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----------

Warnings and Precautions, Peripheral Neuropathy (5.2); Pulmonary Disorders (5.5); Neutropenia (5.8)	3/2006
Indications and Usage, Mantle Cell Lymphoma (1.2)	12/2006
Warnings and Precautions, RPLS (5.6)	12/2006
Patients with Renal Impairment (8.6)	tbd

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

VELCADE is a proteasome inhibitor indicated for:

- treatment of patients with multiple myeloma who have received at least 1 prior therapy (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^2 administered as a bolus intravenous injection twice weekly for 2 weeks (Days 1, 4, 8, and 11) every 21 days. (2.1)
- 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. (2.1)
- VELCADE therapy should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved, VELCADE therapy may be reinitiated at a 25% reduced dose (1.3 mg/m^2 /dose reduced to1 mg/m^2/dose, 1 mg/m^2/dose reduced to 0.7 mg/m^2/dose). (2.2, 5.2)
- Manage peripheral neuropathy with dose modification. (2.2)

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

- 1 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)
- Peripheral neuropathy, including severe cases, may occur - manage with dose modification or discontinuation. (2.2) Patients with preexisting severe neuropathy should be treated with VELCADE after careful risk-benefit assessment. (2.2, 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 common adverse reactions (incidence ≥30%) include asthenic conditions, diarrhea, nausea, constipation, peripheral neuropathy, vomiting, pyrexia, thrombocytopenia, psychiatric disorders, anorexia and decreased appetite. 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 www.mlnm.com) or FDA at 1-800-FDA-1088 or *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, 8.3)
- Dosing adjustments are not necessary for patients with renal insufficiency, including those requiring dialysis. (8.6)
- No overall differences in safety or effectiveness were observed between patients ≥ age 65 and younger patients receiving VELCADE; but greater sensitivity of some older individuals cannot be ruled out. (8.5)
- Patients with diabetes may require close monitoring of blood glucose and adjustment of antidiabetic medication. (8.8)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: [3/2007]

FULL PRESCRIBING INFORMATION: CONTENTS*

*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 who have received at least 1 prior therapy.

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

The recommended dose of VELCADE is 1.3 mg/m^2/dose 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.

2.2 Dose Modification and Re-initiation of Therapy

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 mg/m^2/dose reduced to 1 mg/m^2/dose; 1 mg/m^2/dose reduced to 0.7 mg/m^2/dose).

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

Table 1: Recommended Dose Modification for VELCADE related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

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

Grading based on NCI Common Toxicity Criteria CTCAE v3.0

2.3 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 for specific recommendations and guidelines.

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

2.4 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 25ºC (77ºF). 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 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^2 in the rat and 0.05 mg/kg; 0.6 mg/m^2 in the rabbit) when administered during organogenesis. These dosages are approximately half the clinical dose of 1.3 mg/m^2 based on body surface area.

Pregnant rabbits given bortezomib during organogenesis at a dose of 0.05mg/kg (0.6 mg/m^2) 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^2 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.

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)]***. Following dose adjustments, improvement in or resolution of peripheral neuropathy was reported in 51% of patients with ≥Grade 2 peripheral neuropathy in the phase 3 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 (6.1)]*** 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(6.1)]***

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 phase 3 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 rare 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. A higher proportion of these events have been reported in Japan.

In a clinical trial, the first two patients given high-dose cytarabine (2g/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 rare 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 rare 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. Fluid and electrolyte replacement should be administered to prevent dehydration.

5.8 Thrombocytopenia/Neutropenia

VELCADE is associated with thrombocytopenia and neutropenia. Platelets and neutrophils were lowest at Day 11 of each cycle of VELCADE treatment and typically recovered to baseline by the next 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 2.** In the phase 3 multiple myeloma study, the incidence of significant bleeding events (≥Grade 3) was similar on both the VELCADE (4%) and dexamethasone (5%) arms. Platelet counts should be monitored prior to each dose of VELCADE. VELCADE therapy should be held when the platelet count is <25,000/μL and reinitiated at a reduced dose ***[see Dosage and Administration (2.2); Adverse Reactions (6)]***. 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 2: Severity of Thrombocytopenia Related to Pretreatment Platelet Count in the Phase 3 Myeloma Study

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

* A baseline platelet count of 50,000/μL 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

Rare 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's clearance may decrease in patients with hepatic impairment. These patients should be closely monitored for toxicities when treated with VELCADE. *[see Drug Interactions (7); Use In Specific Populations (8.7)]*

5.11 Drug / Laboratory Test Interactions

None known.

