

PRODUCT MONOGRAPH

PrVELCADE*

bortezomib mannitol boronic ester for Injection

3.5 mg/vial bortezomib

Antineoplastic Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Pharmaceutical Form / Strength	Clinically Relevant Nonmedicinal Ingredients
intravenous	sterile lyophilized powder for injection/3.5 mg	None

VELCADE (bortezomib mannitol boronic ester) for Injection will be referenced throughout the Product Monograph as either VELCADE (bortezomib) for Injection, VELCADE or bortezomib.

INDICATIONS AND CLINICAL USE

VELCADE (bortezomib) for Injection is indicated as follows:

- as part of combination therapy for the treatment of patients with previously untreated multiple myeloma who are unsuitable for stem cell transplantation.
- for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for stem cell transplantation.
- for the treatment of patients with mantle cell lymphoma who have relapsed or were refractory to at least 1 prior therapy.

Geriatrics (> 65 years of age):

No overall differences in safety or effectiveness of VELCADE were observed between younger patients and patients \geq 65 years of age. Greater sensitivity of some older individuals cannot be ruled out (see **ADVERSE REACTIONS, ACTION AND CLINICAL PHARMACOLOGY**, and *Product Monograph PART II, CLINICAL TRIALS*).

Pediatrics and Adolescents (< 18 years of age):

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

CONTRAINDICATIONS

VELCADE (bortezomib) for Injection is contraindicated in patients with hypersensitivity to bortezomib, boron or any of the excipients.

WARNINGS AND PRECAUTIONS**Serious Warnings and Precautions**

- VELCADE must be administered under the supervision of a physician qualified in the use of antineoplastic agents.
- Twice the recommended dose has been fatal (see **WARNINGS AND PRECAUTIONS, General**)
- Hypotension and other serious cardiac disorders (see **WARNINGS AND PRECAUTIONS, Cardiovascular**, and **ADVERSE REACTIONS, Randomized Open-Label Phase III Clinical Study**)
- Hemorrhage (gastrointestinal and intracerebral) (see **WARNINGS AND PRECAUTIONS, Hematologic** and **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**)
- Severe motor neuropathy, including fatalities (see **WARNINGS AND PRECAUTIONS, Neurologic**)
- Acute diffuse infiltrative pulmonary disease (see **WARNINGS AND PRECAUTIONS, Respiratory**)

General**Dose Preparation:**

VELCADE (bortezomib) for Injection has a narrow therapeutic window and has shown high acute toxicity in all animal species evaluated. Fatalities have been reported after accidental administration of at least twice the recommended dose in patients (see **OVERDOSAGE**). Careful attention is required to ensure the recommended dose is not exceeded.

Tumour Lysis Syndrome:

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

Carcinogenesis and Mutagenesis

Carcinogenicity studies have not been conducted. Bortezomib was clastogenic in mammalian cells in the *in vitro* chromosomal aberration assay. Bortezomib was not mutagenic in bacteria (Ames assay) and in the *in vivo* micronucleus assay in mice (see **Product Monograph PART II, TOXICOLOGY**).

Cardiovascular

VELCADE treatment is commonly associated with orthostatic/postural hypotension which is not an acute reaction and is observed throughout treatment (see **ADVERSE REACTIONS**). In the Phase II and III relapsed multiple myeloma studies, the incidence of hypotension (postural, orthostatic, and hypotension NOS) was 11% and 12%, respectively. In the Phase II study, there was no prior history of orthostatic hypotension in these patients but half had pre-existing hypertension, one-third had evidence of peripheral neuropathy, and orthostatic hypotension was associated with syncope in some patients. In another Phase II study, there was evidence of autonomic nervous system abnormalities following VELCADE therapy. The mechanism is unknown although it may be due to bortezomib-induced autonomic neuropathy. Most cases required pharmacological treatment, including hydration and/or adjustment of antihypertensive medications. Administration of mineralocorticoids and/or sympathomimetics was infrequently required. 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. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells.

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.

There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.

Events of pericarditis (<1%) have been reported in clinical trials and during post-marketing use of VELCADE. New or worsening cases of pericarditis should be investigated promptly.

In the Phase III relapsed multiple myeloma study, the incidence of any treatment-emergent cardiac disorder was 15% and 13% in the VELCADE and dexamethasone groups, respectively. The incidence of heart failure events (acute pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock, pulmonary edema) was similar in the VELCADE and dexamethasone groups, 5% and 4%, respectively.

Gastrointestinal

Gastrointestinal events, including nausea, diarrhea, constipation, and vomiting occur frequently during VELCADE treatment (see **ADVERSE REACTIONS**). Events usually occur earlier in treatment (Cycles 1 and 2), and may persist for several cycles, sometimes requiring administration of antiemetics and antidiarrheals. Fluid and electrolyte replacement should be

administered if the patient becomes dehydrated. Cases of ileus have been reported and patients who experience constipation should be closely monitored.

Hematologic

Although VELCADE treatment may be associated with hematological toxicities, significant myelosuppression is uncommon (see **ADVERSE REACTIONS**). The most common hematological toxicity is thrombocytopenia which is generally dose related, occurring during Days 1 to 11 of therapy, with a return to baseline in platelet count during the rest period (Days 12 to 21) in each treatment cycle. Onset is common in Cycles 1 and 2 but can continue throughout therapy. On average, the pattern of platelet count decrease and recovery remained consistent over the 8-cycle study period 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 1.1. In the Phase III relapsed multiple myeloma study, the incidence of significant bleeding events (\geq Grade 3) was similar on both the VELCADE (4%) and dexamethasone (5%) arms. Platelet count should be monitored prior to each dose of VELCADE. VELCADE therapy should be held when the platelet count is $< 25 \times 10^9/L$ and re-initiated at a reduced dose. There have been reports of gastrointestinal and intracerebral hemorrhage in association with VELCADE induced thrombocytopenia (see **DOSAGE AND ADMINISTRATION** and **ADVERSE REACTIONS**). Platelet transfusions, red blood cell transfusions and administration of growth factors may be utilized in the management of hematological toxicities.

Table 1.1: The Severity of Thrombocytopenia Related to Pre-Treatment Platelet Count in the Phase III relapsed multiple myeloma Study

Pre-treatment Platelet Count[†]	Number of Patients (N=331)[‡]	Number (%) of Patients with Platelet Count $<10 \times 10^9/L$	Number (%) of Patients with Platelet Count $10 \times 10^9 - 25 \times 10^9/L$
$\geq 75 \times 10^9/L$	309	8 (3%)	36 (12%)
$\geq 50 \times 10^9/L - <75 \times 10^9/L$	14	2 (14%)	11 (79%)
$\geq 10 \times 10^9/L - <50 \times 10^9/L$	7	1 (14%)	5 (71%)

[†] A baseline platelet count of $50 \times 10^9/L$ was required for study eligibility.

[‡] Data were missing at baseline for 1 patient.

Hepatic/Biliary

Bortezomib is metabolized by liver enzymes and bortezomib's clearance may decrease in patients with hepatic impairment. No formal studies evaluating the effect of liver dysfunction on the pharmacokinetics or pharmacodynamics of VELCADE have been completed. These patients should be treated with extreme caution and monitored for toxicity, and a dose reduction should be considered (see **DOSAGE AND ADMINISTRATION**).

Rare cases of acute liver failure have been reported in VELCADE-treated patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic events include asymptomatic 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.

Neurologic

Treatment with VELCADE is commonly associated with peripheral neuropathy that is predominantly sensory. However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported, including those with fatal outcomes. Rare cases of Guillain-Barré syndrome without established causal relationship to VELCADE and aspiration pneumonia in association with motor neuropathy have also been reported.

In clinical trials, of the patients who experienced treatment-emergent neuropathy, 70% had previously been treated with neurotoxic agents and 80% had signs or symptoms of peripheral neuropathy at baseline. Worsening of existing neuropathy is dose related and cumulative. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy (hyperesthesia, hypoesthesia, paresthesia, neuropathic pain or weakness) may experience worsening during treatment with VELCADE and it is recommended that all patients should be monitored for symptoms of neuropathy.

Complete resolution to baseline has been documented in 14% of patients with severe symptoms in the Phase II studies, with limited follow-up data available. In the Phase III relapsed multiple myeloma study, following dose adjustments, improvement in or resolution of peripheral neuropathy was reported in 51% of patients with \geq Grade 2 peripheral neuropathy, and the median time to improvement or resolution was 107 days. VELCADE was discontinued because of peripheral neuropathy in 8% of patients in the Phase III study, and was the most common adverse event leading to treatment discontinuation. Improvement in or resolution of peripheral neuropathy was reported in 71% of patients who discontinued due to peripheral neuropathy or who had \geq Grade 3 peripheral neuropathy in the Phase II multiple myeloma studies (see **ADVERSE REACTIONS**). The mechanism underlying VELCADE induced peripheral neuropathy is not known and the complete time-course of this toxicity has not been fully characterized. Full reversibility has not been demonstrated in preclinical studies (see **Product Monograph PART II, TOXICOLOGY**).

Patients experiencing new or worsening peripheral neuropathy may require a change in the dose and schedule or cessation of VELCADE therapy (see **DOSAGE AND ADMINISTRATION**).

Autonomic neuropathy may contribute to some adverse reactions, such as postural hypotension, diarrhea, constipation with ileus and pyrexia, but information on this is limited.

Seizures are uncommonly reported in patients without previous history of seizures. Caution should be exercised when treating patients with any risk factors.

There have been rare reports of reversible posterior leukoencephalopathy syndrome (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.

Renal

Hypercalcemia and renal failure are complications of multiple myeloma most often associated with high tumour burden. Supportive treatments for these complications include bisphosphonates (for hypercalcemia and myeloma bone disease), hydration and other measures depending on the patient's status and the type and severity of the complications (see ***Product Monograph PART II, CLINICAL TRIALS***).

VELCADE has not been formally studied in patients with impaired renal function. Limited clinical information is available on the use of VELCADE in patients with varying degrees of impaired renal function (see ***Product Monograph PART II, CLINICAL TRIALS***). No clinical information is available on the use of VELCADE in patients on hemodialysis. Patients with renal impairment, especially if creatinine clearance is ≤ 30 mL/min, should be closely monitored for toxicities when treated with VELCADE (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Respiratory

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 pre-treatment chest radiography should be done to determine if any additional diagnostic measures are necessary and to serve as a baseline for potential post-treatment pulmonary changes.

In the event of new or worsening pulmonary symptoms (e.g. cough, dyspnea), a prompt diagnostic evaluation should be performed and patients treated appropriately. The benefit/risk ratio should be considered prior to continuing VELCADE therapy.

In a clinical trial, two patients given high-dose cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours with daunorubicin and VELCADE for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy. Therefore, this specific regimen is not recommended.

Sexual Function/Reproduction

Fertility studies with bortezomib have not been performed. Degenerative effects in ovaries and testes in the general toxicity studies suggest a potential effect on male and female fertility (see ***Product Monograph PART II, TOXICOLOGY***).

Amyloidosis

The impact of proteasome inhibition by bortezomib on disorders associated with protein accumulation such as amyloidosis is unknown. Caution is advised in these patients.

Special Populations

Pregnant Women:

Women of child-bearing potential should avoid becoming pregnant while being treated with VELCADE. Males and females of child-bearing capacity should use effective contraceptive measures during treatment and for 3 months following treatment.

Bortezomib was not teratogenic in rats and rabbits at the highest dose tested (0.45 and 0.55 mg/m², respectively) but caused post-implantation loss in rabbits (see ***Product Monograph PART II, TOXICOLOGY***).

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 aware of the potential hazard to the fetus.

Nursing Women:

It is not known whether bortezomib is excreted in milk. Because many drugs are excreted in milk and because of the potential for serious adverse reactions from VELCADE in nursing infants, women should be advised against breast-feeding while being treated with VELCADE.

Pediatrics (< 18 years of age):

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

Monitoring and Laboratory Tests

Complete blood counts including platelet counts should be frequently monitored throughout treatment with VELCADE.

Chest radiography should be done prior to initiating VELCADE therapy (see **WARNINGS AND PRECAUTIONS, Respiratory**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Multiple Myeloma

Herpes Zoster Virus Reactivation:

The administration of VELCADE has been associated with herpes zoster reactivation. In the randomized Phase 3 study in relapsed multiple myeloma, the incidence of herpes zoster occurring on treatment with VELCADE was 13% (42/331) versus 5% (15/332) in the high-dose dexamethasone group. In the randomized study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in subjects treated with VELCADE, melphalan and prednisone (VMP) than in the control group treated with melphalan and prednisone (14% vs. 4%, respectively). In this study, antiviral prophylaxis was administered to 26% (90/340) of patients in the VMP treatment group. In this treatment group, herpes zoster virus reactivation was less common in subjects receiving prophylactic antiviral therapy (3% [3/90]) than in subjects who did not receive prophylactic antiviral therapy (17% [43/250]). In the post-market setting, cases of herpes meningoencephalitis and ophthalmic herpes have been reported.

Clinical Trial Adverse Drug Reactions

Multiple Myeloma

Randomized Open-Label Combination Phase III Clinical Study in Patients with Previously Untreated Multiple Myeloma (Front-Line Therapy)

In the VELCADE, melphalan, prednisone (VMP) and melphalan, prednisone (MP) treatment groups, respectively, 99% and 97% of subjects experienced at least 1 treatment-emergent adverse event. Seventy-eight percent of subjects in the VMP treatment group had Blood and Lymphatic System Disorders considered related to study drug, compared with 70% in the MP treatment group. The most commonly reported adverse events thrombocytopenia (52% vs. 47%), neutropenia (49% vs. 46%), and leukopenia (33% vs. 30%) were comparable between the 2 treatment groups (VMP vs. MP). The incidence of lymphopenia was higher in the VMP group (24% vs. 17%). However, anemia was observed in only 43% of subjects in the VMP group compared to 55% in the MP group. The Gastrointestinal Disorders SOC Grades 3 and ≥ 4 were reported more frequently in the VMP treatment group as compared to the MP treatment group (nausea: 48% vs. 28%; diarrhea: 46% vs. 17%; constipation: 37% vs. 16%; vomiting: 33% vs. 16%). As well, the incidence of Nervous System Disorders was higher in the VMP group (VMP vs. MP): peripheral neuropathy (47% vs. 5%), neuralgia (36% vs. 1%), and paraesthesia (13% vs. 4%). The incidence of termination of all study treatment because of adverse events was similar for the VMP and MP treatment groups (15% vs. 14%, respectively).

A total of 155 (46%) patients from the VMP treatment group experienced a serious adverse event (SAE) during the study compared with 121 (36%) patients from the MP treatment group. The most frequently reported serious adverse events in both treatment groups were in the Infections and Infestation SOC (VMP: 17%; MP: 15%), with pneumonia being the predominant serious adverse event in both treatment groups (VMP: 11%, MP: 7%). The incidence of serious adverse events belonging to the Nervous System Disorders was 5% in the VMP treatment group and 2% in the MP treatment group.

