PRODUCT NAME

VELCADE® (bortezomib) for Injection

VELCADE® is a registered trademark of Millennium Pharmaceuticals, Inc.

DOSAGE® FORMS AND STRENGTHS

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.

For excipients, see List of Excipients.

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.

CLINICAL INFORMATION

Indications

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

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

Dosage and Administration

VELCADE® may be administered:

Intravenously (at a concentration of 1 mg/ml) as a 3 to 5 second bolus injection.

VELCADE® IS FOR INTRAVENOUS USE ONLY. Intrathecal administration has resulted in death.

Monotherapy

Recommended 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 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). At least 72 hours should elapse between consecutive doses of VELCADE®.

Dose Modification and Reinitiation 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). 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 1.0 mg/m^2/dose; 1.0 mg/m^2/dose reduced to 0.7 mg/m^2/dose). The following table contains the recommended dose modification for the management of patients who experience VELCADE®-related neuropathic pain and/or peripheral sensory neuropathy **(Table 1)**. Patients with pre-existing 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 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting Instrumental Activities of Daily Living (ADL))**	Reduce VELCADE® to 1.0 mg/m^2 OR Change VELCADE® treatment schedule to 1.3 mg/m^2 once per week
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL ***)	Withhold VELCADE® therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of VELCADE® at 0.7 mg/m^2 once per week.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue VELCADE®

* Grading based on NCI Common Toxicity Criteria CTCAE v 4.0

** *Instrumental ADL*: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money etc

*** *Self care ADL*: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

Administration

VELCADE® is administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with 0.9% sodium chloride solution for injection.

Combination Therapy

Recommended Dosage in Combination with melphalan and prednisone

VELCADE® (bortezomib) for Injection 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 2**. 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).

Table 2: Recommended Dosage Regimen for VELCADE® when used in combination with melphalan and prednisone for Patients with Previously Untreated Multiple Myeloma

Twice Weekly VELCADE® (Cycles 1-4)

Week	1				2		3	4		5		6
Vc (1.3 mg/m^2)	Day 1	--	--	Day 4	Day 8	Day 11	rest period	Day 22	Day 25	Day 29	Day 32	rest period
m (9 mg/m^2) p (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period

Once Weekly VELCADE® (Cycles 5-9)

Week	1				2	3	4	5	6
Vc (1.3 mg/m^2)	Day 1	--	--	--	Day 8	rest period	Day 22	Day 29	rest period
m (9 mg/m^2) p (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	rest period	--	--	rest period

Vc = VELCADE®; m = melphalan; p = prednisone

Dose Management Guidelines for Combination Therapy with melphalan and prednisone

Dose modification and re-initiation of therapy when VELCADE® is administered in combination with melphalan and prednisone

Prior to initiating a new cycle of therapy:

- Platelet count should be ≥ 70 x 10^9/l and the ANC should be ≥ 1.0 x 10^9/l
- Non-hematological toxicities should have resolved to Grade 1 or baseline

Table 3: Dose Modifications during Subsequent Cycles

Toxicity	Dose modification or delay
Hematological toxicity during a cycle:	
• If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25% in the next cycle.
• If platelet count ≤ 30 x 10^9/l or ANC ≤ 0.75 x 10^9/l on a VELCADE® dosing day (other than day 1)	VELCADE® dose should be withheld
• If several VELCADE® doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	VELCADE® dose should be reduced by 1 dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2)
Grade ≥ 3 Non-Hematological Toxicities	VELCADE® therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, VELCADE® may be reinitiated with one dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). For VELCADE®-related neuropathic pain and/or peripheral neuropathy, hold and/or modify VELCADE® as outlined in **Table 1**.

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

Special Populations

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 (see Pharmacokinetic properties).

Patients with Hepatic Impairment

Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended VELCADE® dose. Patients with moderate or severe hepatic impairment should be started on VELCADE® at a reduced dose of 0.7 mg/m^2 per injection during the first cycle, and a subsequent dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 may be considered based on patient tolerance (see **Table 4)**.

Table 4: Recommended Starting Dose Modification for VELCADE® in Patients with Hepatic Impairment			
	Bilirubin Level	**SGOT (AST) Levels**	**Modification of Starting Dose**
Mild	≤ 1.0 x ULN	> ULN	None
	> 1.0 x–1.5 x ULN	Any	None
Moderate	> 1.5 x–3 x ULN	Any	Reduce VELCADE to 0.7 mg/m^2 in the first cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	> 3x ULN	Any	

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

Children (2 to 16 years old)

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

Contraindications

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

Warnings and Precautions

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

There have been fatal cases of inadvertent intrathecal administration of VELCADE®. VELCADE® is for IV use only**. DO NOT ADMINISTER VELCADE® INTRATHECALLY.**

Overall, the safety profile of patients treated with VELCADE® in monotherapy was similar to that observed in patients treated with VELCADE® in combination with melphalan and prednisone.

Peripheral Neuropathy

VELCADE® treatment causes a peripheral neuropathy (PN) that is predominantly sensory. However, cases of severe motor neuropathy with or without sensory 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 a change in the dose and schedule of VELCADE® (see Dosage and Administration). Following dose adjustments, improvement in or resolution of peripheral neuropathy was reported in 51% of patients with ≥ Grade 2 peripheral neuropathy in the single agent phase 3 multiple myeloma study of VELCADE® vs dexamethasone. 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. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

Hypotension

In phase 2 and 3 single agent multiple myeloma studies, the incidence of hypotension (postural,

orthostatic, and Hypotension Not Otherwise Specified) was 11% to 12%. 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, or administration of mineralocorticoids and/or sympathomimetics (see Adverse Reactions).