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 (2.2)*]
- 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 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.

Randomized Open-Label Phase 3 Multiple Myeloma Study

The safety data described below and in Table 3 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^2 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 ≥above and below 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 Phase 3 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 the phase 3 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 Phase 3 Multiple Myeloma Study

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

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

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

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

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 (Multiple Myeloma and Mantle Cell Lymphoma)

Safety data from phase 2 and 3 studies of VELCADE 1.3 mg/m^2/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 4**. 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 4: Most Commonly Reported (≥10% Overall) Adverse Events in Integrated Analyses of Multiple Myeloma and Mantle Cell Lymphoma Studies using the 1.3 mg/m^2 Dose (N=1163)

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

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

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

Gastrointestinal Events:
A total of 87% of patients experienced at least one GI disorder. The most common GI disorders included nausea, diarrhea, constipation, vomiting, and appetite decreased. Other GI disorders included dyspepsia and dysgeusia. Grade 3 GI events occurred in 18% of patients; Grade 4 events were rare (1%). GI events were considered serious in 11% of patients. Five percent (5%) of patients discontinued due to a GI event. Nausea was reported more often in patients with multiple myeloma (57%) compared to patients with mantle cell lymphoma (44%). *[see 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%, ≥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 ≥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 phase 3 multiple myeloma study, among the 87 patients who experienced ≥ 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 ≥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 ≥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 ≥Grade 4 in 3%. Neutropenia was reported as a serious event in <1% of patients and <1% of patients discontinued due to neutropenia. The incidence of neutropenia was higher in patients with multiple myeloma (18%) compared to patients with mantle cell lymphoma (6%). The incidence of ≥Grade 3 neutropenia also was higher in patients with multiple myeloma (14%) compared to patients with mantle cell lymphoma. (4%). *[see 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 ≥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 (>38ºC) was reported as an adverse event for 34% of patients. The event was Grade 3 in 3% and ≥Grade 4 in <1%. Pyrexia was reported as a serious adverse event in 6% of patients and led to VELCADE discontinuation in <1% of patients. The incidence of pyrexia was higher among patients with multiple myeloma (37%) compared to patients with mantle cell lymphoma (19%). The incidence of ≥Grade 3 pyrexia was 3% in patients with multiple myeloma and 1% in patients with mantle cell lymphoma.

Reactivation of Herpes Virus Infection

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

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 spontaneous reports during 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

No formal drug interaction studies have been conducted with VELCADE.

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.

Bortezomib is a poor inhibitor of human liver microsome cytochrome P450 1A2, 2C9, 2D6, and 3A4, with IC_{50} values of >30μM (>11.5μg/mL). Bortezomib may inhibit 2C19 activity (IC_{50} = 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

No overall differences in safety or effectiveness were observed between patients ≥ 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 are not necessary for patients with renal insufficiency. Since dialysis may reduce VELCADE concentrations, the drug should be administered after the dialysis procedure. *[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 overdosage *[see Warnings and Precautions (5.3) and Dosage and Administration (2.3)]*. 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 overdosage, the patient's vital signs should be monitored and appropriate supportive care given.

Studies in monkeys and dogs showed that IV bortezomib doses as low as 2 times the recommended clinical dose on a mg/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 mg/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.

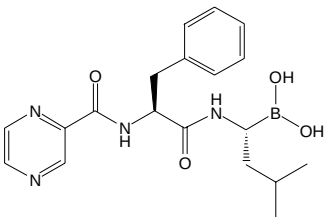
11 DESCRIPTION

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 $C_{19}H_{25}BN_4O_4$. 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^2 and 1.3 mg/m^2 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^2 doses. Maximal inhibition ranged from 70% to 84% and from 73% to 83% for the 1 mg/m^2 and 1.3 mg/m^2 dose regimens, respectively.

