HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BORTEZOMIB FOR INJECTION safely and effectively. See full prescribing information for BORTEZOMIB FOR INJECTION.

BORTEZOMIB for injection, for subcutaneous or intravenous use
Initial U.S. Approval: 2003

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

Indications and Usage, Mantle Cell Lymphoma (1.2), Removed phrase "who have received at least 1 prior therapy"	12/2022
Dosage and Administration (2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 2.10)	12/2022
Warnings and Precautions, Thrombocytopenia/Neutropenia (5.7)	12/2022

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

Bortezomib for Injection is a proteasome inhibitor indicated for:

- Treatment of adult patients with multiple myeloma. (1.1)
- Treatment of adult patients with mantle cell lymphoma. (1.2)

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

- For subcutaneous or intravenous use only. Each route of administration has a different reconstituted concentration; Exercise caution when calculating the volume to be administered. (2.1, 2.10)
- The recommended starting dose of Bortezomib for Injection is 1.3 mg/m^2 administered either as a 3 to 5 second bolus intravenous injection or subcutaneous injection. (2.2, 2.4, 2.6)
- Retreatment for multiple myeloma: May retreat starting at the last tolerated dose. (2.6)
- Hepatic Impairment: Use a lower starting dose for patients with moderate or severe hepatic impairment. (2.8)
- Dose must be individualized to prevent overdose. (2.10)

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

For injection: 1 mg or 2.5 mg of bortezomib as a lyophilized powder in a single-dose vial for reconstitution and withdrawal of the appropriate individual patient dose. (3)

---------- CONTRAINDICATIONS ----------

- Patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol, including anaphylactic reactions. (4)
- Contraindicated for intrathecal administration. (4)

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

- Peripheral Neuropathy: Manage with dose modification or discontinuation. (2.7) Patients with pre-existing severe neuropathy should be treated with Bortezomib for Injection only after careful risk-benefit assessment. (2.7, 5.1)
- Hypotension: Use caution when treating patients taking antihypertensives, with a history of syncope, or with dehydration. (5.2)
- Cardiac Toxicity: Worsening of and development of cardiac failure has occurred. Closely monitor patients with existing heart disease or risk factors for heart disease. (5.3)
- Pulmonary Toxicity: Acute respiratory syndromes have occurred. Monitor closely for new or worsening symptoms and consider interrupting Bortezomib for Injection therapy. (5.4)
- Posterior Reversible Encephalopathy Syndrome: Consider MRI imaging for onset of visual or neurological symptoms; discontinue Bortezomib for Injection if suspected. (5.5)
- Gastrointestinal Toxicity: Nausea, diarrhea, constipation, and vomiting may require use of antiemetic and antidiarrheal medications or fluid replacement. (5.6)
- Thrombocytopenia/Neutropenia: Monitor complete blood counts regularly throughout treatment. (5.7)
- Tumor Lysis Syndrome: Closely monitor patients with high tumor burden. (5.8)
- Hepatic Toxicity: Monitor hepatic enzymes during treatment. Interrupt Bortezomib for Injection therapy to assess reversibility. (5.9)
- Thrombotic Microangiopathy: Monitor for signs and symptoms. Discontinue Bortezomib for Injection if suspected. (5.10)
- Embryo-Fetal Toxicity: Bortezomib for Injection can cause fetal harm. Advise females of reproductive potential and males with female partners of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.11)

---------- ADVERSE REACTIONS ----------

Most commonly reported adverse reactions (incidence ≥20%) in clinical studies include nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, and anorexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc., at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- DRUG INTERACTIONS ----------

- Strong CYP3A4 Inhibitors: Closely monitor patients with concomitant use. (7.1)
- Strong CYP3A4 Inducers: Avoid concomitant use. (7.1)

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

Patients with diabetes may require close monitoring of blood glucose and adjustment of antidiabetic medication. (8.8)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma

Bortezomib for Injection is indicated for the treatment of adult patients with multiple myeloma.

1.2 Mantle Cell Lymphoma

Bortezomib for Injection is indicated for the treatment of adult patients with mantle cell lymphoma.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Guidelines

Bortezomib for Injection is for intravenous or subcutaneous use only. Do not administer Bortezomib for Injection by any other route.

Because each route of administration has a different reconstituted concentration, use caution when calculating the volume to be administered.