Cardiac Disorders

Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported, including reports in patients with few or no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or existing heart disease should be closely monitored. In the single agent phase 3 multiple myeloma study of VELCADE® vs dexamethasone, the incidence of any treatment-emergent cardiac disorder was 15% and 13% 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.

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.

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 the event of new or worsening pulmonary symptoms, a prompt diagnostic evaluation should be performed and patients treated appropriately.

In a clinical trial, two patients given high-dose cytarabine (2 g/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. Therefore, this specific regimen with concomitant administration with high-dose cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours is not recommended.

Laboratory Tests

Complete blood counts (CBC) should be frequently monitored throughout treatment with VELCADE®.

Thrombocytopenia

VELCADE® is associated with thrombocytopenia (see Adverse Reactions). Platelets 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 count decrease and recovery remained consistent over the 8 cycles of twice weekly dosing, and there was no evidence of cumulative thrombocytopenia. The mean platelet count nadir measured was approximately 40% of baseline. The severity of thrombocytopenia related to pre-treatment platelet count is shown in **Table 5**. In the single agent phase 3 multiple myeloma study of VELCADE® vs dexamethasone, 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 < 25000/µl and reinitiated at a reduced dose (see Dosage and Administration and Adverse Reactions). There have been reports of gastrointestinal and intracerebral hemorrhage in association with VELCADE®. Transfusion may be considered.

Table 5: Severity of Thrombocytopenia Related to Pre-treatment Platelet Count in the Single Agent Phase 3 Multiple Myeloma Study of VELCADE® vs Dexamethasone

Pre-treatment Platelet Count*	Number of Patients (N = 331)**	Number (%) of Patients with Platelet Count < 10000/µl	Number (%) of Patients with Platelet Count 10000-25000/µl
≥ 75000/µl	309	8 (3%)	36 (12%)
≥ 50000/µl - < 75000/µl	14	2 (14%)	11 (79%)
≥ 10000/µl - < 50000/µl	7	1 (14%)	5 (71%)

* A baseline platelet count of 50000/µl was required for study eligibility.

** Data were missing at baseline for 1 patient.

Gastrointestinal Adverse Events

VELCADE® treatment can cause nausea, diarrhea, constipation, and vomiting (see Adverse Reactions) sometimes requiring use of antiemetics and antidiarrheal medications. Fluid and electrolyte replacement should be administered to prevent dehydration. 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.

Tumor Lysis Syndrome

Because VELCADE® is a cytotoxic agent and can rapidly kill malignant cells the complications of tumor lysis syndrome may occur. The 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.

Patients with Hepatic Impairment

Bortezomib is metabolized by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment, these patients should be treated with VELCADE® at reduced starting doses and closely monitored for toxicities (see Dosage and Administration and Pharmacokinetic Properties).

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.

Interactions

In vitro and animal *ex vivo* studies indicate that bortezomib is a weak inhibitor of cytochrome P450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6 and 3A4. Based on the limited contribution (7%) of CYP2D6 to the metabolism of bortezomib, the CYP2D6 poor metabolizer phenotype is not expected to affect the overall disposition of bortezomib. A drug-drug interaction study assessing the effect of ketoconazole, a potent CYP3A4-inhibitor, on the pharmacokinetics of VELCADE®, showed a bortezomib AUC mean increase of 35%, based on data from 12 patients. Therefore

patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors (e.g. ketoconazole, ritonavir).
In a drug-drug interaction study assessing the effect of omeprazole, a potent inhibitor of CYP2C19, on the pharmacokinetics of VELCADE® there was no significant effect on the pharmacokinetics of bortezomib, based on data from 17 patients. A drug-drug interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of VELCADE® showed a mean bortezomib AUC reduction of 45% based on data from 6 patients. The concomitant use of VELCADE® with strong CYP3A4 inducers is therefore not recommended, as efficacy may be reduced. Examples of CYP3A4 inducers are rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort. In the same drug-drug interaction study, the effect of dexamethasone, a weaker CYP3A4 inducer was assessed. There was no significant effect on bortezomib pharmacokinetics based on data from 7 patients.
A drug-drug interaction study assessing the effect of melphalan-prednisone on VELCADE® showed a 17% increase in mean bortezomib AUC based on data from 21 patients. This is not considered clinically relevant.
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.
Patients should be cautioned about the use of concomitant medications that may be associated with peripheral neuropathy (such as amiodarone, anti-virals, isoniazid, nitrofurantoin, or statins), or with a decrease in blood pressure.
Drug Laboratory Test Interactions
None known.

Pregnancy, Breast-feeding and Fertility

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 0.05 mg/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.
No placental transfer studies have been conducted with bortezomib. 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.
Patients should be advised to use effective contraceptive measures to prevent pregnancy and to avoid breast feeding during treatment with VELCADE®
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®, women should be advised against breast feeding while being treated with VELCADE®.

Effects on Ability to Drive and Use Machines

VELCADE® may cause tiredness, dizziness, fainting, or blurred vision. Patients should be

advised not to drive or operate machinery if they experience these symptoms.

Adverse Reactions

Summary of Clinical Trials of VELCADE® IV in patients with relapsed/refractory multiple myeloma:

The safety and efficacy of VELCADE® were evaluated in 3 studies at the recommended dose of 1.3 mg/m^2. These included a phase 3 randomized, comparative study, versus dexamethasone of 669 patients with relapsed or refractory multiple myeloma who had received 1-3 prior lines of therapy (M34101-039); a phase 2 single arm, open-label, multicenter study of 202 patients who had received at least 2 prior therapies and demonstrated disease progression on their most recent therapy (M34100-025); and a phase 2 dose-response clinical study in relapsed multiple myeloma for patients who had progressed or relapsed on or after first line therapy with VELCADE® 1.0 mg/m^2 or 1.3 mg/m^2 (M34100-024).