Drug related adverse events that led to death during the study occurred in 2% of subjects in both treatment groups (6 subjects in the VMP treatment group and 8 subjects in the MP treatment

group). The most frequent drug-related adverse events leading to death were of infectious origin: drug-related pneumonia/bronchopneumonia led to death in 3 subjects in the VMP treatment group and 4 subjects in the MP treatment group and drug-related sepsis led to death in 1 subject in the VMP treatment group and 3 subjects in the MP treatment group.

Table 1.2 describes safety data from 340 patients with previously untreated multiple myeloma who received VELCADE (1.3 mg/m²) in combination with melphalan (9 mg/m²) and prednisone (60 mg/m²) in a prospective Phase 3 study. Overall, the safety profile of VELCADE in combination with melphalan/prednisone is consistent with the known safety profiles of both VELCADE and melphalan/prednisone.

Table 1.2-Most Commonly Reported Adverse Events ($\geq 10\%$ in VELCADE, Melphalan and Prednisone arm) with Grades 3 and ≥ 4 Intensity in the Previously Untreated Multiple Myeloma Study

MedDRA System Organ Class Preferred Term	VELCADE, Melphalan and Prednisone (N=340)			Melphalan and Prednisone (N=337)		
	Total n (%)	Toxicity Grade, n (%)		Total n (%)	Toxicity Grade, n (%)	
		3	≥ 4		3	≥ 4
Blood and Lymphatic System Disorders						
Thrombocytopenia	178 (52)	68 (20)	59 (17)	159 (47)	55 (16)	47 (14)
Neutropenia	165 (49)	102 (30)	35 (10)	155 (46)	79 (23)	49 (15)
Anemia	147 (43)	53 (16)	9 (3)	187 (55)	66 (20)	26 (8)
Leukopenia	113 (33)	67 (20)	10 (3)	100 (30)	55 (16)	13 (4)
Lymphopenia	83 (24)	49 (14)	18 (5)	58 (17)	30 (9)	7 (2)
Gastrointestinal Disorders						
Nausea	164 (48)	14 (4)	0	94 (28)	1 (<1)	0
Diarrhea	157 (46)	23 (7)	2 (1)	58 (17)	2 (1)	0
Constipation	125 (37)	2 (1)	0	54 (16)	0	0
Vomiting	112 (33)	14 (4)	0	55 (16)	2 (1)	0
Abdominal Pain	49 (14)	7 (2)	0	22 (7)	1 (<1)	0
Abdominal Pain Upper	40 (12)	1 (<1)	0	29 (9)	0	0
Dyspepsia	39 (11)	0	0	23 (7)	0	0
Nervous System Disorders						
Peripheral Neuropathy	159 (47)	43 (13)	2 (1)	18 (5)	0	0
Neuralgia	121 (36)	28 (8)	2 (1)	5 (1)	1 (<1)	0
Dizziness	56 (16)	7 (2)	0	37 (11)	1 (<1)	0
Headache	49 (14)	2 (1)	0	35 (10)	4 (1)	0
Paresthesia	45 (13)	6 (2)	0	15 (4)	0	0
General Disorders and Administration Site Conditions						
Pyrexia	99 (29)	8 (2)	2 (1)	64 (19)	6 (2)	2 (1)
Fatigue	98 (29)	23 (7)	2 (1)	86 (26)	7 (2)	0
Asthenia	73 (21)	20 (6)	1 (<1)	60 (18)	9 (3)	0
Edema Peripheral	68 (20)	2 (1)	0	34 (10)	0	0
Infections and Infestations						
Pneumonia	56 (16)	16 (5)	13 (4)	36 (11)	13 (4)	9 (3)
Herpes Zoster	45 (13)	11 (3)	0	14 (4)	6 (2)	0
Bronchitis	44 (13)	4 (1)	0	27 (8)	4 (1)	0
Nasopharyngitis	39 (11)	1 (<1)	0	27 (8)	0	0
Musculoskeletal and Connective Tissue Disorders						
Back Pain	58 (17)	9 (3)	1 (<1)	62 (18)	11 (3)	1 (<1)
Pain In Extremity	47 (14)	8 (2)	0	32 (9)	3 (1)	1 (<1)
Bone Pain	37 (11)	7 (2)	1 (<1)	35 (10)	7 (2)	0
Arthralgia	36 (11)	4 (1)	0	50 (15)	2 (1)	1 (<1)
Metabolism and Nutrition Disorders						
Anorexia	77 (23)	9 (3)	1 (<1)	34 (10)	4 (1)	0
Hypokalemia	44 (13)	19 (6)	3 (1)	25 (7)	8 (2)	2 (1)
Skin and Subcutaneous Tissue Disorders						
Rash	66 (19)	2 (1)	0	24 (7)	1 (<1)	0
Pruritus	35 (10)	3 (1)	0	18 (5)	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	71 (21)	0	0	45 (13)	2 (1)	0
Dyspnea	50 (15)	11 (3)	2 (1)	44 (13)	5 (1)	4 (1)
Psychiatric Disorders						
Insomnia	69 (20)	1 (<1)	0	43 (13)	0	0
Vascular Disorders						
Hypertension	45 (13)	8 (2)	1 (<1)	25 (7)	2 (1)	0
Hypotension	41 (12)	4 (1)	3 (1)	10 (3)	2 (1)	2 (1)

Randomized Open-Label Phase III Multiple Myeloma Clinical Study

The incidence of treatment-emergent adverse events during the study was 100% in VELCADE-treated patients and 98% in dexamethasone-treated patients. Among the 331 VELCADE treated patients, the most commonly reported adverse events overall were asthenic conditions (61%), diarrhea (58%), nausea (57%), constipation (42%), peripheral neuropathy (36%), vomiting, pyrexia, thrombocytopenia (each 35%), anorexia and decreased appetite (34%), anemia and headache (each 26%), dyspnea (25%), myalgia, muscle cramps, spasms and stiffness (24%), rash (24%), and cough and paresthesia (each 21%). The most commonly reported adverse events among the 332 patients in the dexamethasone group were psychiatric disorders (49%), asthenic conditions (45%), insomnia (27%), anemia (22%), and diarrhea (21%). Fourteen percent (14%) of patients in the VELCADE treatment arm experienced a Grade 4 adverse event; the most common Grade 4 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%).

A total of 144 (44%) patients from the VELCADE treatment arm experienced a serious adverse event (SAE) during the study, as did 144 (43%) dexamethasone-treated patients. An SAE is 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. 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 the 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).

Of the 669 patients enrolled in this study, 37% were 65 years of age or older. The incidence of Grade 3 and 4 events was 64%, 78% and 75% for VELCADE patients \leq 50, 51-64 and \geq 65 years of age, respectively.

Four deaths were considered to be VELCADE related in the Phase III 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.

Non-randomized Phase II Relapsed Multiple Myeloma Clinical Studies

Two Phase II studies (see *Product Monograph PART II, CLINICAL TRIALS*) evaluated 228 patients with multiple myeloma receiving VELCADE (bortezomib) for Injection 1.3 mg/m²/dose twice weekly for 2 weeks followed by a 10-day rest period (21-day treatment cycle length) for a maximum of 8 treatment cycles.

The most commonly reported adverse events were asthenic conditions (65%), nausea (64%), diarrhea (55%), anorexia and decreased appetite (43%), constipation (43%), thrombocytopenia (43%), peripheral neuropathy (37%), pyrexia (36%), vomiting (36%), and anemia (32%). Fourteen percent (14%) of patients experienced at least one episode of Grade 4 toxicity, with the most common toxicity being thrombocytopenia (3%) and neutropenia (3%).

During the studies, a total of 113 (50%) of the 228 patients experienced SAEs. The most commonly reported SAEs included pyrexia (7%), pneumonia (7%), diarrhea (6%), vomiting (5%), dehydration (5%), and nausea (4%).

Adverse events thought by the investigator to be drug related and leading to discontinuation occurred in 18% of patients. The reasons for discontinuation included peripheral neuropathy (5%), thrombocytopenia (4%), diarrhea (2%), and fatigue (2%).

In the Phase II clinical study of 202 patients, 35% of whom were 65 years of age or older, the incidence of \geq Grade 3 adverse events was 74%, 80% and 85% for VELCADE-treated patients \leq 50, 51-64 and \geq 65 years of age, respectively.

Two deaths were reported and considered by the investigator to be possibly related to study drug: one case of cardiopulmonary arrest and one case of respiratory failure.

Patients from the two Phase II studies who, in the investigators' opinion, would experience additional clinical benefit were allowed to receive VELCADE beyond 8 cycles on an extension study (see **Product Monograph PART II, CLINICAL TRIALS**). Compared to the parent studies, patients in this extension study experienced a greater incidence of selected adverse events including edema overall (41% versus 29%), Grade 4 adverse events (22% versus 5%), and serious adverse events (48% versus 33%). As well, there was a greater incidence of lower limb edema (27% versus 10%), hyperglycemia (19% versus 5%), increased blood creatinine (13% versus 3%), productive cough (13% versus 2%), hypoproteinemia (10% versus 0%) and chest wall pain (10% versus 0%) in this extension study compared to the parent Phase II studies. Most of these adverse events were mild or moderate in intensity, and none was reported as an SAE. Of the commonly reported side effects attributable to VELCADE treatment, there was no evidence of their increase with cumulative dosing.

Mantle Cell Lymphoma

Non-randomized Phase II Mantle Cell Lymphoma Study

Safety data for patients with mantle cell lymphoma were evaluated in a phase II study, which included 155 patients treated with VELCADE at the recommended dose of 1.3 mg/m² twice weekly on days 1, 4, 8 and 11 of a 21-day cycle. The most commonly reported adverse events were asthenic conditions (72%), peripheral neuropathy (55%), constipation (50%), diarrhea (47%), nausea (44%), decreased appetite (39%), vomiting (27%), rash (28%), edema (28%), anemia (17%), dizziness (excluding vertigo) (23%), dyspnea (23%), thrombocytopenia (21%), insomnia (21%). 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 pruritis were higher among patients with mantle cell lymphoma

compared to patients with multiple myeloma. The most common adverse event leading to the discontinuation of VELCADE-treated patients was peripheral neuropathy (10%).

The most common treatment-emergent adverse drug reactions occurring at $\geq 10\%$ incidence for Phase III and Phase II relapsed multiple myeloma studies are presented in Table 1.3 and Table 1.4, respectively, by System Organ Class. As well the most common treatment-emergent adverse drug reactions occurring at $\geq 10\%$ incidence for the Phase II mantle cell lymphoma study is presented in Table 1.5 by System Organ Class.

Table 1.3: Most Commonly Reported Adverse Events (≥10% in VELCADE arm), with Grades 3 and 4 Intensity in the Phase III Multiple Myeloma Randomized Study (N=663)

System Organ Class	Treatment Group					
	VELCADE (n=331)			Dexamethasone (n=332)		
	All Events	[n (%)] Grade 3 Events	Grade 4 Events	All Events	[n (%)] Grade 3 Events	Grade 4 Events
Blood and lymphatic system disorders						
Thrombocytopenia	115 (35)	85 (26)	12 (4)	36 (11)	18 (5)	4 (1)
Anemia NOS	87 (26)	31 (9)	2 (<1)	74 (22)	32 (10)	3 (<1)
Neutropenia	62 (19)	40 (12)	8 (2)	5 (2)	4 (1)	0
Gastrointestinal disorders						
Diarrhea NOS, loose stools	192 (58)	24 (7)	0	70 (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
Vomiting NOS	117 (35)	11 (3)	0	20 (6)	4 (1)	0
Abdominal pain NOS	53 (16)	6 (2)	0	12 (4)	1 (<1)	0
Dyspepsia	32 (10)	2 (<1)	0	28 (8)	0	0
General disorders and administration site conditions						
Asthenia (fatigue, weakness, malaise, fatigue aggravated, lethargy)	201 (61)	39 (12)	1 (<1)	148 (45)	20 (6)	0
Pyrexia	116 (35)	6 (2)	0	54 (16)	4 (1)	1 (<1)
Edema lower limb, edema peripheral, peripheral swelling, edema NOS‡	56 (17)	0	0	65 (20)	1 (<1)	0
Rigors	37 (11)	0	0	8 (2)	0	0
Pain NOS	33 (10)	7 (2)	0	12 (4)	2 (<1)	1 (<1)
Infections and Infestations						
Nasopharyngitis	45 (14)	1 (<1)	0	22 (7)	0	0
Herpes Zoster (including multi-dermatomal or disseminated)	42 (13)	6 (2)	0	15 (5)	4 (1)	1 (<1)
Metabolism and nutrition disorders						
Anorexia, appetite decreased NOS	112 (34)	9 (3)	0	31 (9)	1 (<1)	0
Musculoskeletal and connective tissue disorders						
Bone pain, bone pain aggravated	54 (16)	12 (4)	0	53 (16)	11 (3)	0
Muscle cramps, muscle spasms, muscle stiffness, myalgia	78 (24)	2 (<1)	0	66 (20)	5 (2)	0
Arthralgia, joint stiffness	49 (15)	3 (<1)	0	35 (11)	5 (2)	0
Pain in the limb	50 (15)	5 (2)	0	24 (7)	2 (<1)	0
Back pain	46 (14)	10 (3)	0	33 (10)	4 (1)	0
Musculoskeletal pain	33 (10)	3 (<1)	0	11 (3)	3 (<1)	0
Nervous system disorders						
Peripheral neuropathy NOS, peripheral neuropathy aggravated, peripheral sensory neuropathy	119 (36)	24 (7)	2 (<1)	28 (8)	1 (<1)	1 (<1)
Headache NOS	85 (26)	3 (<1)	0	43 (13)	2 (<1)	0
Paresthesia, burning sensation NOS	70 (21)	5 (2)	0	28 (8)	0	0
Dizziness (excluding vertigo)	45 (14)	3 (<1)	0	34 (10)	0	0
Psychiatric disorders						
Insomnia	60 (18)	1 (<1)	0	90 (27)	5 (2)	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea NOS, dyspnea exertional	84 (25)	17 (5)	1 (<1)	65 (20)	9 (3)	2 (<1)
Cough	70 (21)	2 (<1)	0	35 (11)	1 (<1)	0
Skin and subcutaneous tissue disorders						
Rash NOS, rash pruritic, rash erythematous, rash generalized, rash macular, rash papular, erythema, urticaria NOS	79 (24)	6 (2)	0	28 (8)	0	0
Vascular disorders						
Orthostatic hypotension, hypotension NOS, postural hypotension	38 (11)	3 (<1)	0	6 (2)	2 (<1)	1 (<1)

‡ Preferred terms mapped to General Disorders and Administration Site Conditions SOC or Musculoskeletal and Connective Tissue Disorders SOC

Table 1.4: Most Commonly Reported (≥10% overall) Adverse Events Reported from 2 Phase II Clinical Trials in Multiple Myeloma Patients (N=228)