The recommended starting dose of Bortezomib for Injection is 1.3 mg/m^2. Bortezomib for Injection is administered intravenously at a concentration of 1 mg/mL, or subcutaneously at a concentration of 2.5 mg/mL *[see Dosage and Administration (2.10)]*.

Bortezomib for Injection retreatment may be considered for patients with multiple myeloma who had previously responded to treatment with Bortezomib for Injection and who have relapsed at least six months after completing prior Bortezomib for Injection treatment. Treatment may be started at the last tolerated dose *[see Dosage and Administration (2.6)]*.

When administered intravenously, administer Bortezomib for Injection as a 3 to 5 second bolus intravenous injection.

2.2 Dosage in Previously Untreated Multiple Myeloma

Bortezomib for Injection is administered in combination with oral melphalan and oral prednisone for 9, six-week treatment cycles as shown in *Table 1*. In Cycles 1 to 4, Bortezomib for Injection is administered twice weekly (Days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5 to 9, Bortezomib for Injection is administered once weekly (Days 1, 8, 22 and 29). At least 72 hours should elapse between consecutive doses of Bortezomib for Injection.

Table 1: Dosage Regimen for Patients with Previously Untreated Multiple Myeloma

Twice Weekly Bortezomib for Injection (Cycles 1 to 4)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
Bortezomib for Injection (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)	Day	Day	Day	Day	--	--	rest	--	--	--	--	rest

Prednisone (60 mg/m^2)	1	2	3	4			period					period
Once Weekly Bortezomib for Injection (Cycles 5 to 9 when used in combination with Melphalan and Prednisone)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
Bortezomib for Injection (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

2.3 Dose Modification Guidelines for Bortezomib for Injection When Given in Combination with Melphalan and Prednisone

Prior to initiating any cycle of therapy with Bortezomib for Injection in combination with melphalan and prednisone:

- Platelet count should be at least 70 x 10^9/L and the absolute neutrophil count (ANC) should be at least 1 x 10^9/L
- Non-hematological toxicities should have resolved to Grade 1 or baseline

Table 2: Dose Modifications During Cycles of Combination Bortezomib for Injection, Melphalan and Prednisone Therapy

Toxicity	Dose Modification or Delay
Hematological toxicity during a cycle: If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25% in the next cycle
If platelet count is not above 30 x 10^9/L or ANC is not above 0.75 x 10^9/L on a Bortezomib for Injection dosing day (other than Day 1)	Withhold Bortezomib for Injection dose
If several Bortezomib for Injection doses in consecutive cycles are withheld due to toxicity	Reduce Bortezomib for Injection dose by one dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2)
Grade 3 or higher non-hematological toxicities	Withhold Bortezomib for Injection therapy until symptoms of toxicity have resolved to Grade 1 or baseline. Then, Bortezomib for Injection 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 Bortezomib for Injection-related neuropathic pain and/or peripheral neuropathy, hold or modify Bortezomib for Injection as outlined in *Table 5*.

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

Dose modifications guidelines for peripheral neuropathy are provided *[see Dosage and Administration (2.7)]*.

2.4 Dosage in Previously Untreated Mantle Cell Lymphoma

Bortezomib (1.3 mg/m^2) is administered intravenously in combination with intravenous rituximab, cyclophosphamide, doxorubicin and oral prednisone (VcR-CAP) for 6, three week treatment cycles as shown in *Table 3*. Bortezomib is administered first followed by rituximab. Bortezomib is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a ten day rest period on Days 12 to 21. For

patients with a response first documented at Cycle 6, two additional VcR-CAP cycles are recommended. At least 72 hours should elapse between consecutive doses of bortezomib.

Table 3: Dosage Regimen for Patients with Previously Untreated Mantle Cell Lymphoma Twice Weekly Bortezomib (6, Three Week Cycles)*

Week	1					2		3
Bortezomib (1.3 mg/m^2)	Day 1	--	--	Day 4	--	Day 8	Day 11	rest period
Rituximab (375 mg/m^2) Cyclophosphamide (750 mg/m^2) Doxorubicin (50 mg/m^2)	Day 1	--	--			--	--	rest period
Prednisone (100 mg/m^2)	Day 1	Day 2	Day 3	Day 4	Day 5	--	--	rest period

* Dosing may continue for two more cycles (for a total of eight cycles) if response is first seen at Cycle 6.