Table 6: VELCADE® Adverse Drug Reactions in Phase 2 and Phase 3 Relapsed/Refractory Multiple Myeloma Studies

Body System:	**Study No.**	
	039 (N = 331)	024/025 (N = 228†)
Blood and lymphatic system disorders		
Thrombocytopenia	115 (35%)	97 (43%)
Anemia	87 (26%)	74 (32%)
Neutropenia	62 (19%)	55 (24%)
Leucopenia	24 (7%)	15 (7%)
Lymphopenia	15 (5%)	11 (5%)
Pancytopenia	2 (< 1%)	6 (3%)
Febrile Neutropenia	1 (< 1%)	1 (< 1%)
Cardiac disorders		
Arrhythmias	4 (1%)	2 (< 1%)
Tachycardia	9 (3%)	17 (7%)
Atrial Fibrillation	6 (2%)	2 (< 1%)
Palpitations	5 (2%)	4 (2%)
Acute Development or exacerbation of cardiac failure, including CHF	7 (2%)	8 (4%)
Pulmonary edema	6 (2%)	3 (1%)
*Cardiogenic shock**	1 (< 1%)	-
New onset of decreased left ventricular ejection fraction	1 (< 1%)	-
Atrial Flutter	1 (< 1%)	-
Bradycardia	3 (< 1%)	1 (< 1%)
Ear & labyrinth disorders		
Hearing Impairment	1 (< 1%)	1 (< 1%)
Eye disorders		
Blurred Vision	9 (3%)	25 (11%)
Conjunctival infection and irritation	14 (4%)	7 (3%)
Gastrointestinal (GI) disorders		
Constipation	140 (42%)	97 (43%)
Diarrhea	190 (57%)	116 (51%)
Nausea	190 (57%)	145 (64%)

Body System:	**Study No.**	
	039 (N = 331)	024/025 (N = 228†)
Vomiting	117 (35%)	82 (36%)
Gastrointestinal and abdominal pain, excluding oral and throat	80 (24%)	48 (21%)
Dyspepsia	32 (10%)	30 (13%)
Pharyngolaryngeal pain	25 (8%)	19 (8%)
Gastroesophageal reflux	10 (3%)	1 (< 1%)
Eructation	2 (< 1%)	4 (2%)
Abdominal distension	14 (4%)	13 (6%)
Stomatitis and mouth ulceration	24 (7%)	10 (4%)
Dysphagia	4 (1%)	5 (2%)
*GI hemorrhage (upper and lower GI tract)**	7 (2%)	3 (1%)
Rectal hemorrhage (includes hemorrhagic diarrhea)	7 (2%)	3 (1%)
Tongue ulceration	2 (< 1%)	1 (< 1%)
Retching	3 (< 1%)	2 (< 1%)
Upper GI hemorrhage	1 (< 1%)	-
Hematemesis	1 (< 1%)	-
Oral mucosal petechiae	3 (< 1%)	-
Ileus Paralytic	1 (< 1%)	2 (< 1%)
General disorders and administration site conditions		
Asthenic conditions	201 (61%)	149 (65%)
Weakness	40 (12%)	44 (19%
Fatigue	140 (42%)	118 (52%)
Lethargy	12 (4%)	9 (4%)
Malaise	13 (4%)	22 (10%)
Pyrexia	116 (35%)	82 (36%)
Rigors	37 (11%)	27 (12%)
Edema of the lower limbs	35 (11%)	27 (12%)
Neuralgia	21 (6%)	5 (2%)
Chest Pain	26 (8%)	16 (7%)
Injection site pain and irritation	1 (< 1%)	1 (< 1%)
Injection site phlebitis	1 (< 1%)	1 (< 1%)
Hepatobiliary disorders		
Hyperbilirubinemia	1 (< 1%)	-
Abnormal liver function tests	3 (< 1%)	2 (< 1%)
Hepatitis	2 (< 1%) in study M34101-040‡	-
Immune system disorders		
Drug hypersensitivity	1 (< 1%)	1 (< 1%)
Infections and infestations		
Upper respiratory tract infection	26 (8%)	41 (18%)
Nasopharyngitis	45 (14%)	17 (7%)
Lower respiratory tract and lung infections	48 (15%)	29 (13%)
*Pneumonia**	21 (6%)	23 (10%)