12.3 Pharmacokinetics

Following intravenous administration of 1 mg/m^2 and 1.3 mg/m^2 doses to 24 patients with multiple myeloma (n=12, per each dose level), the mean maximum plasma concentrations of bortezomib (C_{max}) after the first dose (Day 1) were 57 and 112 ng/mL, respectively. In subsequent doses, when administered twice weekly, the mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1 mg/m^2 dose and 89 to 120 ng/mL for the 1.3 mg/m^2 dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours after the 1 mg/m^2 dose and 76 to 108 hours after the 1.3mg/m^2 dose. The mean total body clearances was 102 and 112 L/h following the first dose for doses of 1 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1 and 1.3 mg/m^2, respectively.

Distribution: The mean distribution volume of bortezomib ranged from approximately 498 to 1884 L/m^2 following single- or repeat-dose administration of 1 mg/m^2 or 1.3mg/m^2 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^2 and 1.3 mg/m^2 showed that both dose-normalized AUC and C_{max} tend to be less in younger patients. Patients < 65 years of age (n=26) had about 25% lower mean dose-normalized AUC and C_{max} than those ≥ 65 years of age (n=13).

Gender: Mean dose-normalized AUC and C_{max} values were comparable between male (n=22) and female (n=17) patients after the first dose of Cycle 1 for the 1 and 1.3 mg/m^2 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^2, N=12), Mild (CrCl=40-59 mL/min/1.73 m^2, N=10), Moderate (CrCl=20-39 mL/min/1.73 m^2, N=9), and Severe (CrCl < 20 mL/min/1.73 m^2, 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^2 of bortezomib twice weekly. Exposure of bortezomib (dose-normalized AUC and C_{max}) was comparable among all the groups. *[See Specific Populations (8.6)]*

Pediatric: There are no pharmacokinetic data in pediatric patients.

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 ≥0.3 mg/m^2 (one-fourth of the recommended clinical dose), and degenerative changes in the testes occurred at 1.2 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 ≥1.2 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, Phase 3 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 ≥2 peripheral neuropathy or platelet counts <50,000/μL. 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 β_2-microglobulin levels (≤2.5 mg/L versus >2.5 mg/L).

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

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

Patient Characteristics	VELCADE N=333	Dexamethasone N=336
Median age in years (range)	62.0 (33, 84)	61.0 (27, 86)
Gender: Male/female	56% / 44%	60% / 40%
Race: Caucasian/black/other	90% / 6% / 4%	88% / 7% / 5%
Karnofsky performance status score ≤70	13%	17%
Hemoglobin <100 g/L	32%	28%
Platelet count <75 x 10^9/L	6%	4%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	60% / 23% / 12%	59% / 24% / 13%
Median β_2-microglobulin (mg/L)	3.7	3.6
Median albumin (g/L)	39.0	39.0
Creatinine clearance ≤30 mL/min [n (%)]	17 (5%)	11 (3%)
Median Duration of Multiple Myeloma Since Diagnosis (Years)	3.5	3.1
Number of Prior Therapeutic Lines of Treatment		
Median	2	2
1 prior line	40%	35%
>1 prior line	60%	65%
Previous Therapy		
Any prior steroids, e.g., dexamethasone, VAD	98%	99%
Any prior anthracyclines, e.g., VAD, mitoxantrone	77%	76%
Any prior alkylating agents, e.g., MP, VBMCP	91%	92%
Any prior thalidomide therapy	48%	50%
Vinca alkaloids	74%	72%
Prior stem cell transplant/other high-dose therapy	67%	68%
Prior experimental or other types of therapy	3%	2%

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

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

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

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

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 phase 3 multiple myeloma study are presented in **Table 6**. Response and progression were assessed using the European Group for Blood and Marrow Transplantation (EBMT) criteria.[l] 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 ≥50% reduction in serum myeloma protein and ≥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^+).