2.5 Dose Modification Guidelines for Bortezomib When Given in Combination with Rituximab, Cyclophosphamide, Doxorubicin and Prednisone

Prior to the first day of each cycle (other than Cycle 1):

- Platelet count should be at least 100 x 10^9/L and absolute neutrophil count (ANC) should be at least 1.5 x 10^9/L
- Hemoglobin should be at least 8 g/dL (at least 4.96 mmol/L)
- Nonhematologic toxicity should have recovered to Grade 1 or baseline

Interrupt bortezomib treatment at the onset of any Grade 3 hematologic or nonhematological toxicities, excluding neuropathy *[see Table 5, Warnings and Precautions (5)]*. For dose adjustments, see *Table 4* below.

Table 4: Dose Modifications on Days 4, 8, and 11 During Cycles of Combination Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin and Prednisone Therapy

Toxicity	Dose Modification or Delay
Hematological Toxicity	
Grade 3 or higher neutropenia, or a platelet count not at or above 25 x 10^9/L	Withhold bortezomib therapy for up to 2 weeks until the patient has an ANC at or above 0.75 x 10^9/L and a platelet count at or above 25 x 10^9/L. • If, after bortezomib has been withheld, the toxicity does not resolve, discontinue bortezomib. • If toxicity resolves such that the patient has an ANC at or above 0.75 x 10^9/L and a platelet count at or above 25 x 10^9/L, bortezomib dose should be reduced by 1 dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2).
Grade 3 or higher nonhematological toxicities	Withhold bortezomib therapy until symptoms of the toxicity have resolved to Grade 2 or better. Then, bortezomib 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 bortezomib-related neuropathic pain and/or peripheral neuropathy, hold or modify bortezomib as outlined in *Table 5*.

For information concerning rituximab, cyclophosphamide, doxorubicin and prednisone, see manufacturer's prescribing information.

2.6 Dosage and Dose Modifications for Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma

Bortezomib for Injection (1.3 mg/m^2/dose) is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a ten day rest period (Days 12 to 21). For extended therapy of more than eight cycles, Bortezomib for Injection may be administered on the standard schedule or, for relapsed multiple myeloma, on a maintenance schedule of once weekly for four weeks (Days 1, 8, 15, and 22) followed by a 13 day rest period (Days 23 to 35) *[see Clinical Studies (14)]*. At least 72 hours should elapse between consecutive doses of Bortezomib for Injection.

Patients with multiple myeloma who have previously responded to treatment with Bortezomib for Injection (either alone or in combination) and who have relapsed at least six months after their prior Bortezomib for Injection therapy may be started on Bortezomib for Injection at the last tolerated dose. Retreated patients are administered Bortezomib for Injection twice weekly (Days 1, 4, 8, and 11) every three weeks for a maximum of eight cycles. At least 72 hours should elapse between consecutive doses of Bortezomib for Injection. Bortezomib for Injection may be administered either as a single agent or in combination with dexamethasone *[see Clinical Studies (14.1)]*.

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

For dose modifications guidelines for peripheral neuropathy, see section 2.7.

2.7 Dose Modifications for Peripheral Neuropathy

Starting Bortezomib for Injection subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy. Patients with pre-existing severe neuropathy should be treated with Bortezomib for Injection only after careful risk-benefit assessment.

Patients experiencing new or worsening peripheral neuropathy during Bortezomib for Injection therapy may require a decrease in the dose and/or a less dose-intense schedule.

For dose or schedule modification guidelines for patients who experience Bortezomib for Injection-related neuropathic pain and/or peripheral neuropathy, see *Table 5*.

Table 5: Recommended Dose Modification for Bortezomib for Injection related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms[a]	Modification of Dose and Regimen
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL)[b])	Reduce Bortezomib for Injection to 1 mg/m^2

Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL[c])	Withhold Bortezomib for Injection therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of Bortezomib for Injection at 0.7 mg/m^2 once per week.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue Bortezomib for Injection

[a] Grading based on NCI Common Terminology Criteria CTCAE v4.0
[b] Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc.;
[c] Self care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

2.8 Dosage in Patients with Hepatic Impairment

Do not adjust the starting dose for patients with mild hepatic impairment.