Body System:	**Study No.**	
	039 (N = 331)	024/025 (N = 228†)
Herpes zoster (including multidermatomal or disseminated)	42 (13%)	26 (11%)
Herpes simplex	25 (8%)	13 (6%)
Bronchitis	26 (8%)	6 (3%)
Postherpetic neuralgia	4 (1%)	1 (< 1%)
Sinusitis	14 (4%)	15 (7%)
Pharyngitis	6 (2%)	2 (< 1%)
Oral candidiasis	6 (2%)	3 (1%)
Urinary tract infection	13 (4%)	14 (6%)
Catheter related infection	10 (3%)	6 (3%)
*Sepsis and bacteremia**	9 (3%)	9 (4%)
Gastroenteritis	7 (2%)	-
Injury, poisoning, and procedural complications		
Catheter related complication	7 (2%)	8 (4%)
Investigations		
Increased ALT	3 (< 1%)	10 (4%)
Increased AST	5 (2%)	12 (5%)
Increased alkaline phosphatase	6 (2%)	8 (4%)
Increased GGT	1 (< 1%)	4 (2%)
Metabolism and nutritional disorders		
Decreased appetite and anorexia	112 (34%)	99 (43%)
Dehydration	24 (7%)	42 (18%)
Hyperglycemia	5 (2%)	16 (7%)
Hypoglycemia	7 (2%)	4 (2%)
Hyponatremia	8 (2%)	18 (8%)
Tumor Lysis Syndrome	2 (< 1%) in study M34101-040‡	-
Musculoskeletal and connective tissue disorders		
Pain in limb	50 (15%)	59 (26%)
Myalgia	39 (12%)	32 (14%)
Arthralgia	45 (14%)	60 (26%)
Nervous system disorders		
Peripheral neuropathy§	120 (36%)	84 (37%)
Paresthesia and dysesthesia	91 (27%)	53 (23%)
Dizziness, excluding vertigo	45 (14%)	48 (21%)
Headache	85 (26%)	63 (28%)
Dysgeusia	17 (5%)	29 (13%)
Polyneuropathy	9 (3%)	1 (< 1%)
Syncope	8 (2%)	17 (7%)
Convulsions	4 (1%)	-
Loss of consciousness	2 (< 1%)	-
Ageusia	2 (< 1%)	-
Psychiatric disorders		

Body System:	Study No.	
	039 (N = 331)	024/025 (N = 228†)
Anxiety	31 (9%)	32 (14%)
Renal and urinary disorders		
Renal Impairment and Failure	21 (6%)	21 (9%)
Difficulty in micturition	2 (1%)	3 (1%)
Hematuria	5 (2%)	4 (2%)
Respiratory, thoracic, and mediastinal disorders		
Epistaxis	21 (6%)	23 (10%)
Cough	70 (21%)	39 (17%)
Dyspnea	65 (20%)	50 (22%)
Exertional dyspnea	21 (6%)	18 (8%)
Pleural effusion	4 (1%)	9 (4%)
Rhinorrhea	4 (1%)	14 (6%)
Hemoptysis	3 (< 1%)	2 (< 1%)
Skin and subcutaneous tissue disorders		
Skin rash, which can be pruritic, erythematous, and can include evidence of leukocytoclastic vasculitis	61 (18%)	47 (21%)
Urticaria	7 (2%)	5 (2%)
Vascular disorders		
Hypotension	20 (6%)	27 (12%)
Orthostatic/postural hypotension	14 (4%)	8 (4%)
Petechiae	6 (2%)	7 (3%)
*Cerebral hemorrhage**	1 (< 1%)	-

† All 228 patients received VELCADE® at a dose of 1.3 mg/m^2

* includes fatal outcome

‡ A study of VELCADE® at the recommended dose of 1.3 mg/m^2 in multiple myeloma patients who experienced progressive disease after receiving at least four previous therapies or after receiving high-dose dexamethasone in Protocol M34101-039

§ including all preferred terms under the MedDRA HLT "peripheral neuropathy NEC"

Summary of Clinical Trials in patients with previously untreated multiple myeloma:

The following table describes safety data from 340 patients with previously untreated multiple myeloma who received VELCADE® IV (1.3 mg/m^2) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in a prospective phase 3 study.

Table 7: Treatment Emergent Drug-Related Adverse Events reported in ≥ 10% of patients treated with VELCADE® IV in combination with melphalan and prednisone

	Vc-MP (n = 340)			MP (n = 337)		
MedDRA System Organ Class	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
Preferred Term	n (%)	3	≥ 4	n (%)	3	≥ 4
Blood and Lymphatic System Disorders						
Thrombocytopenia	164 (48)	60 (18)	57 (17)	140 (42)	48 (14)	39 (12)
Neutropenia	160 (47)	101 (30)	33 (10)	143 (42)	77 (23)	42 (12)
Anemia	109 (32)	41 (12)	4 (1)	156 (46)	61 (18)	18 (5)
Leukopenia	108 (32)	64 (19)	8 (2)	93 (28)	53 (16)	11 (3)
Lymphopenia	78 (23)	46 (14)	17 (5)	51 (15)	26 (8)	7 (2)

Gastrointestinal Disorders						
Nausea	134 (39)	10 (3)	0	70 (21)	1 (< 1)	0
Diarrhea	119 (35)	19 (6)	2 (1)	20 (6)	1 (< 1)	0
Vomiting	87 (26)	13 (4)	0	41 (12)	2 (1)	0
Constipation	77 (23)	2 (1)	0	14 (4)	0	0
Abdominal Pain Upper	34 (10)	1 (< 1)	0	20 (6)	0	0
Nervous System Disorders						
Peripheral Neuropathy	156 (46)	42 (12)	2 (1)	4 (1)	0	0
Neuralgia	117 (34)	27 (8)	2 (1)	1 (< 1)	0	0
Paresthesia	42 (12)	6 (2)	0	4 (1)	0	0
General Disorders and Administration Site Conditions						
Fatigue	85 (25)	19 (6)	2 (1)	48 (14)	4 (1)	0
Asthenia	54 (16)	18 (5)	0	23 (7)	3 (1)	0
Pyrexia	53 (16)	4 (1)	0	19 (6)	1 (< 1)	1 (< 1)
Infections and Infestations						
Herpes Zoster	39 (11)	11 (3)	0	9 (3)	4 (1)	0
Metabolism and Nutrition Disorders						
Anorexia	64 (19)	6 (2)	0	19 (6)	0	0
Skin and Subcutaneous Tissue Disorders						
Rash	38 (11)	2 (1)	0	7 (2)	0	0
Psychiatric Disorders						
Insomnia	35 (10)	1 (< 1)	0	21 (6)	0	0

Herpes zoster virus reactivation:

Physicians should consider using antiviral prophylaxis in patients being treated with VELCADE®. In the phase 3 study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in patients treated with VcMP compared with MP (14% vs 4% respectively). Antiviral prophylaxis was administered to 26% of the patients in the VcMP arm. The incidence of herpes zoster among patients in the VcMP treatment group was 17% for patients not administered antiviral prophylaxis compared to 3% for patients administered antiviral prophylaxis.

