your December 20, 2007 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Velcade (bortezomib) for Injection.

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 February 18, 2008 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

Please indicate where in the application the information on the three reported interim analyses can be found. If the information was not provided, please provide a separate report with details on interim analyses including purpose, timing, calculated statistical boundaries, and analysis results along with corresponding IDMC meeting reports.

We are providing the above comment to give you preliminary notice of potential 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. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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

Sincerely,

*{See appended electronic signature page}*

Ann Farrell, MD  
Deputy Director  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

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/s/

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Ann Farrell

1/31/2008 03:16:53 PM

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 21-602 Supplement # 015 Efficacy Supplement Type SE- 1

Proprietary Name: Velcade  
Established Name: Bortezomib  
Strengths: 3.5 mg

Applicant: Millennium Pharmaceuticals, Inc.  
Agent for Applicant (if applicable):

Date of Application: December 20, 2007  
Date of Receipt: December 20, 2007  
Date clock started after UN: December 20, 2007  
Date of Filing Meeting: January 16, 2008  
Filing Date: February 18, 2008  
Action Goal Date (optional):

User Fee Goal Date: June 20, 2008

Indication(s) requested: Treatment of patients with previously untreated multiple myeloma

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.) ODE

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 May 13, 2010

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  NO

• Exclusivity requested? YES,  X  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  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

If yes, contact PMHT in the OND-IO

• Financial Disclosure forms included with authorized signature? YES  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? Yes. 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) \_\_\_\_\_ NO   
If yes, distribute minutes before filing meeting.

• Pre-NDA Meeting(s)? Date(s) \_\_\_\_\_ NO   
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) 2-3-2005 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:
- 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: January 16, 2008

NDA #: 21-602 S-015

DRUG NAMES: Velcade (bortezomib) for Injection

APPLICANT: Millennium Pharmaceuticals, Inc.

BACKGROUND: The original NDA for Velcade was approved on May 13, 2003. The sponsor has submitted a supplemental new drug application (sNDA) to support a new indication for the use of Velcade (bortezomib) for Injection in patients with previously untreated multiple myeloma.

ATTENDEES: Justice, Robert; Farrell, Ann T; Kane, Robert; Verbois, Leigh; Ko, Chia-wen (Kiki); Sridhara, Rajeshwari; Abraham, Sophia; Jenney, Susan; Lee, JuWon;

ASSIGNED REVIEWERS (including those not present at filing meeting):

**Discipline/Organization**

**Reviewer**

Medical:	Robert Kane, MD
Statistical:	Chia-Wen Ko, PhD
Pharmacology:	Leigh Verbois, PhD
Chemistry:	Cheng Yi Liang, PhD
Clinical Pharmacology:	Sophia Abraham, PhD
Regulatory Project Management:	Tammie Brent, RN, MSN

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

- Clin. Pharm. study site audits(s) needed? YES  NO

PHARMACOLOGY/TOX	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• GLP audit needed?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	
CHEMISTRY		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• Establishment(s) ready for inspection?	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>	
• Sterile product?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	
If yes, was microbiology consulted for validation of sterilization?	YES <input type="checkbox"/>	NO <input type="checkbox"/>	

**ELECTRONIC SUBMISSION:**

Any comments: SPL submitted January 16, 2008.

**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:  
Please point out where in the application the information on the three reported interim analyses can be found. If this information was not provided, please provide a separate report with details on interim analyses including purpose, timing, calculated statistical boundaries, and analysis results along with corresponding IDMC meeting reports.

**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 RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4.  If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5.  Convey document filing issues/no filing issues to applicant by Day 74.

Tammie Brent, 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

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

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Tammie Brent-Steele  
1/25/2008 01:52:16 PM  
CSO



NDA 21-602/S-015

**PRIOR APPROVAL SUPPLEMENT**

Millennium Pharmaceuticals, Inc.  
Attention: Tanya Lewis, M.S.  
Sr. Director, Regulatory Affairs  
40 Landsdowne Street  
Cambridge, MA 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

NDA Number: 21-602

Supplement number: 015

Review Priority Classification: Priority (P)

Date of supplement: December 20, 2007

Date of receipt: December 20, 2007

This supplemental application proposes the following change(s):

New Indication: Velcade (bortezomib) for Injection is indicated for the treatment of patients with multiple myeloma.

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 February 18, 2008 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 20, 2008.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

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 note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application and we are waiving the pediatric study requirement 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, Regulatory Project Manager, at (301) 796-1409.

Sincerely,

*{See appended electronic signature page}*

Tammie Brent, RN, MSN  
Regulatory Project Manager  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

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

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Tammie Brent-Steele  
1/24/2008 01:27:38 PM