Start patients with moderate or severe hepatic impairment at a reduced dose of 0.7 mg/m^2 per injection during the first cycle, and consider subsequent dose escalation to 1 mg/m^2 or further dose reduction to 0.5 mg/m^2 based on patient tolerance *(see Table 6) [see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

Table 6: Recommended Starting Dose Modification for Bortezomib for Injection in Patients with Hepatic Impairment

	Bilirubin Level	**SGOT (AST) Levels**	**Modification of Starting Dose**
Mild	Less than or equal to 1x ULN	More than ULN	None
	More than 1x to 1.5x ULN	Any	None
Moderate	More than 1.5x to 3x ULN	Any	Reduce dose to 0.7 mg/m^2 in the first cycle. Consider dose escalation to 1 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	More than 3x ULN	Any	

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

2.9 Administration Precautions

The drug quantity contained in one vial (1 mg or 2.5 mg) may exceed the usual dose required. Use caution when calculating the dose to prevent overdose *[see Dosage and Administration (2.10)]*.

When administered subcutaneously, rotate sites for each injection (thigh or abdomen). Give new injections at least one inch from an old site and never into areas where the site is tender, bruised, erythematous, or indurated.

If local injection site reactions occur following Bortezomib for Injection administration subcutaneously, a less concentrated Bortezomib for Injection solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously *[see Dosage and Administration (2.10)]*. Alternatively, consider use of the intravenous route of administration *[see Dosage and Administration (2.10)]*.

Bortezomib for Injection is a hazardous drug. Follow applicable special handling and disposal procedures. [1]

2.10 Reconstitution/Preparation for Intravenous and Subcutaneous Administration

Use proper aseptic technique. Reconstitute **only with 0.9% Sodium Chloride Injection, USP**. The reconstituted product should be a clear and colorless solution.

Different volumes of 0.9% Sodium Chloride Injection, USP are used to reconstitute the product for the different routes of administration. The reconstituted concentration of bortezomib for subcutaneous administration (2.5 mg/mL) is greater than the reconstituted concentration of bortezomib for intravenous administration (1 mg/mL). **Because each route of administration has a different reconstituted concentration, use caution when calculating the volume to be administered** *[see Dosage and Administration (2.9)]*.

For each 1 mg or 2.5 mg single-dose vial of bortezomib, reconstitute with the following volume of 0.9% Sodium Chloride Injection, USP based on route of administration *(Table 7)*:

Table 7: Reconstitution Volumes and Final Concentration for Intravenous and Subcutaneous Administration

Route of Administration	Bortezomib (mg/vial)	Diluent (0.9% Sodium Chloride Injection, USP)	Final Bortezomib Concentration
Intravenous	1 mg	1 mL	1 mg/mL
Subcutaneous	1 mg	0.4 mL	2.5 mg/mL*
Intravenous	2.5 mg	2.5 mL	1 mg/mL
Subcutaneous	2.5 mg	1 mL	2.5 mg/mL

*Actual vial content results in a final concentration of 1 mg/0.4 mL

Dose must be individualized to prevent overdosage. After determining patient body surface area (BSA) in square meters, use the following equations to calculate the total volume (mL) of reconstituted Bortezomib for Injection to be administered:

- **Intravenous Administration [1 mg/mL concentration]**

$$\frac{\text{Bortezomib for Injection dose } (\text{mg/m}^2) \times \text{patient BSA } (\text{m}^2)}{1 \text{ mg/mL}} = \text{Total Bortezomib for Injection volume (mL) to be administered}$$

- **Subcutaneous Administration [2.5 mg/mL concentration]**

$$\frac{\text{Bortezomib for Injection dose } (\text{mg/m}^2) \times \text{patient BSA } (\text{m}^2)}{2.5 \text{ mg/mL}} = \text{Total Bortezomib for Injection volume (mL) to be administered}$$

Stickers that indicate the route of administration are provided with each Bortezomib for Injection vial. These stickers should be placed directly on the syringe of Bortezomib for Injection once Bortezomib for Injection is prepared to help alert practitioners of the correct route of administration for Bortezomib for Injection.

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

Stability

Unopened vials of Bortezomib for Injection are stable until the date indicated on the package when stored in the original package protected from light.