System Organ Class	VELCADE-Treated Patients at 1.3 mg/m ² /dose (N=228)		
	All Events n (%)	Grade 3 Events n (%)	Grade 4 Events n (%)
Blood and lymphatic system disorders			
Thrombocytopenia	97 (43)	61 (27)	7 (3)
Anemia NOS or anemia NOS aggravated, hemoglobin decreased, red blood cell count decreased†	74 (32)	21 (9)	0
Neutropenia or neutropenia aggravated	54 (24)	29 (13)	6 (3)
Eye disorders			
Vision blurred	25 (11)	1 (<1)	0
Gastrointestinal disorders			
Nausea or nausea aggravated	145 (64)	15 (7)	0
Diarrhea NOS or loose stools	125 (55)	16 (7)	2 (1)
Constipation or constipation aggravated	99 (43)	5 (2)	0
Vomiting NOS	82 (36)	16 (7)	1 (<1)
Abdominal pain NOS, abdominal pain upper or abdominal discomfort	45 (20)	5 (2)	0
Dyspepsia	30 (13)	0	0
General disorders and administration site conditions			
Asthenia (fatigue, weakness, malaise, fatigue aggravated, lethargy)	149 (65)	42 (18)	1 (<1)
Pyrexia	82 (36)	9 (4)	0
Edema peripheral, edema lower limb, peripheral swelling‡	48 (21)	2 (1)	0
Rigors	27 (12)	1 (<1)	0
Pain NOS	22 (10)	3 (1)	0
Infections and infestations			
Upper respiratory tract infection NOS	41 (18)	0	0
Herpes zoster (including multidermatomal or disseminated)	26 (11)	2 (1)	0
Pneumonia NOS	23 (10)	12 (5)	0
Metabolism and nutrition disorders			
Anorexia, appetite decreased NOS	99 (43)	6 (3)	0
Dehydration	42 (18)	15 (7)	0
Weight decreased, failure to thrive‡	26 (11)	2 (1)	0
Musculoskeletal and connective tissue disorders			
Arthralgia, joint stiffness	63 (28)	11 (5)	0
Pain in the limb	59 (26)	16 (7)	0
Muscle cramps, muscle spasms, muscle stiffness, myalgia	60 (26)	8 (4)	0
Bone pain, bone pain aggravated	39 (17)	11 (5)	0
Back pain	31 (14)	9 (4)	0
Nervous system disorders			
Peripheral neuropathy NOS, peripheral neuropathy aggravated, peripheral sensory neuropathy	84 (37)	31 (14)	0
Headache NOS	63 (28)	8 (4)	0
Dizziness (excluding vertigo)	48 (21)	3 (1)	0
Paresthesia, burning sensation NOS	32 (14)	5 (2)	0
Dysgeusia	29 (13)	1 (<1)	0
Hypoesthesia	26 (11)	1 (<1)	0
Psychiatric disorders			
Insomnia	62 (27)	3 (1)	0
Anxiety NEC	32 (14)	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnea NOS, dyspnea exertional, dyspnea exacerbated	66 (29)	8 (4)	1 (<1)
Cough	39 (17)	1 (<1)	0
Epistaxis	23 (10)	1 (<1)	0
Skin and subcutaneous tissue disorders			
Rash NOS, rash pruritic, rash erythematous, rash generalized, rash macular, rash papular, erythema, urticaria NOS	63 (28)	1 (<1)	0
Pruritus NOS, pruritus generalized	28 (12)	0	0
Vascular disorders			
Orthostatic hypotension, hypotension NOS, postural hypotension	27 (12)	8 (4)	0

† Preferred terms mapped to Blood and Lymphatic System Disorders System Organ Class (SOC) or Investigations SOC

‡ Preferred terms mapped to General Disorders and Administration Site Conditions SOC or Musculoskeletal and Connective Tissue Disorders SOC

‡ Preferred terms mapped to Investigations SOC or Metabolism and Nutrition Disorders SOC

Table 1.5: Most Commonly Reported Adverse Events (≥10% overall) Reported in the Phase II Mantle Cell Lymphoma Study

System Organ Class	VELCADE-Treated Patients at 1.3 mg/m ² /dose (N=155)	
	All Events n (%)	≥Grade 3 n (%)
Blood and lymphatic system disorders		
Thrombocytopenia	33 (21)	17 (11)
Anemia	27 (17)	4 (3)
Gastrointestinal disorders		
Constipation	77 (50)	4 (3)
Diarrhea	73 (47)	11 (7)
Nausea	68 (44)	4 (3)
Vomiting	42 (27)	4 (3)
Abdominal pain	24 (15)	8 (5)
General disorders and administration site conditions		
Asthenic conditions	112 (72)	29 (19)
Edema	44 (28)	4 (3)
Pyrexia	30 (19)	2 (1)
Infections and infestations		
Upper respiratory tract infection	24 (15)	1 (<1)
Metabolism and nutrition disorders		
Appetite decreased	60 (39)	5 (3)
Musculoskeletal and connective tissue disorders		
Arthralgia	20 (13)	2 (1)
Myalgia	15 (10)	0
Nervous system disorders		
Peripheral neuropathy [†]	85 (55)	20 (13)
Dizziness (excluding vertigo)	36 (23)	5 (3)
Headache	26 (17)	0
Psychiatric disorders		
Insomnia	33 (21)	1 (<1)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	35 (23)	7 (5)
Cough	30 (19)	0
Skin and subcutaneous tissue disorders		
Rash	43 (28)	4 (3)
Vascular disorders		
Hypotension	23 (15)	5 (3)

[†]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).

Serious Adverse Events from Other Clinical Studies (hematological malignancy and solid tumours)

The following clinically important serious adverse events 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 tumours.

Blood and lymphatic system disorders: Disseminated intravascular coagulation

Cardiac disorders: Angina pectoris, atrial fibrillation aggravated, atrial flutter, bradycardia, sinus arrest, cardiac amyloidosis, cardiac arrest, congestive heart failure, myocardial ischemia, myocardial infarction, pericarditis, pericardial effusion, pulmonary edema, ventricular tachycardia

One case of torsades de pointes (not described above) has been reported in a patient receiving VELCADE; causality has not been established.

Ear and labyrinth disorders: Hearing impaired

Eye disorders: Diplopia

Gastrointestinal disorders: Ascites, dysphagia, fecal impaction, gastroenteritis, gastritis hemorrhagic, gastrointestinal hemorrhage, hematemesis, hemorrhagic duodenitis, ileus paralytic, large intestinal obstruction, paralytic intestinal obstruction, small intestinal obstruction, large intestinal perforation, stomatitis, melena, pancreatitis acute

General disorders and administration site conditions: Injection site erythema

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

Immune system disorders: Anaphylactic reaction, drug hypersensitivity, immune complex mediated hypersensitivity, acute renal failure (proliferative glomerulonephropathy), diffuse polyarthritis and rash

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

Injury, poisoning and procedural complications: Skeletal fracture, subdural hematoma

Metabolism and nutrition disorders: Hypocalcemia, hyperuricemia, hypokalemia, hyperkalemia, hyponatremia, hyponatremia, tumour lysis syndrome

Nervous system: Ataxia, coma, dizziness, dysarthria, dysautonomia, encephalopathy, cranial palsy, grand mal convulsion, hemorrhagic stroke, motor dysfunction, spinal cord compression, paraplegia, transient ischemic attack

Psychiatric: Agitation, confusion, mental status changes, psychotic disorder, suicidal ideation

Renal and urinary: 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: Acute respiratory distress syndrome, aspiration pneumonia, atelectasis, chronic obstructive airways disease exacerbated, dysphagia, epistaxis, hemoptysis, hypoxia, lung infiltration, pleural effusion, pneumonitis, respiratory distress, respiratory failure.

Skin and subcutaneous tissue disorders: Urticaria, face edema

Vascular: Cerebrovascular accident, deep venous thrombosis, peripheral embolism, pulmonary embolism, pulmonary hypertension

Abnormal Hematologic and Clinical Chemistry Findings

Hematological abnormalities are expected in patients with advanced multiple myeloma. With bortezomib, cyclical thrombocytopenia was seen, with a general progressive decrease in platelet count during the bortezomib dosing period (Days 1 to 11) and a return to baseline in platelet count during the rest period (Days 12 to 21) in each treatment cycle. A trend towards an increase in hemoglobin and absolute neutrophil count across treatment cycles was noted especially with an improvement in the underlying disease. A trend towards a decrease in the absolute lymphocyte count was noted across the 8 treatment cycles; however, no trend was noted by cycle. Effects on electrolytes and calcium (hyper- and hypokalemia, hyper- and hyponatremia, hyper- and hypocalcemia) and hypophosphatemia, hypochloremia and hypomagnesemia were noted.

Post-Market Adverse Drug Reactions

The following adverse events have been reported from post-marketing experience:

- central neurotoxicity/psychiatric events including seizures, mental status changes, encephalopathy, acute psychosis, bilateral hearing loss, dysautonomia, reversible posterior leukoencephalopathy syndrome
- cardiovascular and pulmonary events including tachycardia, heart failure, cardiac tamponade, pericarditis, pulmonary hypertension, cardiac and cardiopulmonary arrest, complete heart block, pneumonitis, respiratory failure, pulmonary alveolar hemorrhage, pleural effusion, acute pulmonary edema, cardiogenic shock
- serious bleeding events including subarachnoid hemorrhage, intracerebral hemorrhage, disseminated intravascular coagulation, ischemic stroke
- hypersensitivity events including immune complex type diseases, angioedema
- tumour lysis syndrome
- amyloidosis
- hepatic abnormalities including increased transaminases, alkaline phosphatase, gamma-glutamyl transferase, hepatocellular damage, hepatitis, pancreatitis

- renal abnormalities including acute renal failure, nephrotic syndrome, renal tubular acidosis
- sepsis and septic shock
- gastrointestinal events including ischemic colitis and paralytic ileus
- hyper- and hypocalcemia, hyper- and hypokalemia, severe hyponatremia, inappropriate ADH secretion
- acute diffuse infiltrative pulmonary disease
- Stevens-Johnson Syndrome and toxic epidermal necrolysis
- herpes meningoencephalitis and ophthalmic herpes

DRUG INTERACTIONS

Drug-Drug Interactions

No formal drug interaction studies have been conducted with bortezomib.

Bortezomib is a substrate for cytochrome P450 (CYP) 3A4, 2C19, 1A2, 2D6 and 2C9 in human liver microsomes and a weak inhibitor of CYP isozymes 1A2, 2C9, 2D6 and 3A4 ($IC_{50} \geq 30 \mu\text{M}$ or $11.5 \mu\text{g/mL}$) and CYP2C19 ($IC_{50} \geq 18 \mu\text{M}$ or $6.9 \mu\text{g/mL}$).

The effect of concomitant medicinal products that are potent CYP inhibitors and inducers on the pharmacokinetics of bortezomib is unknown at this time. With bortezomib's extensive metabolism, caution must be used in the co-administration of VELCADE with agents that are known to be potent inducers and inhibitors of the CYP3A4 and 2C19 isoforms.

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.

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.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with results of laboratory tests have not been established.

Drug-Lifestyle Interactions

VELCADE may be associated with fatigue, dizziness, syncope, orthostatic/postural hypotension or blurred vision. Therefore, patients are advised to be cautious when operating machinery, or when driving.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Treatment must be administered under the supervision of a physician qualified and experienced in the use of antineoplastic agents.

VELCADE (bortezomib) for Injection has not been formally studied in patients with impaired renal function. Patients with compromised renal function should be monitored carefully, especially if creatinine clearance is ≤ 30 mL/minute (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

VELCADE has not been studied in patients with impaired hepatic function. Patients with impaired liver function should be treated with extreme caution and a dose reduction should be considered (see **WARNINGS AND PRECAUTIONS**).

There is no evidence to suggest that dose adjustments are necessary in elderly patients (see **ADVERSE REACTIONS**).

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

Dosage in Previously Untreated Multiple Myeloma

VELCADE (bortezomib) is administered as a 3-5 second bolus IV injection in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in Table 1.6. In Cycles 1-4, VELCADE is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, VELCADE is administered once weekly (days 1, 8, 22 and 29). At least 72 hours should elapse between consecutive doses of VELCADE.

Table 1.6: Dosage Regimen for Patients with Previously Untreated Multiple Myeloma

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

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

See *Product Monograph* PART II, CLINICAL TRIALS

Dose Modification Guidelines for Combination Therapy with VELCADE, 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 $\geq 70 \times 10^9/L$ and the ANC should be $\geq 1.0 \times 10^9/L$
- Non-hematological toxicities should have resolved to Grade 1 or baseline

Table 1.7: Dose Modifications During Subsequent Cycles of Combination VELCADE, Melphalan and Prednisone Therapy

Toxicity	Dose modification or delay
<i>Hematological toxicity during a cycle:</i>	
If prolonged (≥ 5 days) Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25% in the next cycle.
If platelet count $\leq 30 \times 10^9/L$ or ANC $\leq 0.75 \times 10^9/L$ on a VELCADE dosing day (other than day 1)	VELCADE dose should be withheld
If several VELCADE doses in 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)
<u>Grade ≥ 3 non-hematological toxicities</u>	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 1.8.

Please refer to the melphalan and prednisone Product Monographs for additional information.

Dosage in Relapsed Multiple Myeloma and Mantle Cell Lymphoma

The recommended starting dose of bortezomib is 1.3 mg/m² body surface area administered as a 3 to 5 second bolus intravenous injection twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12-21). This 3-week period is considered a treatment cycle. For extended therapy beyond 8 cycles, VELCADE may be administered 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). At least 72 hours should elapse between consecutive doses of VELCADE to minimize drug accumulation.

For tolerability reasons, dose reduction to 1.0 mg/m² has been found effective. VELCADE therapy should be withheld at the onset of any Grade 3 non-hematological or any Grade 4 hematological toxicities, excluding neuropathy as discussed below (see **WARNINGS AND PRECAUTIONS**). Once the symptoms of the toxicity have resolved, VELCADE treatment may be re-initiated at a 25% reduced dose (1.3 mg/m² reduced to 1.0 mg/m²; 1.0 mg/m² reduced to 0.7 mg/m²). If toxicity is not resolved or if it recurs at the lowest dose, discontinuation of VELCADE must be considered unless the benefit of treatment clearly outweighs the risk.

Treatment with VELCADE may be associated with a dose-related, transient decrease in platelet count. It is recommended that platelets be monitored before each dose, and that therapy be held if platelet counts are < 25 x 10⁹/L and re-initiated at a reduced dose after resolution (see **WARNINGS AND PRECAUTIONS**).

In a supportive Phase 2 relapsed multiple myeloma study in which the majority of patients were not refractory and had received less than 2 prior lines of therapy, a dose of 1.0 mg/m² was investigated (see *Product Monograph PART II, CLINICAL TRIALS*).

It is recommended that patients with a confirmed complete response receive 2 additional cycles of VELCADE beyond a confirmation. It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of VELCADE therapy.

Currently there are limited data concerning retreatment with VELCADE.

Patients who experience VELCADE related neuropathic pain and/or peripheral sensory neuropathy are to be managed as presented in Table 1.8. Patients with pre-existing severe neuropathy may be treated with VELCADE only after careful risk/benefit assessment.