Table 6: Summary of Efficacy Analyses in the Phase 3 Multiple Myeloma Study

	All Patients		**1 Prior Line of Therapy**		**> 1 Prior Line of Therapy**	
	VELCADE	**Dex**	**VELCADE**	**Dex**	**VELCADE**	**Dex**
Efficacy Endpoint	**n=333**	**n=336**	**n=132**	**n=119**	**n=200**	**n=217**
Time to Progression						
Events n (%)	147 (44)	196 (58)	55 (42)	64 (54)	92 (46)	132 (61)
Median [a]	6.2 mo	3.5 mo	7.0 mo	5.6 mo	4.9 mo	2.9 mo
(95% CI)	(4.9, 6.9)	(2.9, 4.2)	(6.2, 8.8)	(3.4, 6.3)	(4.2, 6.3)	(2.8, 3.5)
Hazard ratio [b]	0.55		0.55		0.54	
(95% CI)	(0.44, 0.69)		(0.38, 0.81)		(0.41, 0.72)	
p-value [c]	<0.0001		0.0019		<0.0001	
Overall Survival						
Events (deaths) n (%)	51 (15)	84 (25)	12 (9)	24 (20)	39 (20)	60 (28)
Hazard ratio [b]	0.57		0.39		0.65	
(95% CI)	(0.40, 0.81)		(0.19, 0.81)		(0.43, 0.97)	
p-value [c,d]	<0.05		<0.05		<0.05	
Response Rate						
Population [e] n = 627	n=315	n=312	n=128	n=110	n=187	n=202
CR [f] n (%)	20 (6)	2 (<1)	8 (6)	2 (2)	12 (6)	0 (0)
PR [f] n(%)	101 (32)	54 (17)	49 (38)	27 (25)	52 (28)	27 (13)
nCR [f,g] n(%)	21 (7)	3 (<1)	8 (6)	2 (2)	13 (7)	1 (<1)
CR + PR [f] n (%)	121 (38)	56 (18)	57 (45)	29 (26)	64 (34)	27 (13)
p-value [h]	<0.0001		0.0035		<0.0001	
Median Response Duration						
CR [f]	9.9 mo	NE [i]	9.9 mo	NE	6.3 mo	NA [j]
nCR [f]	11.5 mo	9.2 mo	NE	NE	11.5 mo	9.2 mo
CR + PR [f]	8.0 mo	5.6 mo	8.1 mo	6.2 mo	7.8 mo	4.1 mo

[a] Kaplan-Meier estimate.

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

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

[d] Precise p-value cannot be rendered.

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

[f] EBMT criteria[l]; nCR meets all EBMT criteria for CR but has positive IF. Under EBMT criteria. nCR is in the PR category.

[g] In 2 patients, the IF was unknown.

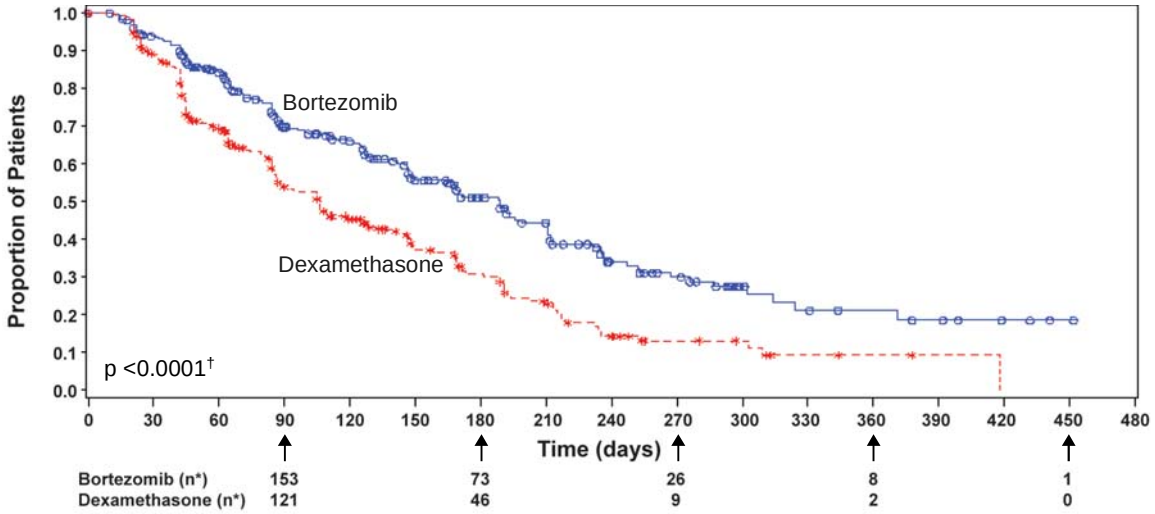
[h] p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors;

[i] Not Estimable.