Bortezomib for Injection contains no antimicrobial preservative. Administer reconstituted Bortezomib for Injection within eight hours of preparation. When reconstituted as directed, Bortezomib for Injection may be stored at 25ºC (77ºF). The reconstituted material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for up to eight hours in a syringe; however, total storage time for the reconstituted material must not exceed eight hours when exposed to normal indoor lighting.

3 DOSAGE FORMS AND STRENGTHS

For injection: Each single-dose vial of Bortezomib for Injection contains 1 mg or 2.5 mg of bortezomib as a sterile lyophilized white to off-white powder for reconstitution and withdrawal of the appropriate individual patient dose *[see Dosage and Administration (2.10)]*.

4 CONTRAINDICATIONS

Bortezomib for Injection is contraindicated in patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol. Reactions have included anaphylactic reactions *[see Adverse Reactions (6.1)]*.

Bortezomib for Injection is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of bortezomib products.

5 WARNINGS AND PRECAUTIONS

5.1 Peripheral Neuropathy

Bortezomib treatment causes a peripheral neuropathy that is predominantly sensory; however, cases of severe sensory and motor peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral neuropathy (including ≥Grade 3) during treatment with Bortezomib for Injection. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness. In the Phase 3 relapsed multiple myeloma trial comparing bortezomib subcutaneous vs intravenous, the incidence of Grade ≥2 peripheral neuropathy was 24% for subcutaneous and 39% for intravenous. Grade ≥3 peripheral neuropathy occurred in 6% of patients in the subcutaneous treatment group, compared with 15% in the intravenous treatment group *[see Adverse Reactions (6.1)]*. Starting Bortezomib for Injection subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy.

Patients experiencing new or worsening peripheral neuropathy during Bortezomib for Injection therapy may require a decrease in the dose and/or a less dose-intense schedule *[see Dosage and Administration (2.7)]*. In the bortezomib vs dexamethasone Phase 3 relapsed multiple myeloma study, improvement in or resolution of peripheral neuropathy was reported in 48% of patients with ≥Grade 2 peripheral neuropathy following dose adjustment or interruption. Improvement in or resolution of peripheral neuropathy was reported in 73% of patients who discontinued due to Grade 2 neuropathy or who had ≥Grade 3 peripheral

neuropathy in the Phase 2 multiple myeloma studies. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

5.2 Hypotension

The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 8% *[see Adverse Reactions (6.1)]*. These events are observed throughout therapy. Patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated may be at increased risk of hypotension. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetics.

5.3 Cardiac Toxicity

Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have occurred during bortezomib therapy, including reports in patients with no risk factors for decreased left ventricular ejection fraction *[see Adverse Reactions (6.1)]*. Patients with risk factors for, or existing heart disease should be frequently monitored. In the relapsed multiple myeloma study of bortezomib vs dexamethasone, the incidence of any treatment-related cardiac disorder was 8% and 5% in the bortezomib and dexamethasone groups, respectively. The incidence of adverse reactions suggestive of heart failure (acute pulmonary edema, pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock) was ≤1% for each individual reaction in the bortezomib group. In the dexamethasone group the incidence was ≤1% for cardiac failure and congestive cardiac failure; there were no reported reactions of acute pulmonary edema, pulmonary edema, or cardiogenic shock. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.

5.4 Pulmonary Toxicity

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

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

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

In the event of new or worsening cardiopulmonary symptoms, consider interrupting Bortezomib for Injection until a prompt and comprehensive diagnostic evaluation is conducted.

5.5 Posterior Reversible Encephalopathy Syndrome (PRES)

Posterior Reversible Encephalopathy Syndrome (PRES; formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS)) has occurred in patients receiving bortezomib. PRES 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 PRES,

discontinue Bortezomib for Injection. The safety of reinitiating Bortezomib for Injection therapy in patients previously experiencing PRES is not known.

5.6 Gastrointestinal Toxicity

Bortezomib treatment can cause nausea, diarrhea, constipation, and vomiting *[see Adverse Reactions (6.1)]* sometimes requiring use of antiemetic and antidiarrheal medications. Ileus can occur. Fluid and electrolyte replacement should be administered to prevent dehydration. Interrupt Bortezomib for Injection for severe symptoms.