Table 1.8: 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 (paresthesia, weakness and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce VELCADE to 1.0 mg/m ²
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold VELCADE treatment until symptoms of toxicity have resolved. When toxicity resolves, re-initiate VELCADE treatment and reduce dose to 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

NCI Common Toxicity Criteria

Missed Dose

A minimum of 72 hours is required between doses. In a Day 1, 4, 8 and 11 dose schedule, if Day 4, 8 or 11 dose is missed, that dose is not made up.

Administration

The reconstituted solution 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 Injection, USP.

VELCADE is a cytotoxic agent. Caution should be used during handling and preparation. Proper aseptic technique should be used since no preservative is present. 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.

Reconstitution:

Prior to use, the contents of each vial must be reconstituted with 3.5 mL of 0.9% Sodium Chloride Injection, USP. The reconstituted product should be a clear and colourless 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.

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
10 mL	3.5 mL 0.9% Sodium Chloride Injection, USP	3.5 mL	1 mg/mL

Stability:

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

OVERDOSAGE

Cardiovascular safety pharmacology studies in monkeys and dogs show that single IV doses approximately two to three times the recommended clinical dose on a mg/m² basis are associated with hypotension, increases in heart rate, decreases in contractility, altered temperature control and death. The decreased cardiac contractility and hypotension responded to acute intervention with positive inotropic or pressor agents. In dog studies, increases in the QT and corrected QT interval were observed at lethal doses (see **Product Monograph PART II, DETAILED PHARMACOLOGY**).

Accidental overdosage of at least twice the recommended dose has been associated 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**).

ACTION AND CLINICAL PHARMACOLOGY

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 signalling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death.

The mechanism of action of VELCADE suggests that it should be active in MCL. Proteasome inhibition blocks degradation of IκB and inhibits NFκB. NFκB activates transcription of many genes that inhibit apoptosis and promote proliferation in lymphoma cells. Proteasome inhibition

also leads to accumulation of p27 and other cyclin D kinase inhibitors. Low levels of p27 correlate with poor survival in MCL.

Pharmacodynamics

Bortezomib is a selective, reversible proteasome inhibitor and experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types. Bortezomib causes a reduction of tumour growth *in vivo* in many preclinical tumour models, including multiple myeloma.

Pharmacokinetics

Following intravenous bolus administration of 1.0 mg/m² and 1.3 mg/m² doses to 24 patients with multiple myeloma (n = 12 per each dose level), the mean first-dose maximum plasma concentrations of bortezomib were 57 and 112 ng/mL, respectively. In subsequent doses administered twice weekly, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1.0 mg/m² dose and 89 to 120 ng/mL for the 1.3 mg/m² dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours for the 1.0 mg/m² dose, and 49 to 109 hours for the 1.3 mg/m² dose. 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/m² and 1.3 mg/m², respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1.0 mg/m² and 1.3 mg/m², respectively (see ***Product Monograph PART II, DETAILED PHARMACOLOGY, Clinical Pharmacology***).

Absorption: VELCADE is administered intravenously and therefore has 100% bioavailability.

Distribution: The mean distribution volume of bortezomib ranged from 489 to 1884 L/m² following single- or repeat-dose administration of 1.0 mg/m² or 1.3 mg/m² to patients with multiple myeloma. This suggests that bortezomib distributes widely to peripheral tissues. *In vitro* bortezomib binding to human plasma protein averaged 83% over a concentration range of 10 to 1000 ng/mL.

Metabolism: Bortezomib is primarily metabolized via cytochrome P450-mediated deboronation to metabolites that subsequently are hydroxylated. *In vitro* studies indicate that CYP3A4 and 2C19 are quantitatively the major isoforms with CYP1A2, 2C9 and 2D6 having a minor contribution to the overall metabolism of bortezomib. Evaluated 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 pathway of elimination of bortezomib has not been characterized in humans. The predominant route of elimination is biliary excretion in the rat whereas in the monkey, renal elimination is higher than biliary/fecal elimination.

Special Populations and Conditions

Gender and Race, Pediatrics, Geriatrics, Hepatic Insufficiency and Renal Insufficiency:

There are no data on effects of bortezomib on the pharmacokinetics in these special populations and conditions.

STORAGE AND STABILITY

Unopened vials may be stored between 15 and 30° C. Retain in original package to protect from light.

Single-use vials. Discard unused portion.

The product may be stored for up to eight hours in a syringe; however, total storage time for the reconstituted material must not exceed eight hours when exposed to normal indoor lighting.

SPECIAL HANDLING INSTRUCTIONS

VELCADE (bortezomib) for Injection is a cytotoxic agent. Caution should be used during handling and preparation. Proper aseptic technique should be used since no preservative is present. Use of gloves and other protective clothing to prevent skin contact is recommended.

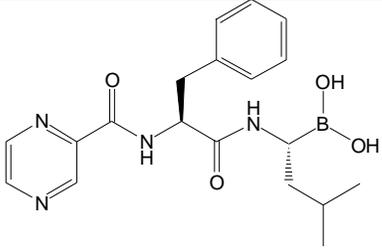
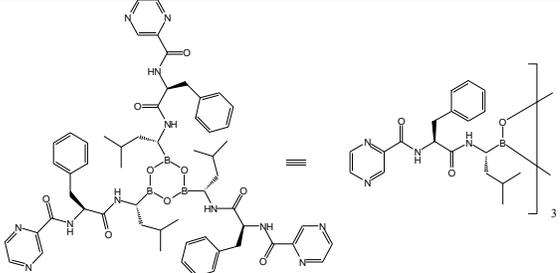
DOSAGE FORMS, COMPOSITION AND PACKAGING

VELCADE (bortezomib) for Injection is supplied in individually cartoned 10 mL vials containing 3.5 mg of bortezomib as a mannitol boronic ester, as a white to off-white cake or powder. The only nonmedicinal ingredient is mannitol.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

	Boronic Acid (biologically active moiety)	Cyclic Anhydride
Proper name	bortezomib	not available
Chemical name	[(1R)-3-methyl-1-[[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]boronic acid	<i>N,N',N''</i> -[2,4,6-Boroxintriyltris [[(1R)-3-methylbutylidene] imino [(1S)-2-oxo-1-(phenylmethyl)-2,1-ethanediyl]]] trispyrazinecarboxamide
Molecular formula	C ₁₉ H ₂₅ BN ₄ O ₄	C ₅₇ H ₆₉ B ₃ N ₁₂ O ₉
Molecular mass	384.24	1098.67
Structural formula		

Physicochemical properties: 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 solubility of bortezomib, as the monomeric boronic acid, in water is 3.3-3.8 mg/mL over a pH range of 2-6.5.

CLINICAL TRIALS

Randomized, Open-Label Clinical Study in Patients with Previously Untreated Multiple Myeloma (Front-Line Therapy)

A prospective phase 3, international, randomized (1:1), open-label clinical study of 682 patients was conducted to determine whether a combination of intravenous VELCADE with oral melphalan and prednisone represented a major improvement in time to progression (TTP) when compared to oral melphalan and prednisone in patients with previously untreated multiple myeloma.

In the VMP treatment group during Cycles 1 to 4, subjects received VELCADE 1.3 mg/m² as an i.v. bolus injection on Days 1, 4, 8, 11, 22, 25, 29, and 32 followed by a 10-day rest period (Days 33 to 42), and oral melphalan 9 mg/m² and oral prednisone 60 mg/m² once daily on Days 1 to 4, followed by a 38-day rest period (Days 5 to 42). During Cycles 5 to 9, subjects received VELCADE 1.3 mg/m² as an i.v. bolus injection on Days 1, 8, 22, and 29 followed by a 13-day rest period (Days 30 to 42), and oral melphalan 9 mg/m² and oral prednisone 60 mg/m² once daily on Days 1 to 4, followed by a 38-day rest period (Days 5 to 42).

Patients in the MP treatment group received oral melphalan 9 mg/m² and oral prednisone 60 mg/m² once daily on Days 1 to 4, followed by a 38-day rest period (Days 5 to 42) during the Cycles 1-9.

Treatment was administered for a maximum of 9 cycles (approximately 54 weeks) and was discontinued early for disease progression or unacceptable toxicity (see **Product Monograph PART I, DOSAGE AND ADMINISTRATION**). Baseline demographics and patient characteristics are summarized in Table 2.1.

Table 2.1: 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%)
ISS Staging n (%)		
I	64 (19)	64 (19)
II	161 (47)	159 (47)
III	119 (35)	115 (34)

VMP=VELCADE, melphalan, prednisone; MP = melphalan, prednisone

At the time of the third pre-specified interim analysis, the primary endpoint, time to progression, was met and patients in the MP arm were offered VMP treatment. TTP was defined as the time

from randomization to the date of the first observation of either disease progression or relapse from immunofixation-negative CR. PFS, a secondary endpoint, was defined as the time between randomization and either disease progression or death, whichever occurred first. Survival continued to be followed after the interim analysis. Median follow-up was 16.3 months. Efficacy results are presented in Table 2.2 and Figures 2.1, 2.2 and 2.3.

Table 2.2: Summary of Efficacy Analyses in the Phase III Previously Untreated Multiple Myeloma Study

Efficacy Endpoint	VMP n=344	MP n=338	p-value	Odds Ratio^h
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)	0.000002 ^c	
Hazard ratio ^b (95% CI)	0.54 (0.42, 0.70)			
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)	0.00001 ^c	
Hazard ratio ^b (95% CI)	0.61 (0.49, 0.76)			
Overall Survival				
Events (deaths) n (%)	45 (13)	76 (23)	0.00782 ^c	
Hazard ratio ^b (95% CI)	0.61 (0.42, 0.88)			
Response Rate				
Population ^d n = 668	n=337	n=331		
CR ^e n (%)	102 (30)	12 (4)	<10 ^{-10c}	11.2 (6.1, 20.6)
PR ^e n (%)	136 (40)	103 (31)		
nCR n (%)	5 (1)	0		
CR + PR ^e n (%)	238 (71)	115 (35)	<10 ^{-10f}	4.5 (3.2, 6.2)
CR + PR ^e + MR n (%)	270 (80)	187 (56)	<10 ^{-7c}	3.2 (2.2, 4.5)
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		
Time to Best Response in CR + PR				
Median	2.3 mo	4.9 mo		
Time to CR				
Median	4.2 mo	5.3 mo		
Median^a Response Duration				
CR ^e	24.0 mo	12.8 mo		
CR + PR ^e	19.9 mo	13.1 mo		
Time to Next Therapy				
Events n (%)	73 (21)	127 (38)		
Median ^a (95% CI)	NE (26.1, NE)	20.8 mo (18.3, 28.5)	0.000009 ^c	
Hazard ratio ^b (95% CI)	0.52 (0.39, 0.70)			

NE=not estimable; CR=complete response; nCR= near complete response; PR= partial response; MR = minimal response

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

^d Response population includes patients who had measurable disease at baseline

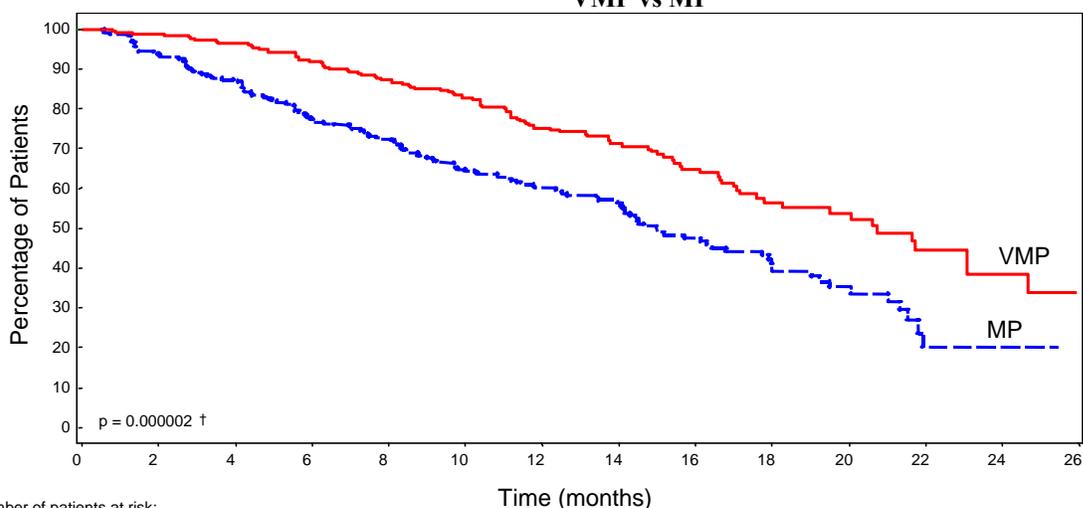
^e EBMT criteria

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

^g All randomized patients with secretory disease

^h Mantel-Haenszel estimate of the common odds ratio for stratified tables is used.

**Figure 2.1: Time to Progression
VMP vs MP**



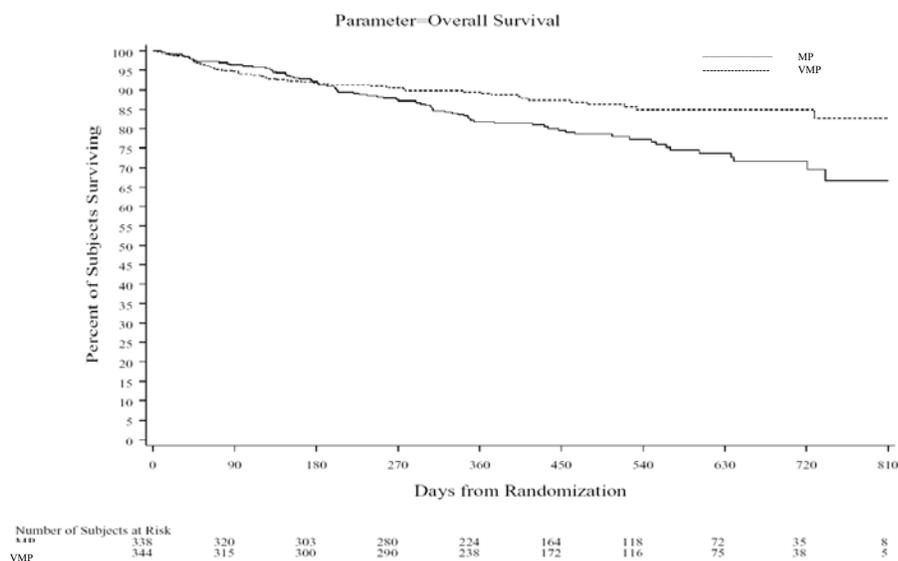
A significant survival benefit favouring the VMP treatment group was demonstrated (hazard ratio=0.617; p=0.00782) (see Table 2.2 and Figure 2.2). While the median OS has not been reached in either treatment group, the 1-year and 2-year survival rates based on Kaplan-Meier estimates in the VMP and MP treatment groups are presented in Table 2.3.