[j] Not Applicable, no patients in category.

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

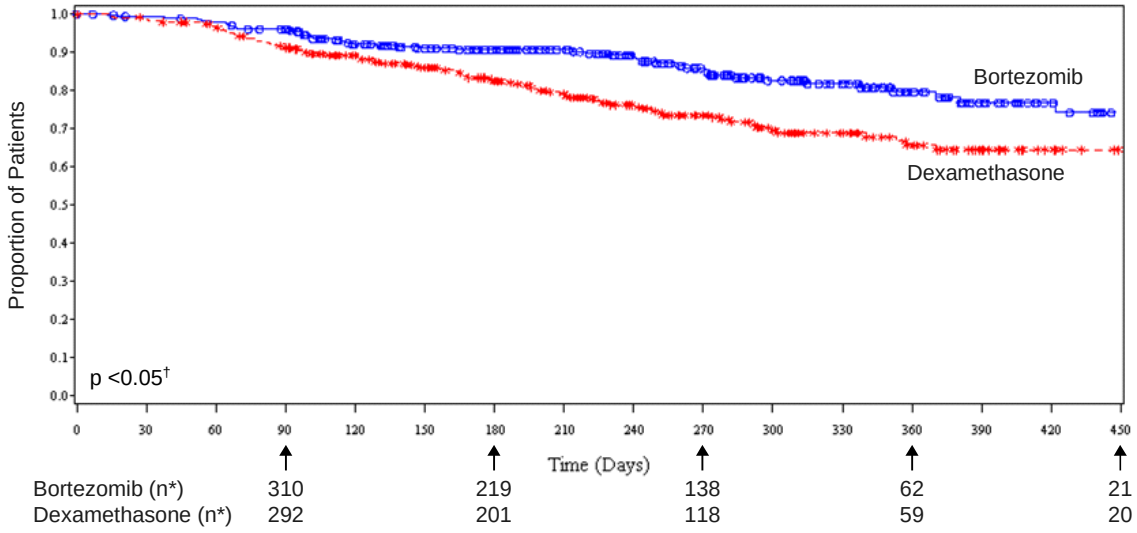
Figure 1: Time to Progression
Bortezomib vs. Dexamethasone



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

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

Figure 2: Overall Survival
Bortezomib vs. Dexamethasone



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

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 β_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^2 or 1.3 mg/m^2 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^2 and 38% (10/26) at 1.3 mg/m^2.

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^2/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 (2.2)]*

Responses to VELCADE are shown in **Table 9**. Response rates to VELCADE were determined according to the International Workshop Response Criteria (IWRC)[2] 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 9: Response Outcomes in a Phase 2 Mantle Cell Lymphoma Study

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

15 REFERENCES

1. Bladé J, Samson D, Reece D, Apperley J, Bjorkstrand B, Gahrton G et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high- dose therapy and haematopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *British Journal of Haematology* 1998;102(5):1115-1123. **2.** Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI,

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16 HOW SUPPLIED/STORAGE AND HANDLING

VELCADE® (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 25ºC (77ºF); excursions permitted from 15 to 30ºC (59 to 86ºF) [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[3-6].

Caution: R_x 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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MILLENNIUM

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17 PATIENT COUNSELING INFORMATION

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

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 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.

PATIENT INFORMATION

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

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability:
VELCADE may cause tiredness, dizziness, fainting, or blurred vision. Do not drive any vehicle or operate any dangerous tools or machinery if you experience these side effects. Even if you have not felt these effects previously, you must still be cautious.

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

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

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

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

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

Herpes zoster (Shingles):
Contact your doctor if you develop a rash.

Heart Failure and Lung Disease:
Contact your doctor if you experience shortness of breath, cough, or swelling of the feet, ankles, or legs.

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

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