Patients with mantle cell lymphoma:

Safety data for patients with mantle cell lymphoma were evaluated in a phase 2 study, which included 155 patients treated with VELCADE® at the recommended dose of 1.3 mg/m^2. The safety profile of VELCADE® in these patients was similar to that observed in patients with multiple myeloma. Notable differences between the two patient populations were that thrombocytopenia, neutropenia, anemia, nausea, vomiting and pyrexia were reported more often in the patients with multiple myeloma than in those with mantle cell lymphoma; whereas peripheral neuropathy, rash and pruritus were higher among patients with mantle cell lymphoma compared to patients with multiple myeloma.

Post-Marketing Experience

Clinically significant adverse drug reactions are listed here if they have not been reported above.

The frequencies provided below reflect reporting rates of adverse drug reactions from the worldwide post-marketing experience with VELCADE®. The frequencies provided below reflect reporting rates and precise estimates of incidence cannot be made. These adverse drug reactions are ranked by frequency, using the following convention: Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1000 and < 1/100), rare (≥ 1/10000 and < 1/1000), very rare (< 1/10000, including isolated reports).

Table 8: Post-marketing Reports of Adverse Reactions

Blood and lymphatic system disorders	
Disseminated intravascular coagulation	Rare
Cardiac Disorders	
Atrioventricular block complete, cardiac tamponade	Rare
Ear and labyrinth disorders	
Deafness bilateral	Rare
Eye Disorders	
Ophthalmic herpes, optic neuropathy, blindness	Rare
Gastrointestinal Disorders	
Ischemic colitis, acute pancreatitis	Rare
Infections and infestations	
Herpes meningoencephalitis, septic shock	Rare
Progressive multifocal leukoencephalopathy	Very rare
Immune System Disorders	
Angioedema	Rare
Nervous System Disorders	
Encephalopathy, autonomic neuropathy, reversible posterior leukoencephalopathy syndrome	Rare
Respiratory, thoracic and mediastinal disorders	
Acute diffuse infiltrative pulmonary disease *Pulmonary hypertension*	Rare Rare
Skin and subcutaneous tissue disorders	
Stevens-Johnson Syndrome and toxic epidermal necrolysis	Very Rare
Acute febrile neutrophilic dermatosis (Sweet's syndrome)	Rare

Overdose

Cardiovascular safety pharmacology studies in monkeys and dogs show that IV doses approximately two to three times the recommended clinical dose on a mg/m^2 basis are associated with increases in heart rate, decreases in contractility, hypotension and death. The decreased cardiac contractility and hypotension responded to acute intervention with positive inotropic or pressor agents. In dog studies, a slight increase in the corrected QT interval was observed at a lethal dose.

Overdosage more than twice the recommended dose has been associated in patients with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes.

There is no known specific antidote for VELCADE® overdosage. In the event of an overdosage, the patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or inotropic agents) and body temperature **(**see Warnings and Precautions and Dosage and Administration**).**

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

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.

Data from *in vitro*, *ex-vivo*, and animal models with bortezomib suggest that it increases osteoblast differentiation and activity and inhibits osteoclast function. These effects have been observed in patients with multiple myeloma affected by an advanced osteolytic disease and treated with bortezomib.

Clinical Trials

Phase 2 Clinical Studies in Relapsed Multiple Myeloma:

The safety and efficacy of VELCADE® IV were evaluated in an open-label, single-arm, multicenter study of 202 patients who had received at least 2 prior therapies and demonstrated disease progression on their most recent therapy. The median number of prior therapies was six. Baseline patient and disease characteristics are summarized in **Table 9**.

An IV bolus injection of VELCADE® 1.3 mg/m^2/dose was administered twice weekly for 2 weeks, followed by a 10-day rest period (21 day treatment cycle) for a maximum of 8 treatment cycles. The study employed dose modifications for toxicity (see Dosage and Administration). Patients who experienced a response to VELCADE® treatment were allowed to continue VELCADE® treatment in an extension study.

Table 9: Summary of Multiple Myeloma Patient Population and Disease Characteristics*

	N = 202
Patient Characteristics	
Median age in years (range)	59 (34, 84)
Gender: male/female	60% / 40%
Race: Caucasian/black/other	81% / 10% /8%
Karnofsky Performance Status score ≤ 70	20%
Hemoglobin < 100 g/l	44%
Platelet count < 75 x 10^9/l	21%
Disease Characteristics	
Type of myeloma (%): IgG/IgA/Light chain	60% / 24% / 14%
Median β_2-microglobulin (mg/l)	3.5
Median creatinine clearance (ml/min)	73.9
Abnormal cytogenetics	35%
Chromosome 13 deletion	15%

Median Duration of Multiple Myeloma Since Diagnosis in Years	4.0
Previous Therapy	
Any prior steroids, e.g., dexamethasone, VAD	99%
Any prior alkylating agents, e.g., MP, VBMCP	92%
Any prior anthracyclines, e.g., VAD, mitoxantrone	81%
Any prior thalidomide therapy	83%
Received at least 2 of the above	98%
Received at least 3 of the above	92%
Received all 4 of the above	66%
Any prior stem cell transplant/other high-dose therapy	64%
Prior experimental or other types of therapy	44%