Table 2.3: Summary of 1-Year and 2-year Survival Benefit in Previously Untreated Patients Based on Kaplan-Meier Estimate

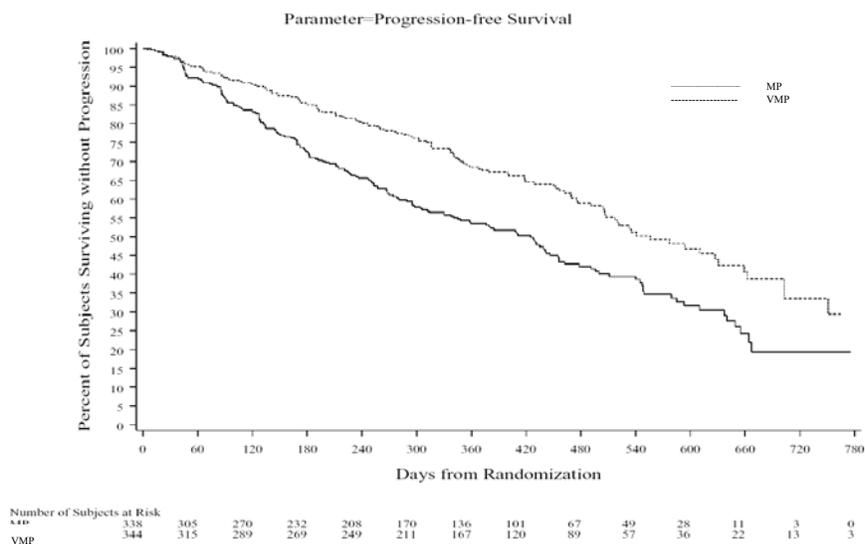
Efficacy Endpoint	VMP (N=344)	MP (N=338)
1-Year Survival % (95% CI)	89.1 (85.7; 92.4)	81.8 (77.6; 86.1)
2-Year Survival % (95% CI)	82.6 (76.5; 88.7)	69.5 (62.3; 76.7)

VMP=VELCADE, melphalan, prednisone; MP = melphalan, prednisone

**Figure 2.2: Overall Survival Based on Kaplan-Meier Estimate
VMP vs MP**



**Figure 2.3: Progression-Free Survival
VMP vs MP**



To explore the association of response status (CR, PR, or no response) over-time on the long-term outcomes, including TTP, PFS, and OS, multivariate Cox regression analyses with time-dependent covariates were performed that also adjusted for baseline prognostic factors. Strong associations were seen between response (CR + PR) and longer TTP, PFS, and OS, and there was incremental benefit in terms of those outcomes for the achievement of CR compared with PR.

Subgroup Analyses

TTP, PFS and OS were evaluated relative to baseline stratification factors, demographic data (sex, race, and age) and disease characteristics (ISS staging and bone marrow cytogenetic abnormalities). The prespecified analyses of the TTP, PFS and OS across all subgroups were consistent with the overall analyses of these endpoints. The hazard ratios for all subgroups were consistently <1, demonstrating a benefit for subjects in the VMP treatment group compared with the MP treatment group for all subgroups with respect to these endpoints.

TTP, PFS, OS, ORR and CR were evaluated for 3 renal function categories (≤ 30 mL/min; 31 to 60 mL/min and >60 mL/min). For all endpoints the benefit of VMP over MP is maintained in all 3 renal function subgroups. The hazard ratios for all subgroups were consistently <1, demonstrating a benefit for subjects in the VMP treatment group compared with the MP treatment group for all 3 renal function subgroups.

Randomized, Open-Label Clinical Study in Relapsed or Refractory Multiple Myeloma

A prospective Phase III, 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 who had received 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 $< 50 \times 10^9/L$. A total of 627 patients were evaluable for response. The study excluded patients with a corrected serum calcium of ≥ 3.5 mmol/L. All patients with hypercalcemia were required to receive intravenous bisphosphonates concomitantly with bortezomib or dexamethasone (depending on treatment randomization).

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 2.4.

Table 2.4: Summary of Baseline Patient and Disease Characteristics in the Phase III 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%
Prior 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/m²/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/m²/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 **Product Monograph PART I, 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.

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 III trial are presented in Table 2.5. Response and progression were assessed using the European Group for Blood and Marrow Transplantation (EBMT) criteria. Complete response (CR) required < 5% plasma cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test (IF-). Partial Response (PR) required $\geq 50\%$ reduction in serum myeloma protein and $\geq 90\%$ reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks along with stable bone disease and normal calcium. Near complete response (nCR) was defined as meeting all the criteria for complete response including 100% reduction in M-protein by protein electrophoresis; however, M-protein was still detectable by immunofixation (IF+).

Table 2.5: Summary of Efficacy Analyses in the Randomized Phase III Previously Treated Multiple Myeloma Study

Efficacy Endpoint	All Patients		1 Prior Line of Therapy		> 1 Prior Line of Therapy	
	VELCADE N=333	Dex N=336	VELCADE N=132	Dex N=119	VELCADE N=200	Dex N=217
Time to progression -						
Event 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 (2.8, 4.2)	7.0 mo (6.2, 8.8)	5.5 mo (3.4, 6.3)	4.9 mo (4.2, 6.3)	2.9 mo (2.8, 3.5)
Hazard ratio ^b (95% CI)	0.55 (0.44, 0.69)		0.56 (0.38, 0.81)		0.55 (0.41, 0.72)	
p-value ^c	<0.0001		0.0021		<0.0001	
Response Rate						
population ^d n=627	n=315	n=312	n=128	n=110	n=187	n=202
CR ^e n (%)	20 (6)	2 (<1)	8 (6)	2 (2)	12 (6)	0 (0)
PR ^e n (%)	101 (32)	54 (17)	49 (38)	27 (25)	52 (28)	27 (13)
nCR ^{e,f} n (%)	21 (7)	3 (<1)	8 (6)	2 (2)	13 (7)	1 (<1)
CR + PR ^e n (%)	121 (38)	56 (18)	57 (45)	29 (26)	64 (34)	27 (13)
p-value ^g	<0.0001		0.0035		<0.0001	
Median Response Duration						
CR ^e	9.9 mo	NE ^h	9.9 mo	NE	6.3 mo	NA ⁱ
nCR ^e	11.5 mo	9.2 mo	NE	NE	11.5 mo	9.2 mo
CR+PR ^e	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 stratified log-rank test including randomization stratification factors.

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

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

^f In 2 patients the IF was unknown.

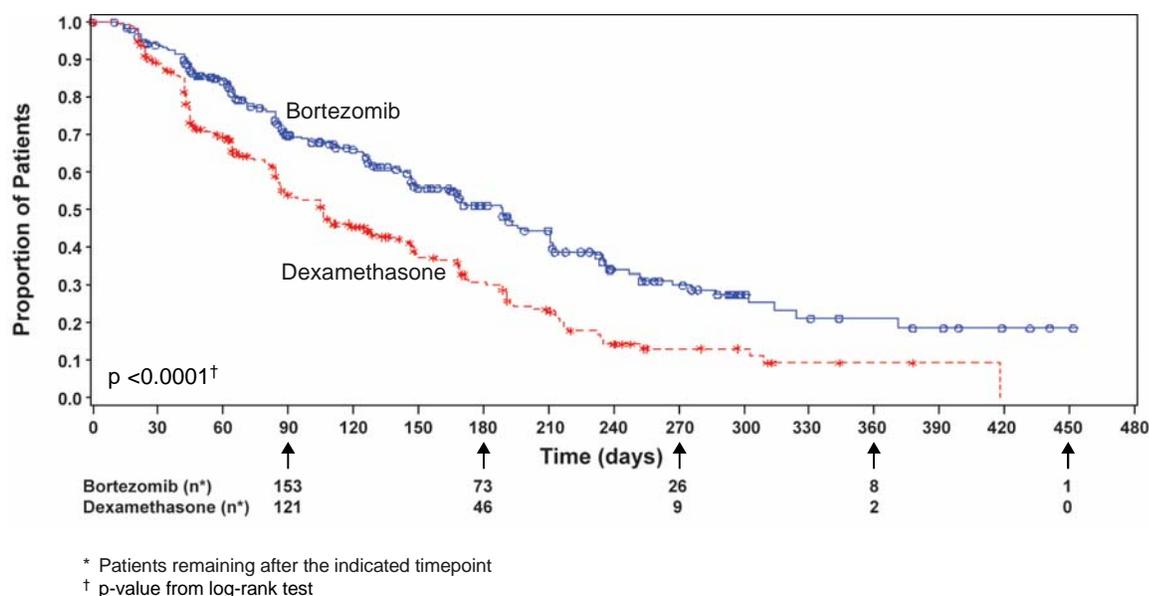
^g p-value for Response Rate (CR+PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors.

^h Not Estimable

ⁱ Not Applicable, no patients in category

There was a statistically significant increase in TTP on the VELCADE arm (see Figure 2.4).

Figure 2.4: Time to Progression in the Randomized Phase III Multiple Myeloma Trial (Bortezomib vs. Dexamethasone) (N=669)



There was a statistically significant improvement in both overall and 1-year survival on the VELCADE arm (see Table 2.6, Figure 2.5 and Figure 2.6) as compared to the dexamethasone arm in all patients as well as in patients who had received 1 prior line of therapy. The efficacy endpoints appear durable, based on the median follow-up of 21.9 months (data not shown).

Table 2.6: Summary of 1-Year and Overall Survival Benefit in the Randomized Phase III Multiple Myeloma Study

Efficacy Endpoint	All Patients		1 Prior Line of Therapy		> 1 Prior Line of Therapy	
	VELCADE	Dex	VELCADE	Dex	VELCADE	Dex
	N=333	N=336	N=132	N=119	N=200	N=217
1-Year Survival % (95% CI)	80 (74, 85)	66 (59, 72)	89 (82, 95)	72 (62, 83)	73 (64, 82)	62 (53, 71)
p-value	0.0025		0.0082		0.0787	
Overall Survival						
Events (deaths) n (%)	51 (15)	84 (25)	12 (9)	24 (20)	39 (20)	60 (28)
Hazard ratio (95% CI)	0.57 (0.40, 0.81)		0.42 (0.21, 0.85)		0.63 (0.42, 0.94)	
p-value	0.0013		0.0130		0.0231	

Figure 2.5: Overall Survival in the Randomized Phase III Multiple Myeloma Trial (Bortezomib vs. Dexamethasone) (N=669)

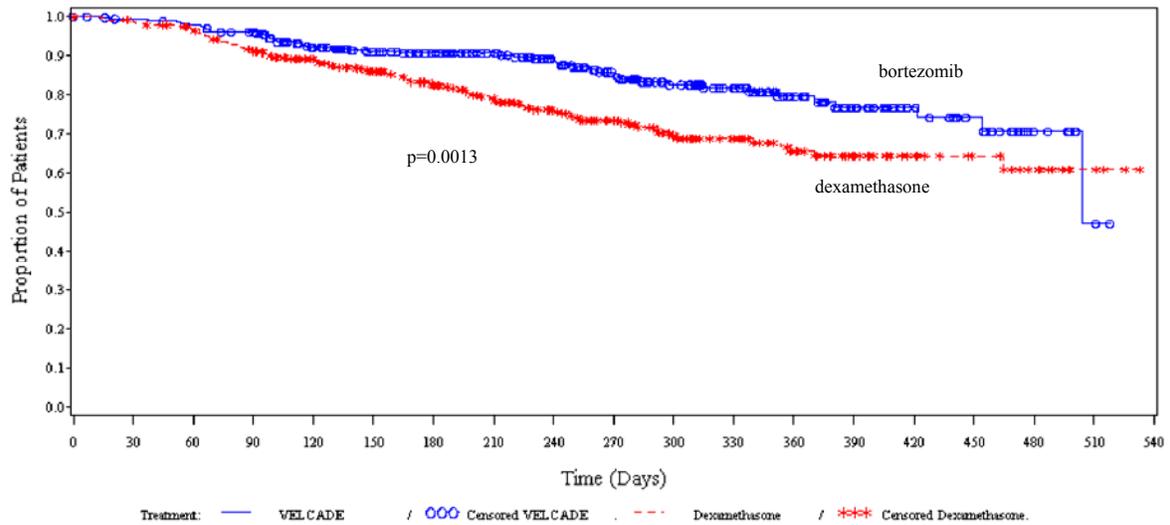
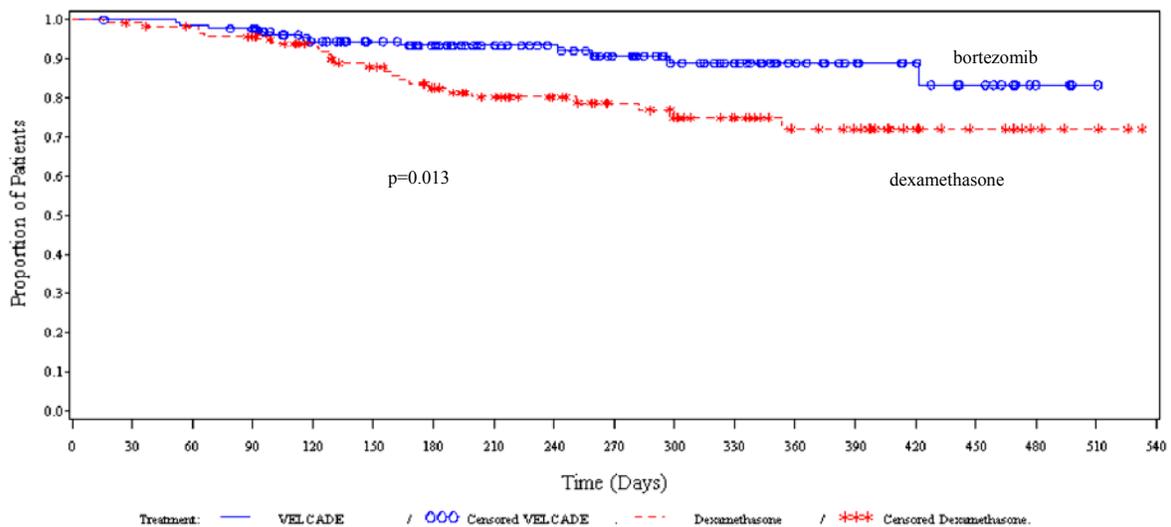


Figure 2.6: Overall Survival in Patients with One Prior Line of Therapy in the Randomized Phase III Multiple Myeloma Trial (Bortezomib vs. Dexamethasone) (N=251)



Regardless of β_2 -microglobulin levels at baseline, TTP and overall survival were significantly longer on the VELCADE arm (β_2 -microglobulin ≤ 2.5 mg/L: p=0.0004, p=0.0222, respectively; > 2.5 mg/L: p<0.0001, p=0.0061, respectively). Similarly, the response rate was significantly higher on the VELCADE arm regardless of screening β_2 -microglobulin levels (β_2 -microglobulin ≤ 2.5 mg/L: p=0.0049; > 2.5 mg/L: p<0.0001).

Phase II Single-Arm Clinical Study in Relapsed Multiple Myeloma

Study Demographics and Trial Design:

The safety and efficacy of VELCADE for Injection were evaluated in an open-label, single-arm, multicentre clinical trial of 202 enrolled patients, 183 of whom had relapsed and refractory myeloma. Patients had received at least 2 prior lines of treatment and were progressing on their most recent treatment. The majority of patients had a very good performance status (only 20% ≤ 70 KPS) as patients with low performance status (KPS ≤ 60) were excluded from this study. Baseline patient and disease characteristics are summarized in Table 2.7. Type and duration of multiple myeloma are summarized in Table 2.8.