* Based on number of patients with baseline data available

Responses to VELCADE® alone are shown in **Table 10**. Response rates to VELCADE® alone were determined by an independent review committee (IRC) based on criteria published by Bladé and others.[1] Complete response required < 5% plasma cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test (IF^-). Response rates using the SWOG criteria are also shown. SWOG response required a ≥ 75% reduction in serum myeloma protein and/or ≥ 90% urine protein.[2] A total of 188 patients were evaluated for response; 9 patients with nonmeasurable disease could not be evaluated for response by the IRC. Five patients were excluded from the efficacy analyses because they had minimal prior therapy.

Ninety-eight percent of study patients received a starting dose of 1.3 mg/m^2 administered IV. Twenty-eight percent of these patients received a dose of 1.3 mg/m^2 throughout the study, while 33% of patients who started at a dose of 1.3 mg/m^2 had to have their dose reduced during the study. Sixty-three percent of patients had at least one dose held during the study. In general, patients who had a confirmed CR received 2 additional cycles of VELCADE® treatment beyond confirmation. It was recommended that responding patients receive up to 8 cycles of VELCADE® therapy. The mean number of cycles administered was six.

The median time to response was 38 days (range 30 to 127 days).

The median survival of all patients enrolled was 16 months (range < 1 to 18 + months).

Table 10: Summary of Disease Outcomes

Response Analyses (VELCADE® monotherapy) N = 188	**N (%)**	**(95% CI)**
Overall Response Rate (Bladé) (CR + PR)	52 (27.7%)	(21, 35)
Complete Response (CR)[1]	5 (2.7%)	(1, 6)
Partial Response (PR)[2]	47 (25%)	(19, 32)
Clinical Remission (SWOG)[3]	33 (17.6%)	(12, 24)
Kaplan-Meier Estimated Median Duration of Response (95% CI)	365 Days	(224, NE)

[1] **Complete Response** required < 5% plasma cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test (IF^-).

[2] **Partial Response** 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, stable bone disease and calcium.

[3] **Clinical Remission (SWOG)** required ≥ 75% reduction in serum myeloma protein and/or ≥ 90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.

In this study, the response rate to VELCADE® was independent of the number and types of prior therapies. There was a decreased likelihood of response in patients with either > 50% plasma cells or abnormal cytogenetics in the bone marrow. Responses were seen in patients with chromosome 13 abnormalities.

A small dose-response study was performed in 54 patients with multiple myeloma who received

a 1.0 mg/m^2/dose or a 1.3 mg/m^2/dose twice weekly for two out of three weeks. A single complete response was seen at each dose, and there were overall (CR + PR) response rates of 30% (8/27) at 1.0 mg/m^2 and 38% (10/26) at 1.3 mg/m^2.

Patients who did not obtain an optimal response to therapy with VELCADE® alone (progressive or stable disease after 2 or 4 cycles, respectively) were able to receive high-dose dexamethasone in conjunction with VELCADE® (i.e., 40 mg dexamethasone with each dose of VELCADE® administered orally as 20 mg on the day of and 20 mg the day after VELCADE® administration, (i.e., Days 1, 2, 4, 5, 8, 9, 11, and 12), thus 160 mg over 3 weeks). A total of 74 patients were administered dexamethasone in combination with VELCADE® and were assessed for response. Eighteen percent (13/74) of patients achieved or had an improved response (CR 11% or PR 7%) with combination treatment.

Randomized, Open-Label Clinical Study in Relapsed Multiple Myeloma comparing VELCADE® to Dexamethasone:

A prospective phase 3, international, randomized (1:1), stratified, open-label clinical trial 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 < 50000/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 ($\leq$ 2.5 mg/l versus > 2.5 mg/l).

Baseline patient and disease characteristics are summarized in **Table 11**.

Table 11: Summary of Baseline Patient and Disease Characteristics in the Phase 3 Multiple Myeloma Trial

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%

All Patients	(N = 333)	(N = 336)
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®. Within each 3-week treatment cycle, VELCADE® 1.3 mg/m^2/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^2/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).

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

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 phase 3 trial are presented in **Table 12**. Response and progression were assessed using the European Group for Blood and Marrow Transplantation (EBMT) criteria.[1] 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 12: Summary of Efficacy Analyses in the Multiple Myeloma Randomized Phase 3 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] (95% CI)	6.2 mo (4.9, 6.9)	3.5 mo (2.9, 4.2)	7.0 (6.2, 8.8)	5.6 (3.4, 6.3)	4.9 (4.2, 6.3)	2.9 (2.8, 3.5)
Hazard ratio [b] (95% CI)	0.55 (0.44, 0.69)		0.55 (0.38, 0.81)		0.54 (0.41, 0.72)	
p-value [c]	< 0.0001		0.0019		< 0.0001	
Overall Survival Events (deaths) n (%)	51(15)	84(25)	12(9)	24(20)	39(20)	60(28)
Hazard ratio [b] (95% CI)	0.57 (0.40, 0.81)		0.39 (0.19, 0.81)		0.65 (0.43, 0.97)	
p-value [c,d]	< 0.05		< 0.05		< 0.05	
Response Rate population[e] n = 627	n = 315	n = 312	n = 128	n = 110	n = 187	n = 202
CR[f] n (%)	20(6)	2(< 1)	8(6)	2(2)	12(6)	0(0)
PR[f] n(%)	101(32)	54(17)	49(38)	27(25)	52(28)	27(13)
nCR[f,g] n(%)	21(7)	3(< 1)	8(6)	2(2)	13(7)	1(< 1)
CR + PR[f] n (%)	121 (38)	56 (18)	57(45)	29(26)	64(34)	27(13)
p-value [h]	< 0.0001		0.0035		< 0.0001	
Median Response Duration						
CR[f]	9.9 mo	NE[i]	9.9 mo	NE	6.3 mo	NA[j]
nCR[f]	11.5 mo	9.2 mo	NE	NE	11.5 mo	9.2 mo
CR + PR[f]	8.0 mo	5.6 mo	8.1 mo	6.2 mo	7.8 mo	4.1 mo

[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[1]; 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.

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

A prospective phase 3, international, randomized (1:1), open-label clinical study of 682 patients was conducted to determine whether VELCADE® (1.3 mg/m^2) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) resulted in improvement in time to progression (TTP)

when compared to melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in patients with previously untreated multiple myeloma. This study included patients who were not candidates for stem-cell transplant. Treatment was administered for a maximum of 9 cycles (approximately 54 weeks) and was discontinued early for disease progression or unacceptable toxicity. Baseline demographics and patient characteristics are summarized in **Table 13**.

Table 13: Summary of Baseline Patient and Disease Characteristics in the VISTA Study

Patient Characteristics	**VMP N = 344**	**MP N = 338**
Median age in years (range)	71.0 (57, 90)	71.0 (48, 91)
Gender: male/female	51% / 49%	49% / 51%
Race: Caucasian/asian/black/other	88% / 10% / 1% / 1%	87% / 11% / 2% / 0%
Karnofsky performance status score ≤ 70	35%	33%
Hemoglobin < 100 g/l	37%	36%
Platelet count < 75 x 10^9/l	< 1%	1%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	64% / 24% / 8%	62% / 26% / 8%
Median β_2-microglobulin (mg/l)	4.2	4.3
Median albumin (g/l)	33.0	33.0
Creatinine clearance ≤ 30 ml/min [n (%)]	20 (6%)	16 (5%)

At the time of a pre-specified interim analysis, the primary endpoint, time to progression, was met and patients in the MP arm were offered VcMP treatment. Median follow-up was 16.3 months. The final survival update was performed with a median duration of follow-up at 60.1 months. A statistically significant survival benefit in favor of the VcMP treatment group was observed (HR = 0.695; p = 0.00043) despite subsequent therapies that included VELCADE® based regimens. The median survival in MP treatment group has been estimated at 43.1 months, and the median survival on the VcMP treatment group has been estimated at 56.4 months. Efficacy results are presented in **Table 14**.

Table 14: Summary of Efficacy Analyses in the VISTA study

Efficacy Endpoint	**VMP n = 344**	**MP n = 338**
Time to Progression – Events n (%)	101 (29)	152 (45)
Median[a] (95% CI)	20.7 mo (17.6, 24,7)	15.0 mo (14.1, 17.9)
Hazard ratio[b] (95% CI)	0.54 (0.42, 0.70)	
p-value[c]	0.000002	
Progression-free Survival Events n (%)	135 (39)	190 (56)
Median[a] (95% CI)	18.3 mo (16.6, 21.7)	14.0 mo (11.1, 15.0)
Hazard ratio[b] (95% CI)	0.61 (0.49, 0.76)	
p-value[c]	0.00001	
Overall Survival* Events (deaths) n (%)	176 (51.2)	211 (62.4)
Median[a] (95% CI)	56.4 mo (52.8, 60.9)	43.1 mo (35.3, 48.3)
Hazard ratio[b] (95% CI)	0.695 (0.567, 0.852)	
p-value[c]	0.00043	

Efficacy Endpoint	VMP n = 344	MP n = 338
Response Rate Population[e] n = 668	**n = 337**	**n = 331**
CR[f] n (%)	102 (30)	12 (4)
PR[f] n (%)	136 (40)	103 (31)
nCR n (%)	5 (1)	0
CR + PR[f] n (%)	238 (71)	115 (35)
p-value[d]	$<10^{-10}$	
Reduction in Serum M-protein Population[g] n = 667	n = 336	n = 331
> = 90% n (%)	151 (45)	34 (10)
Time to First Response in CR + PR		
Median	1.4 mo	4.2 mo
Median[a] Response Duration		
CR[f]	24.0 mo	12.8 mo
CR + PR[f]	19.9 mo	13.1 mo
Time to Next Therapy Events n (%)	224 (65.1)	260 (76.9)
Median[a] (95% CI)	27.0 mo (24.7, 31.1)	19.2 mo (17.0, 21.0)
Hazard ratio[b] (95% CI)	0.557 (0.462, 0.671)	
p-value[c]	(< 0.000001)	

Note: All results are based on the analysis performed at a median follow-up duration of 16.3 months except for the overall survival analysis that was performed at a median follow-up duration of 60.1 months.

[a] Kaplan-Meier estimate.

[b] 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 VMP

[c] Nominal p-value based on the stratified log-rank test adjusted for stratification factors: beta2-microglobulin, albumin, and region

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

[e] Response population includes patients who had measurable disease at baseline

[f] EBMT criteria

[g] All randomized patients with secretory disease

* Survival update based on a median duration of follow-up at 60.1 months

NE: Not estimable

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. VELCADE® was administered at the recommended dose of 1.3 mg/m^2. The median number of cycles administered across all patients was 4 (range 1-17); and 8 in responding patients. Response rates to VELCADE® are described in **Table 15**.