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

Table 2.7: Summary of Patient Population and Disease Characteristics[†] in the Phase II Multiple Myeloma Trial

	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
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%
Refractory Disease	91%

[†]Based on number of patients with baseline data available

**Table 2.8: Type and Duration of Multiple Myeloma
(All Patients Treated, N=202)**

Characteristic	Total (N=202)
Type of myeloma [N, (%)]	
N	202
IgG	122 (60)
Kappa	86 (43)
Lambda	36 (18)
IgA	48 (24)
Kappa	30 (15)
Lambda	17 (8)
Kappa + Lambda	1 (<1)
IgD lambda	2 (<1)
IgM lambda	1 (<1)
Light chain	28 (14)
Unspecified	1 (<1)
Patients with oligo- or non-secretory myeloma	19 (9)
Durie-Salmon stage at diagnosis [N (%)]	
N	185
IA	17 (9)
IIA	33 (18)
IIB	2 (<1)
IIIA	117 (63)
IIIB	16 (9)
Duration since diagnosis (years)	
N	202
Mean (\pm SD)	4.5 (3.00)
Median	4.0
Minimum, Maximum	1.0, 18.0

Study Results:

Response rates to VELCADE alone, median duration of response, time to progression and overall survival are presented in Table 2.9. Overall survival and time to progression were based on 202 patients. However, a total of 188 patients were evaluable for response, as 9 patients with non-measurable disease could not be evaluated for response and 5 patients were excluded because of inadequate prior therapy. Response rates to VELCADE alone were determined by an independent review committee (IRC) based on criteria published by Bladé and others. Complete response required < 5% plasma cells in the marrow, 100% reduction in M protein, and a negative immunofixation test (IF-).

Ninety-eight percent (98%) of patients received a starting dose of 1.3 mg/m² with 28% of these receiving this dose throughout the study while 33% of patients who started at a dose of 1.3 mg/m² had dose reductions.

The overall response rate was 28% and the median time to response was 38 days. The median survival of all patients enrolled was 17 months. In general, patients who had a confirmed CR received 2 additional cycles of VELCADE treatment beyond confirmation.

Of 202 patients enrolled, 35% were 65 years of age or older. Nineteen percent (19%) of patients aged 65 years or older experienced responses (CR or PR) versus 32% in patients under the age of 65.

By multivariate analysis, the response rate was independent of the number or type of previous therapies. Responses were seen in patients with chromosome 13 abnormalities. There was a decreased likelihood of response in patients > 65 years of age and with > 50% plasma cells in the bone marrow at screening.

Table 2.9: Summary of Disease Outcomes for VELCADE Monotherapy in Refractory and Relapsed Multiple Myeloma in a Phase II Clinical Study

Response Analyses N=188, 1.3 mg/m² dose	N (%)	(95% CI)
Overall Response Rate (Bladé) (CR+PR)	52 (27.7)	(21, 35)
Complete Response (CR)	5 (2.7)	(1, 6)
Partial Response (PR)	47 (25)	(19, 32)
Kaplan-Meier Estimated Median Duration of Response (CR+PR)	385 Days	(234, 538)
Median Time to Progression - All Patients (N=202)	213 Days	(154, 297)
Median Overall Survival[‡] - All Patients (N=202)	518 Days	(434, 643)

Note: Responses subsequent to the use of dexamethasone are excluded.

[‡]VELCADE alone or in combination with dexamethasone

The protocol allowed patients to receive dexamethasone in conjunction with VELCADE if they had a sub-optimal response to VELCADE alone (i.e., 40 mg dexamethasone with each dose of VELCADE administered as 20 mg PO on the day of and 20 mg PO the day after bortezomib administration if the patient had progressive disease after 2 cycles of VELCADE, or progressive or stable disease after 4 cycles of VELCADE). A total of 74 patients were administered dexamethasone in combination with VELCADE and were assessed for response but were excluded in the assessment of disease outcomes for VELCADE monotherapy. Eighteen percent (13/74) of patients had an improved response (MR (11%) or PR (7%)) with combination treatment.

A Randomized, Phase II, Dose-Response Study in Relapsed or Refractory Multiple Myeloma

In a randomized open-label, single-arm, multicentre study in 54 patients with multiple myeloma who had progressed or relapsed on or after front-line therapy, 28 patients received 1.0 mg/m²/dose and 26 patients received 1.3 mg/m²/dose twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12 to 21). The majority of these patients were not refractory to treatment and had received less than 2 prior lines of therapy. A single complete response was seen at each dose with an additional 2 near complete responses (immunofixation positive) in the 1.0 mg/m² dose group. Based on an update of secondary efficacy endpoints, the median time to progression (TTP) for the 1.0 mg/m² dose was 127 days (4.2 months), while the median TTP for the 1.3 mg/m² dose was 357 days (11.7 months). The median survival for the 1.0 mg/m² dose group was 813 days (26.7 months), while the median survival for the 1.3 mg/m² dose group has not yet been reached.

A Phase II Open-Label Extension Study in Multiple Myeloma

Patients from the two Phase II studies who in the investigators' opinion would experience additional clinical benefit were allowed to receive VELCADE beyond 8 cycles on an extension study. Sixty-three (63) patients from the Phase II 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, although the incidence of some adverse events was higher in this extension study than in the parent studies (see *Product Monograph PART I, ADVERSE REACTIONS*).

A Phase II Single-Arm Clinical Study in Mantle Cell Lymphoma

The safety and efficacy of VELCADE in relapsed or refractory mantle cell lymphoma were evaluated in an open-label, single-arm, multicentre 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. Data on B symptoms were not collected for these patients. 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. Baseline patient and disease characteristics are summarized in Table 2.10.

Table 2.10: Summary of Baseline Patient and Disease Characteristics in the Phase II Mantle Cell Lymphoma Study

	N=155
Patient Characteristics	
Median Age in years (range)	65 (42, 89)
Gender: male/female	81%/19%
Race: Caucasian/black/other	92% /4% /5%
Karnofsky Performance Status, <90	29%
Disease Characteristics	
Median Time Since Initial Diagnosis to First Dose (years)	2.3
Diagnosed < 3 years Prior to First Dose	66%
MCL Stage III or IV at Screening	92%
International Prognostic Index ≥3	44%
Elevated Lactate Dehydrogenase	36%
≥2 Involved Extranodal Sites	34%
Histopathology: Diffuse Growth Pattern	79%
Bone Marrow Positive for MCL	55%
Number of Prior Lines of Therapy	
1	54%
2	42%
3	4%
Received Prior Regimen Containing	
Anthracycline/Mitoxantrone	98%
Alkylating Agents	97%
Rituximab	96%
Received at Least 2 of the Above 3	100%
Received All of the Above 3	91%
Received Prior High-Intensity Therapy	
Received SCT or hyper-CVAD with/without rituximab	37%
Received SCT or hyper-CVAD with/without rituximab	32%
Received Prior High-Intensity Therapy as Last Prior Regimen	30%
Received SCT or hyper-CVAD with/without rituximab as Last Prior Regimen	26%

SCT=stem cell transplant, hyper-CVAD= hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine

VELCADE was administered at the recommended dose of 1.3 mg/m² twice weekly on days 1, 4, 8 and 11 of a 21 day cycle. The median number of cycles administered across all patients was 4 (range 1-17); and 8 in responding patients. The mean number of treated cycles across all patients was 5.7. The median time to response was 40 days (range 31 to 204 days). Response rates to VELCADE are described in Table 2.11. VELCADE demonstrated similar efficacy regardless of the number of prior lines of therapy, with the exception that duration of response was longer in patients who had received only one prior line. Response rates to VELCADE were determined according to the International Workshop Criteria (IWRC) based on independent radiologic review of CT scans.

Table 2.11: Summary of Disease Outcomes in a Phase 2 Mantle Cell Lymphoma Study

	All Patients (N = 141)		1 Prior Line of Therapy (N = 77)		> 1 Prior Line of Therapy (N = 64)	
‡Response Analyses	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
CR + CRu + PR	47 (33)	(26, 42)	23 (30)	(20, 41)	24 (38)	(26, 50)
CR + CRu	11 (8)	(4, 14)	5 (6)	(2, 15)	6 (9)	(4, 19)
CR	9 (6)	(3, 12)	5 (6)	(2, 15)	4 (6)	(2, 15)
CRu	2 (1)	(0, 5)	0		2(3)	(0, 11)
PR	36 (26)	(19, 34)	18 (23)	(14, 34)	18 (28)	(18, 41)
Time to Event Analyses	No. of Events (%)	Median (95% CI)	No. of Events (%)	Median (95% CI)	No. of Events (%)	Median (95% CI)
Kaplan-Meier Estimated Duration of Response						
CR + CRu + PR (N=47)	20 (43)	9.2 months (4.9, 13.5)	11 (48)	9.4 months (5.4, 13.4)	9 (38)	6.1 months (4.2, NE)
CR + CRu (N=11)	3 (27)	13.5 months (13.5, NE)	1 (20)	13.4 months (NE, NE)	2 (33)	NE (4.7, NE)
Kaplan-Meier Estimated Time to Progression (N = 155)	75 (48)	6.2 months (4.0, 6.9)	43 (51)	6.5 months (3.8, 7.2)	32 (45)	5.4 months (3.2, 7.3)
**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 = 45)	12.7 mths	(9.33 NE)				
CR+CRu (N=11)	19.4 mths	(17.8 NE)				

NE=not estimable; CR=complete response; CRu= complete response unconfirmed; PR= partial response

‡Based on International Response Workshop Criteria (IRWC).

**Additional analyses

The Kaplan-Meier curves for the duration of response and the time to progression are presented in Figures (2.7 and 2.8)

Figure 2.7: Duration of Response in the Phase II Mantle Cell Lymphoma Study (N=47)

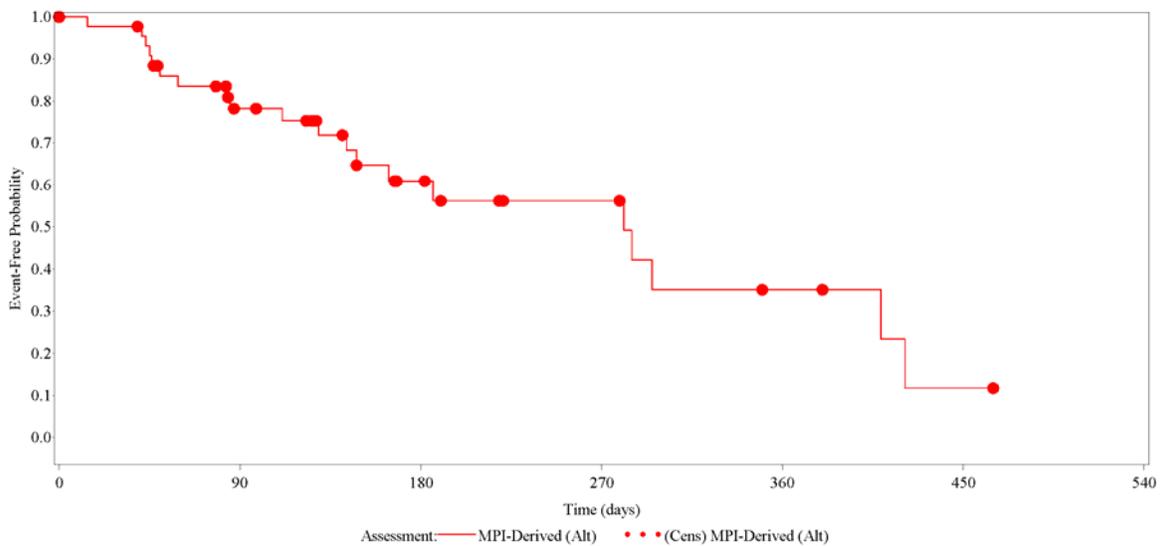
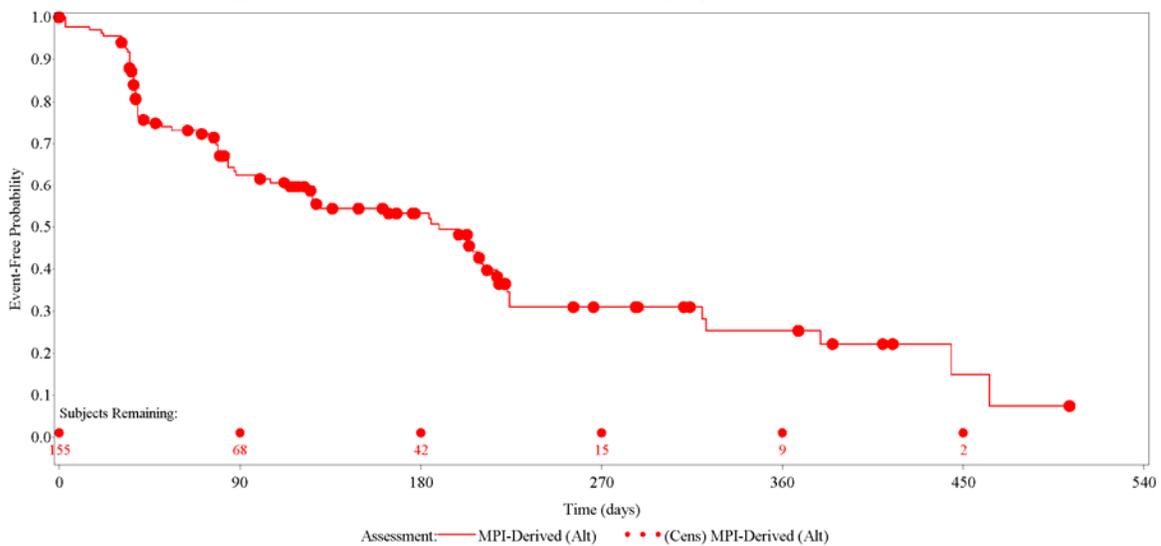
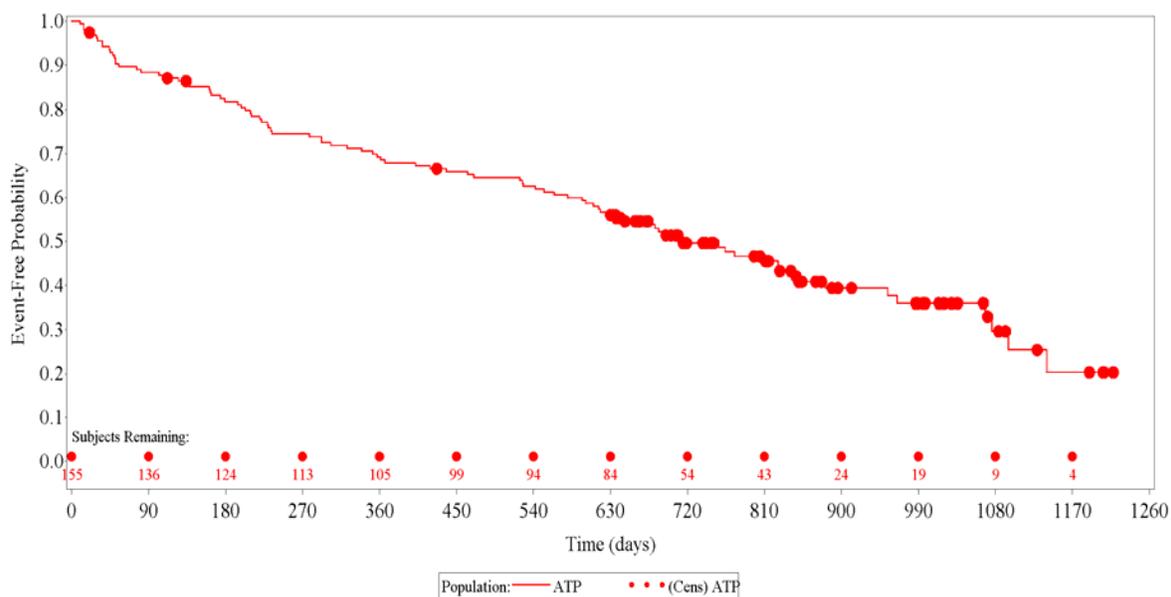


Figure 2.8: Time to Progression in the Phase II Mantle Cell Lymphoma Study (N=155)



With a median duration of follow up of more than 26 months for surviving patients, the median overall survival was 23.6 months with the median survival for responders (CR/CRu/PR) being 35.6 months. The Kaplan-Meier estimate of 1-year survival was 93.5% in responders (CR, CRu, PR). The Kaplan-Meier curve for overall survival of all treated patients is provided in Figure 2.9.