Table 15: Summary of Disease Outcomes in a Phase 2 Mantle Cell Lymphoma Study

*Response Analyses (N = 141)	N (%)	95% CI
Overall Response Rate (IWRC) (CR + CRu + PR)	47 (33)	(26, 42)
Complete Response (CR + CRu)	11 (8)	(4, 14)
CR	9 (6)	(3, 12)
CRu	2 (1)	(0, 5)
Partial Response (PR)	36 (26)	(19, 34)
Time to Event Analyses	**Median**	**95% CI**
Kaplan-Meier Estimated Duration of Response		
CR + CRu + PR (N = 47)	9.2 months	(4.9, 13.5)
CR + CRu (N = 11)	13.5 months	(13.5, NE)
Kaplan-Meier Estimated Time to Progression (N = 155)	6.2 months	(4.0, 6.9)
**Kaplan-Meier Estimated Treatment-free Interval, CR + CRu (N = 11)	13.8 months	(13.4, NE)
Median Time to Next Treatment		
CR + CRu + PR (N = 47)	12.7 months	(9.33, NE)
CR + CRu (N = 11)	19.4 months	(17.8, NE)

*Based on International Response Workshop Criteria (IRWC).
CRu = Complete Response unconfirmed
NE = not estimable, **Additional analyses

With a median duration of follow-up of more than 13 months in surviving patients, the median survival had not yet been reached and the Kaplan Meier estimate of 1-year survival was 69%. The Kaplan-Meier estimate of 1-year survival was 94% in responders and 100% in those achieving CR or CRu.

Patients with previously treated light-chain (AL) Amyloidosis

A Phase 1/2 study was conducted to determine the safety and efficacy of VELCADE® in patients with previously treated light-chain (AL) Amyloidosis. No new safety concerns were observed during the study, and in particular VELCADE® did not exacerbate target organ damage (heart, kidney and liver). In 49 evaluable patients treated at 1.6 mg/m^2 weekly or 1.3 mg/m^2 twice-weekly, a 67.3% response rate (including a 28.6% CR rate) as measured by hematological response (M-protein) was reported. For these dose cohorts, the combined 1-year survival rate was 88.1%.

Pediatric Use

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

Geriatric Use

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.

Pharmacokinetic Properties

Pharmacokinetics

Following intravenous bolus administration of a 1.0 mg/m^2 and 1.3 mg/m^2 dose to eleven patients with multiple myeloma, the mean first-dose maximum plasma concentrations of bortezomib were 57 and 112 ng/ml, respectively. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/ml for the 1.0 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 40-193 hours. Bortezomib is eliminated more rapidly following the first dose

compared to subsequent doses. Mean total body clearances were 102 and 112 l/h following the first dose for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 l/h following subsequent doses for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively.

Distribution

The mean distribution volume of bortezomib ranged from 1659 liters to 3294 liters (489 to 1884 l/m^2) following single- or repeat-dose IV administration of 1.0 mg/m^2 or 1.3 mg/m^2 to patients with multiple myeloma. This suggests that bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100-1000 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 two 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 IV dosing indicate that the plasma levels of metabolites are low compared to the parent drug.

Elimination

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

Special Populations

Age, Gender, and Race

The effects of age, gender, and race on the pharmacokinetics of bortezomib have not been evaluated.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of IV bortezomib was assessed in 60 cancer patients at bortezomib doses ranging from 0.5 to 1.3 mg/m^2. When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-normalized bortezomib AUC. However, the dose-normalized mean AUC values were increased by approximately 60% in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients should be monitored closely.

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 $\geq$ 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 Dosage and Administration).

NON-CLINICAL INFORMATION

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.

PHARMACEUTICAL INFORMATION

List of Excipients

Mannitol (E421) 35 mg USP/EP

Incompatibilities

This product must not be mixed with other medicinal products except those mentioned in Instructions for Use and Handling and Disposal.

Shelf Life

See expiry date on the outer pack.

Storage Conditions

VELCADE® contains no antimicrobial preservative. When reconstituted as directed, VELCADE® may be stored at 25ºC. Reconstituted VELCADE® should be administered within 8 hours of preparation. The reconstituted material may be stored for up to 8 hours in the original vial or in a syringe. The total storage time for the reconstituted material must not exceed 8 hours when exposed to normal indoor lighting.

Do not store unopened vials above 30ºC. Retain in original package to protect from light.

Keep out of reach of children.

Nature and Contents of Container

Ten (10) ml, type 1, glass vial with a gray bromobutyl stopper and aluminum seal. The cap color of the 10 ml vial is royal blue. Each vial is contained in a transparent blister pack consisting of a tray with a lid. One vial contains 38.5 mg powder for solution for injection.

VELCADE® is available in cartons containing 1 single-use vial.

Instructions for Use and Handling

Administration Precautions

VELCADE® is an antineoplastic. Caution should be used during handling and preparation. Proper aseptic technique should be used. Use of gloves and other protective clothing to prevent skin contact is recommended. In clinical trials, local skin irritation was reported in 5% of patients, but extravasation of VELCADE® was not associated with tissue damage.

There have been fatal cases of inadvertent intrathecal administration of VELCADE®. VELCADE® is for IV use only**. DO NOT ADMINISTER VELCADE® INTRATHECALLY.**

Reconstitution/Preparation for Intravenous Administration

Prior to use, the contents of each 10 ml vial must be reconstituted with 3.5 ml of normal (0.9%) saline, Sodium Chloride Injection, USP. 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.

Instructions for Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

MANUFACTURED BY

See outer carton.

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