Figure 2.9: Overall Survival in the Phase II Mantle Cell Lymphoma Study (N=155)



The results of the above phase II study are supported by a second multicentre study sponsored by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG). In this single arm phase II study of 29 patients, which included 15 patients who relapsed after 1 or 2 prior chemotherapy regimens, single agent VELCADE provided durable responses (10.3 months) for patients, with relapsed MCL achieving a response rate of 47%. The results of this study along with the results of the previous phase II MCL study, provide support that VELCADE provides clinical benefit in the form of durable responses. The clinical benefit is manifested by delaying the need for alternate cytotoxic chemotherapy and delay the onset of symptoms typically associated with progressive disease.

DETAILED PHARMACOLOGY

Non-Clinical Pharmacology

Bortezomib-mediated proteasome inhibition affects cancer cells in a number of ways, including, but not limited to, altering regulatory proteins, which control cell cycle progression and Nuclear Factor kappa B (NF- κ B) activation. Inhibition of the proteasome results in cell cycle arrest and apoptosis. NF- κ B is a transcription factor whose activation is required for many aspects of tumorigenesis, including cell growth and survival, angiogenesis, cell:cell interactions, and metastasis. *In vitro*, bortezomib affects the ability of myeloma cells to interact with the bone marrow environment.

Proteasome activity in peripheral blood cells and/or packed whole blood was measured by fluorogenic kinetic assays for both the chymotryptic and tryptic activities of the proteasome.

In *in vivo* studies conducted in Lewis Lung, human prostate carcinoma, and multiple myeloma plasmacytoma xenografts, bortezomib dose-dependently reduced tumour volume when administered intravenously, twice weekly, as a single agent at doses varying between 0.9 and 3.0 mg/m².

Non-Clinical Safety Pharmacology

In monkeys, administration of single IV dosages of ≥ 3.0 mg/m² (approximately twice the recommended clinical dose) resulted in altered temperature control and heart rate elevations, followed by profound progressive hypotension, bradycardia, and death 12-14 hours post-dose. Doses ≥ 1.2 mg/m² induced dose-proportional changes in cardiac parameters (Table 2.12).

In conscious telemetered Beagle dogs, a single intravenous administration of bortezomib at 5.0 or 6.0 mg/m² induced a decline in blood pressure, an increase in heart rate, and a decrease in cardiac contractility and left ventricular end diastolic pressure. Twenty-four hours after bortezomib treatment, animals responded to acute, intravenous, pharmacologic interventions using dopamine and/or phenylephrine, with amelioration of the negative pressor and contractility effects (Table 2.12).

In conscious telemetered Beagle dogs, a single intravenous administration of bortezomib at 1.3 mg/m² had no effect on arterial blood pressure, heart rate, ECG intervals or respiratory rate. At 4.0 mg/m², loose feces, bloated abdomens, vomiting, laboured breathing, slow capillary refill time, cold extremities and gums, hind limb tremors, lip-licking, salivation and subdued behaviour were observed which resulted in the sacrifice of 4 out of 6 dogs. When compared with pre-dose baseline values, QTc intervals increased (Table 2.12).

Table 2.12: Summary of Safety Pharmacology Studies

Study Title	Species/ Number of Animals	Dosage/Route	Principal Findings
Cardiovascular Safety Pharmacology Study of Bortezomib in Telemetered Monkeys†	Cynomolgus monkeys, 1M/group (telemetered animals)	Single dose IV at 1.2, 2.4, 3.0, and 3.6 mg/m ²	Mortality at doses ≥3.0 mg/m ² . Rapid breathing, soft feces/diarrhea, tremors, and drooling at 3.6 mg/m ² , hypoactivity at dosages ≥3.0 mg/m ² , emesis at dosages ≥2.4 mg/m ² . ↑HR, BT, severe ↓BP, death 13 to 14 hours post-dose at dosages ≥3.0 mg/m ² . 2.4 mg/m ² : ↑HR, BT, ↓BP for 12-24 hours, cyclicity affected for 5 days. 1.2 mg/m ² : ↑HR, BT, BP, cyclicity affected for 1 day.
Investigative Cardiovascular Safety Study Following Intravenous Administration of Bortezomib in Telemetered Male Beagle Dogs†	Beagle dogs, 4M/group in definitive study, 5M in pilot study (telemetered animals)	Single dose IV at 5 mg/m ² (pilot study) or 6 mg/m ² (definitive study)	↑HR, ↓BP, ↓contractility, ↓left ventricular end diastolic pressures within 24 hours post-dose. ECG changes: ↑PR, QRS, QT, QTc intervals 12-22 hours post-dose. Animals' responses to the combined dopamine and phenylephrine challenges pre- and post-dosing were unchanged. In addition, animals responded to acute dopamine and/or phenylephrine, with amelioration of the negative pressor and contractility effects.
Cardiovascular Effects of Bortezomib in Conscious, Telemetered Beagle Dogs	Beagle dogs, 4M/group (telemetered animals)	Single dose IV at 1.3 mg/m ² and 4.0 mg/m ²	Mortality at the 4.0 mg/m ² dose. 4.0 mg/m ² : ↑HR, ↓BP, ↓RR, PR, and QT intervals, and sustained prolongation of QTc intervals. 1.3 mg/m ² : no adverse clinical signs and no consistent effect on hemodynamic parameters.

†Non-GLP study

Non-Clinical Pharmacokinetics

The kinetic and metabolic profile of bortezomib is similar in rats and monkeys. In distribution studies in rats and monkeys, bortezomib is rapidly distributed after IV administration. The highest tissue concentrations of radioactivity were initially in organs of excretion and metabolism (i.e. kidney and liver), in some tissues related to endocrine (i.e. adrenal and pituitary gland), and secretory functions (i.e. salivary gland) and in regions of rapidly dividing cells (i.e. mucosal lining of the alimentary canal, bone marrow, and spleen). Radioactivity was not detectable in the brain, spinal cord and various regions of the eye and optic nerve. Radioactivity was detected in pituitary and choroid plexus, suggesting that the blood-brain barrier does not protect against entry into at least these parts of the CNS.

In the majority of the tissues investigated, the highest concentration of radioactivity was observed at 1 h after dosing. In a few tissues (like lymph nodes, spleen and thymus), the highest concentration occurred at a later observed time point (24 to 144 hours after dosing). Studies in a mouse model of efficacy also indicated uptake of [¹⁴C]-bortezomib into tumours.

Kinetic analysis of repeated dose studies using the clinical dosing regimen of IV dosing twice weekly for 2 weeks followed by one week rest in the monkey shows an increase in the terminal elimination half-life and a decrease in clearance with repeated dosing. The area under the plasma concentration versus time curve (0 to 24 h) approximately doubled from the first to the second cycle with no further increases in AUC at cycle 13 (Table 2.13).

Table 2.13: Mean (SD) Area Under the Plasma Concentration Versus Time Curve for Bortezomib in Monkeys Following 13 Cycles of Dosing Twice Weekly, 10 Days Off

		0.6 mg/m ²				0.9 mg/m ²				1.2 mg/m ²			
Week	Cycle	T _{1/2-z}	V _z	Cl	AUC ₀₋₂₄	T _{1/2-z}	V _z	Cl	AUC ₀₋₂₄	T _{1/2-z}	V _z	Cl	AUC ₀₋₂₄
		(hr)	(L/kg)	(L/hr/kg)	(hr*ng/mL)	(hr)	(L/kg)	(L/hr/kg)	(hr*ng/mL)	(hr)	(L/kg)	(L/hr/kg)	(hr*ng/mL)
1	1	2.65	13.7	3.57	12.3	9.91	22.2	1.9	34.6	7.78	17.6	1.74	51.3
		-0.236	-3.69	-0.829	(2.69)	(3.86)	(4.88)	(1.09)	(10.4)	(3.16)	(5.59)	(0.522)	-10.6
5	2	12.9	15.1	0.841	45.1	12.4	11.7	0.676	82.9	9.68	10.5	0.778	111
		(2.92)	-3.27	-0.19	(7.73)	(3.64)	-3.22	(0.191)	(15.2)	(2.59)	(2.72)	(0.214)	(29.5)
37	13	47.9	26	0.644	38.5	130	49.5	0.309	58.4	95.3	53	0.395	72.8
		(43.9)	(12.8)	-0.479	(5.56)	(77.2)	(10.2)	(0.109)	(13.8)	(28.4)	(18.9)	(0.129)	(13.8)
38	13	55	26.4	0.429	45.4	46.7	26.5	0.388	74.9	53.4	31.7	0.423	92.3
		(30.8)	(5.68)	(0.207)	(10.9)	(12)	(9.42)	-0.054	(17.8)	(11.7)	(6.75)	(0.102)	(14.3)

The binding of bortezomib to rat, cynomolgus monkey and human plasma proteins was similar across the three species. Over a bortezomib concentration range of 10 to 1000 ng/mL, the *in vitro* protein binding averaged 84.9% in rat plasma, 72.4% in cynomolgus monkey plasma and 82.9% in human plasma. The percent of bortezomib bound to plasma proteins was not concentration dependent.

In vitro and *in vivo* studies indicated that bortezomib is extensively metabolized in rats, monkeys and humans, producing greater than 30 metabolites through P450 dependent and independent pathways. Bortezomib has not been shown to be metabolized via phase II pathways, e.g., glucuronidation and sulfation.

Bortezomib has been shown to be a poor inhibitor of human recombinant expressed CYP isozymes, with IC₅₀ ≥ 30 μM or 11.5 μg/mL for CYP 1A2, 2C9, 2D6 and 3A4, and IC₅₀ ≥ 18 μM or 6.9 μg/mL for 2C19. Bortezomib did not induce the activities of CYP 3A4 and 1A2 in primary cultured human hepatocytes. In addition, bortezomib does not appear to be a substrate for p-glycoprotein (Pgp) and several other drug efflux pumps.

Biliary excretion is the primary route of elimination of [¹⁴C]-bortezomib-derived radioactivity in rats. In intact rats, 38.6% of the administered radioactivity was recovered in feces, 21.1% was recovered in urine, and 6.12% was recovered in expired air in 72 hours.

In the monkey, [¹⁴C]-bortezomib-derived radioactivity was excreted in both the urine and bile. Within the first 24 hours, 30 to 40% of the total recovered radioactivity was excreted via urine or feces. The remaining 60 to 70% of the recovered radioactivity was eliminated slowly during the next 120 hours.

Transfer of bortezomib across the placenta and secretion in milk have not been determined.

Clinical Pharmacology

Pharmacodynamics:

The level of proteasome inhibition obtained at the therapeutic dose of 1.3 mg/m² appears consistent across different studies. Table 2.14 summarizes data from a Phase I study relative to a range of doses (1.2 to 1.38 mg/m²) similar to the dose used in Phase II studies (1.3 mg/m²), demonstrating a similar mean maximum inhibition and an equally similar inter-individual variability.

Table 2.14: Comparative Values of Proteasome Inhibition Level Across Studies[‡]

Study / Dose (mg/m ²)	Cycle 1, Day 1, 1 Hour Post-Dose		
	N	Mean Percent (%) Inhibition of 20S Proteasome Activity	Range (%)
Phase I Study LCC9834/00-31 (1.2 - 1.38)	18	63	36-92
Phase II Study M34100-025 (1.3)	141	61	14-97
Phase II Study M34100-024 (1.3)	11	71	51-89

[‡]Based on whole blood assay

Pharmacokinetics:

A Phase 1 study was conducted in relapsed multiple myeloma patients to characterize the pharmacokinetics of bortezomib following single and multiple doses. Following intravenous bolus administration of 1.0 mg/m² and 1.3 mg/m² doses to 24 patients (n = 12 per each dose level), the mean first-dose maximum plasma concentrations of bortezomib were 57 and 112 ng/mL, respectively. In subsequent doses administered twice weekly, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1.0 mg/m² dose and 89 to 120 ng/mL for the 1.3 mg/m² dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours for the 1.0 mg/m² dose, and 49 to 109 hours for the 1.3 mg/m² dose. 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/m² and 1.3 mg/m², respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1.0 mg/m² and 1.3 mg/m², respectively.

TOXICOLOGY

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, gastrointestinal, neurological, testicular, ovarian and lymphoid system toxicities. Neurotoxic effects of bortezomib in animal studies included axonal swelling and degeneration in peripheral sensory nerves, dorsal spinal roots, and tracts of the spinal cord. Additionally, in the monkey, multifocal hemorrhage and necrosis in the brain, eye, and heart were observed, these effects considered related to anemia/thrombocytopenia-induced ischemia.

The range between lethal and non-lethal doses after both acute and repeated dose administration is narrow in all species evaluated (mice, rat, monkey and dog). In repeated dose studies, bortezomib lethality occurred after multiple cycles (twice weekly for 2 weeks, 10 days off) at 0.9 mg/m² in both rats and monkeys, i.e. lower than proposed clinical dose with hematopoietic, gastrointestinal and lymphoid system lesions considered to be contributing factors to the debilitated state and early death and lethality.

Table 2.15 summarizes some single-dose and repeat-dose toxicity studies conducted in rats and monkeys.

Table 2.15: Summary of Single-Dose and Repeat-Dose Toxicology Studies

Study Title	Species/ Number of Animals	Dosage/Route	Principal Findings
Single-Dose			
Single Dose Intravenous Toxicity and Toxicokinetic Study with Bortezomib in Rats [†]	Sprague-Dawley rats 5/sex/group main study animals and 6-9/sex/group TK	Single dose IV at 0, 0.18, 0.6, and 1.8 mg/m ²	Mortality at 1.8 mg/m ² , 2/5 F on Day 2. No abnormal clinical signs. ↑WBC, ↓erythroid parameters, platelets at 1.8 mg/m ² . ↑BUN/creat., AST/ALT in individuals at 1.8 mg/m ² . No test article-related macroscopic or microscopic findings. NOAEL and MTD were 0.6 mg/m ² .
Repeat-Dose			
26-Week Intravenous Injection Toxicity Study of Bortezomib in the Albino Rat [†]	Sprague-Dawley rats 10/sex/group main study and 10/sex/group recovery animals and 12/sex/group TK/PD	Twice weekly IV for 2 consecutive weeks with 1 week off (1 cycle). 26 weeks equals 9 cycles. 0, 0.3, 0.6, and 1.2/0.9 mg/m ² . 8-Week recovery period.	Mortality at 1.2/0.9 mg/m ² . ↓Body weights in males at dosages ≥0.6 mg/m ² . ↓Food consumption at 1.2/0.9 mg/m ² . ↓Platelet counts and erythrocytic parameters and cholesterol levels at all dosages and potassium at dosage ≥0.6 mg/m ² and total protein, albumin and globulin at 1.2/0.9 mg/m ² . ↑WBC, fibrinogen, blood glucose and phosphorus at all dosages. ↑Liver weights at all dosages and kidneys (females only) at dosages ≥0.6 mg/m ² . ↓Thymus and epididymal weights at 1.2/0.9 mg/m ² . Microscopic changes to liver, GI and salivary gland at all dosages. Microscopic changes to kidneys, lymphoid organs/tissues, spleen, nasolacrimal ducts, fat (males only) and ovaries at ≥0.6 mg/m ² . Anterior and/or posterior uveitis (males only) and testicular changes at 1.2/0.9 mg/m ² . Hypocellularity/necrosis of bone marrow at dosages ≥0.6 mg/m ² . Reversibility observed except for platelet counts, glucose levels, liver and spleen microscopic changes although trend noted. NOAEL was not determined. MTD was 0.6 mg/m ² .

Study Title	Species/ Number of Animals	Dosage/Route	Principal Findings
4-Week IV Toxicity Study with Bortezomib in Cynomolgus Monkeys [†]	Cynomolgus monkeys 3/sex/group main study animals and 2/sex/group recovery animals	Twice-weekly IV for 4 weeks at 0, 0.54, 0.8, and 1.2 mg/m ² /dose with a 2-week recovery	Mortality at 1.2 mg/m ² in 1M on Day 26. ↑Monocytes, ↓lymphocytes at dosages ≥0.8 mg/m ² . ↓Erythroid parameters in males at 1.2 mg/m ² . ↑Fibrinogen, ↓total protein at 1.2 mg/m ² . Minimal to mild axonal degeneration, slight lymphocytic depletion of the spleen and mild tubular nephrosis and slight glomeruli changes at 1.2 mg/m ² . Trend towards recovery was noted except for ↓lymphocyte count in one male and axonal degeneration in one female at 1.2 mg/m ² . NOAEL was 0.54 mg/m ² . MTD was 0.80 mg/m ² /dose.
A 38-Week (13-Cycles) IV Injection Toxicity Study of Bortezomib in the Cynomolgus Monkey [†]	Cynomolgus monkeys 3/sex/group main study animals and 3/controls/sex and 1F at 0.6 mg/m ² and 3M and 2F at 1.2 mg/m ² assigned to recovery evaluation.	Twice-weekly IV with one week off (3 week cycle) for 38 weeks at 0, 0.6, 0.9, and 1.2 mg/m ² with an 8-week recovery	Mortality at dosages ≥0.9 mg/m ² . 1/6 M and 2/6F at 1.2 mg/m ² and 1/3F at 0.9 mg/m ² . Cause of deteriorating condition was GI intolerance in 1 animal and severe anemia and thrombocytopenia in 3 animals. ↓Erythrocyte, leukocyte and platelet parameters at all dosages with onset between Day 72 and 170. ↑Fibrinogen values at all dosages starting on Day 170. Bone marrow changes at all dosages generally reflective of hematological changes. ↑Liver and kidney weights at all dosages. Microscopic findings in bone marrow, lymphoid organ/tissues at all dosage levels. Peripheral nervous system, kidney, intestinal tract and liver/gallbladder findings at dosages ≥0.9 mg/m ² . Recovery: Bone marrow, mandibular lymph nodes and spleen demonstrated reversible hyperplastic response. Kidney, thymus and PNS showed incomplete reversibility. NOAEL was not determined. MTD was 0.6 mg/m ² .

[†] GLP study
TK = toxicokinetic
PD = pharmacodynamic

Mutagenicity

As summarized in Table 2.16, 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.

Table 2.16: Summary of Mutagenicity Studies

Study Title	Species/ Number of Animals	Dosage/Route	Principal Findings
<i>In vitro</i> Mammalian Chromosome Aberration Test in Chinese Hamster Ovary Cells [†]	Chinese Hamster Ovary cell line	≤200 µg/mL	Bortezomib was positive for induction of structural chromosome aberrations and negative for induction of numerical chromosome aberrations in CHO cells
Mammalian Erythrocyte Micronucleus Test in Mice [†]	ICR mice 5/sex/group	Single dose IV at 0, 0.75, 1.50, and 3.00 mg/m ²	Bortezomib showed no clastogenic potential under the test conditions.
Bacterial Reverse Mutagenicity Assay [†]	<i>Salmonella typhimurium</i> and <i>Escherichia coli</i>	≤5000 µg/plate	Bortezomib showed no mutagenic potential under the test conditions.

[†] GLP study

Reproductive and Developmental Toxicity

There are no dedicated studies to assess effects on fertility but with degenerative effects in the ovary at ≥ 0.3 mg/m² and degenerative changes in the testes at 0.9/1.2 mg/m² in the 6-month rat toxicity study, reduced fertility is expected. Due to maternal toxicity, embryo fetal development studies were conducted at sub-therapeutic doses; however, bortezomib was administered daily (Table 2.17).

Table 2.17: Summary of Embryo Fetal Development Studies

Study Title	Species/ Number of Animals	Dosage/Route	Principal Findings
An Intravenous Injection Teratology Study of Bortezomib in the Sprague-Dawley Rat [†]	Time-mated Sprague-Dawley Rats/22 females/group	Daily IV from gestation day 6 to 17 inclusive at 0, 0.15, 0.30, and 0.45 mg/m ² /day.	↓Transitory body weight at 0.45 mg/m ² . ↓Food consumption at 0.45 mg/m ² . No selective embryo-lethal or fetal-toxic effects were observed at dosages ≤0.45 mg/m ² .
An Intravenous Injection Teratology Study of Bortezomib in the New Zealand White Rabbit [†]	Time-mated New Zealand White rabbits/22 females/group	Daily IV administration from gestation Day 7 to 19 inclusive at 0, 0.11, 0.28, and 0.55 mg/m ² /day.	Mortality in one female at 0.55 mg/m ² and 4 does showed signs of abortion and related clinical signs ↓Weight gain and food consumption at 0.55 mg/m ² ↓Numbers of live fetuses and fetal weight at 0.55 mg/m ² No selective embryo-lethal or fetal-toxic effects were observed at dosages ≤ 0.28 mg/m ² . NOAEL and MTD were 0.28 mg/m ²

[†] GLP study

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PART III: CONSUMER INFORMATION

PrVELCADE*
bortezomib

This leaflet is Part III of a three-part "Product Monograph" published when VELCADE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VELCADE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

VELCADE is used for the treatment of adult patients with:

- Previously untreated Multiple Myeloma (MM) who are unsuitable for stem cell transplantation as part of combination therapy. MM is a cancer of the bone marrow
- Relapsed MM
- Mantle cell lymphoma. Mantle cell lymphoma is a type of non-Hodgkin's lymphoma which is a cancer of the blood that affects the white blood cells.

What it does:

VELCADE is a chemotherapy medicine, which is medicine used to kill cancer cells.

When it should not be used:

Do not use VELCADE if you are allergic (hypersensitive) to bortezomib, boron or to any of the other ingredients of VELCADE.

What the medicinal ingredient is:

The medicinal ingredient is bortezomib mannitol boronic ester.

What the nonmedicinal ingredients are:

The nonmedicinal ingredient is mannitol.

What dosage forms it comes in:

VELCADE is supplied as a powder which will be dissolved in a sterile, sodium chloride (salt) solution before being injected into your vein (intravenous). After reconstitution, 1 mL of solution for injection contains 1 mg bortezomib.

Each pack of VELCADE contains one glass vial. Each vial contains 3.5 mg of bortezomib (as a mannitol boronic ester).

WARNINGS AND PRECAUTIONS**Serious Warnings and Precautions**

VELCADE must be administered under the supervision of a physician qualified in the use of anti-cancer drugs.

Overdose ($\geq 2X$ recommended dose) could result in death.

Serious side effects that may occur with VELCADE include:

- Low blood pressure and other serious heart disorders
- Bleeding into the brain or gastrointestinal tract (stomach or bowel)
- Muscle weakness due to nerve damage (severe motor neuropathy)
- Acute lung disease (acute diffuse infiltrative pulmonary disease)

BEFORE you use VELCADE, talk to your doctor or pharmacist if:

- you have had any bleeding problems, a low level of red blood cells, platelets, or white blood cells, as these conditions may become worse during treatment with VELCADE;
- you are suffering from diarrhea, constipation, nausea or vomiting, as this may become worse during VELCADE treatment;
- you have any problems with your heart or blood pressure including a history of fainting, dizziness or light-headedness;
- you have any problems with your kidneys;
- you have any problems with your liver;
- you have had any problems in the past with numbness, tingling, or pain in the hands or feet (neuropathy); (This effect may become worse during VELCADE treatment.);
- you have been diagnosed in the past with a condition called amyloidosis (abnormal protein deposition in tissues);
- you have shortness of breath with activity (progressively worsens), cough, and difficulty breathing; (Symptoms may develop or worsen during VELCADE treatment.)
- you are pregnant, planning to become pregnant or breast-feeding.

VELCADE has not been studied in children or adolescents.

Contraception and Pregnancy:

Both men and women must use effective contraception while receiving VELCADE, and for 3 months after their treatment. 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 are not given VELCADE if you are pregnant.

Breast-feeding:

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.

Driving and using machines:

VELCADE might cause low blood pressure that may lead to tiredness, dizziness, fainting, or blurred vision. Do not drive or operate any dangerous tools or machines if you experience such side effects. Even if you have not felt these effects, you must still be cautious.

INTERACTIONS WITH THIS MEDICATION

Inform your doctor, medical health personnel or pharmacist about all medicines you are taking, whether prescribed for you or bought without a prescription.

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

PROPER USE OF THIS MEDICATION

Method and route of administration:

Your intravenous treatment (injected into the vein) with VELCADE will take place in a specialized medical facility.

Usual dose:

The dose will be calculated from your height and weight. The usual starting dose is 1.3 milligrams per square metre body surface area. The injection will take 3 to 5 seconds, and the injection syringe will then be rinsed through with a small quantity of sterile sodium chloride (salt) solution.

Frequency of treatment:

Previously Untreated Multiple Myeloma

The treatment consists of nine 6-week treatment cycles. Each treatment cycle consists of 6 weeks. In cycles 1-4, VELCADE is given twice weekly on day 1, 4, 8, 11, 22, 25, 29 and 32. In cycles 5-9, VELCADE is given once a week on day 1, 8, 22 and 29.

Relapsed Multiple Myeloma and Mantle Cell Lymphoma

VELCADE is given twice weekly on days 1, 4, 8 and 11 of a 3-week treatment cycle. In maintenance treatment, VELCADE is given once a week for 4 weeks on days 1, 8, 15 and 22.

Your doctor may change the dosage during the treatment, and will decide the total number of cycles that you need. It all depends on your response to the treatment.

Overdose:

If you think that you have been given VELCADE more frequently than you should, or too high a dose, tell your healthcare provider immediately or contact your local poison control centre immediately.

Missed dose:

If you think that you have missed a dose of VELCADE, tell your healthcare provider immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, VELCADE can have side effects. The following are the most commonly reported side effects ($\geq 10\%$):

Blood and lymph disorders: Low red or white blood cells causing anemia, bruising or bleeding

Eye disorders: blurred vision

Gastrointestinal disorders: feeling sick in the stomach or loss of appetite, diarrhea, constipation, vomiting, abdominal pain, heartburn, stomach ulcers

General disorders: general ill feeling, tiredness, or a feeling of weakness, fever, swelling (around the arms, legs or face), shivering

Infections: shingles (herpes zoster virus), flu-like symptoms, chest and other infections

Metabolism and nutrition disorders: Dehydration, losing weight

Musculoskeletal disorders: joint or muscle stiffness, muscle cramps, muscle or bone pain, back pain

Nervous system disorders: numbness, tingling or burning sensation in the hands or feet, headache, dizziness

Psychiatric disorders: difficulty in sleeping, anxiety or depression (feeling down), confusion

Respiratory disorders: shortness of breath, cough

Skin disorders: rash and/or itching, hives, redness, pain at the injection site

Cardiovascular disorders: sudden fall of blood pressure on standing which may lead to fainting, pericarditis or inflammation of the lining around the heart

If you notice these or any other effects not mentioned in this leaflet, inform your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist	
	Only if severe	In all cases
Common		
Fever		✓
Chest and other infections including shingles		✓
Diarrhea	✓	
Vomiting	✓	
Dehydration (dry mouth, excessive thirst, dark yellow urine)		✓
Nausea	✓	
Difficulty breathing/breathlessness	✓	
Altered sensation/pins and needles in hands or feet	✓	
Pain and altered sensation		✓
Bleeding from gums or other sites or abnormal bruising		✓
Tiredness/lethargy	✓	
Joint pain and muscle cramps	✓	
Headache	✓	
Low blood pressure (dizziness or fainting)		✓
Uncommon		
Swelling of face or neck		✓
Swelling of ankles	✓	
Chest palpitations/awareness of abnormal heart rhythm	✓	
Angina (chest pain)	✓	
Loss of appetite	✓	
Constipation	✓	
Yellowing of skin or whites of eyes		✓
Skin rash		✓
Difficulty moving limbs, walking or speaking, stroke		✓
Confusion		✓
Seizure (fits)		✓
Loss of control of or inability to pass urine		✓
Muscle weakness	✓	

This is not a complete list of side effects. For any unexpected effects while taking VELCADE, contact your doctor or pharmacist.

HOW TO STORE IT

VELCADE should be kept out of the reach of children.

VELCADE should be stored between 15 to 30°C. Keep the container in the outer carton in order to protect it from light. Do not use after the expiry date stated on the vial and the carton.

The reconstituted solution may be stored for 8 hours at 25°C in the original vial or a syringe prior to administration, with a maximum of 8 hours in the syringe.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be found at: <http://www.janssen-ortho.com> or by contacting the sponsor, Janssen-Ortho Inc., at: 1-800-567-3331

This leaflet was prepared by Janssen-Ortho Inc. Toronto, Ontario M3C 1L9

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