5.7 Thrombocytopenia/Neutropenia

Bortezomib is associated with thrombocytopenia and neutropenia that follow a cyclical pattern with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of the subsequent cycle. The cyclical pattern of platelet and neutrophil decreases and recovery remain consistent in the studies of multiple myeloma and mantle cell lymphoma, with no evidence of cumulative thrombocytopenia or neutropenia in the treatment regimens studied.

Monitor complete blood counts (CBC) frequently during treatment with Bortezomib for Injection. Measure platelet counts prior to each dose of Bortezomib for Injection. Adjust dose/schedule for thrombocytopenia *[see Dosage and Administration (2.6)]*. Gastrointestinal and intracerebral hemorrhage has occurred during thrombocytopenia in association with bortezomib. Support with transfusions and supportive care, according to published guidelines.

In the single agent, relapsed multiple myeloma study of bortezomib vs dexamethasone, the mean platelet count nadir measured was approximately 40% of baseline. The severity of thrombocytopenia related to pretreatment platelet count is shown in *Table 8*. The incidence of bleeding (≥Grade 3) was 2% on the bortezomib arm and was <1% in the dexamethasone arm.

Table 8: Severity of Thrombocytopenia Related to Pretreatment Platelet Count in the Relapsed Multiple Myeloma Study of Bortezomib vs Dexamethasone

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

[a] A baseline platelet count of 50,000/μL was required for study eligibility
[b] Data were missing at baseline for one patient

In the combination study of bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone (VcR-CAP) in previously untreated mantle cell lymphoma patients, the incidence of thrombocytopenia (≥Grade 4) was 32% vs 1% for the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) arm as shown in *Table 12*. The incidence of bleeding events (≥Grade 3) was 1.7% in the VcR-CAP arm (four patients) and was 1.2% in the R-CHOP arm (three patients).

Platelet transfusions were given to 23% of the patients in the VcR-CAP arm and 3% of the patients in the R-CHOP arm.

The incidence of neutropenia (≥Grade 4) was 70% in the VcR-CAP arm and was 52% in the R-CHOP arm. The incidence of febrile neutropenia (≥Grade 4) was 5% in the VcR-CAP arm and was 6% in the R-CHOP arm. Myeloid growth factor support was provided at a rate of 78% in the VcR-CAP arm and 61% in the R-CHOP arm.

5.8 Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with bortezomib therapy. Patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor patients closely and take appropriate precautions.

5.9 Hepatic Toxicity

Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic reactions include hepatitis, increases in liver enzymes, and hyperbilirubinemia. Interrupt Bortezomib for Injection therapy to assess reversibility. There is limited rechallenge information in these patients.

5.10 Thrombotic Microangiopathy

Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in the postmarketing setting in patients who received bortezomib. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop bortezomib and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting bortezomib. The safety of reinitiating Bortezomib for Injection therapy in patients previously experiencing TTP/HUS is not known.

5.11 Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, Bortezomib for Injection can cause fetal harm when administered to a pregnant woman. Bortezomib administered to rabbits during organogenesis at a dose approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area caused post-implantation loss and a decreased number of live fetuses *[see Use in Specific Populations (8.1)]*.

Females of reproductive potential should avoid becoming pregnant while being treated with Bortezomib for Injection. Advise females of reproductive potential to use effective contraception during treatment with Bortezomib for Injection and for seven months following treatment. Advise males with female partners of reproductive potential to use effective contraception during treatment with Bortezomib for Injection and for four months following treatment. If Bortezomib for Injection is used during pregnancy or if the patient becomes pregnant during Bortezomib for Injection treatment, the patient should be apprised of the potential risk to the fetus *[see Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)]*.

6 ADVERSE REACTIONS

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

- Peripheral Neuropathy *[see Warnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.2)]*

- Cardiac Toxicity *[see Warnings and Precautions (5.3)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.4)]*
- Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.5)]*
- Gastrointestinal Toxicity *[see Warnings and Precautions (5.6)]*
- Thrombocytopenia/Neutropenia *[see Warnings and Precautions (5.7)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.8)]*
- Hepatic Toxicity *[see Warnings and Precautions (5.9)]*
- Thrombotic Microangiopathy *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

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

Summary of Clinical Trial in Patients with Previously Untreated Multiple Myeloma

Table 9 describes safety data from 340 patients with previously untreated multiple myeloma who received bortezomib (1.3 mg/m^2) administered intravenously in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in a prospective randomized study.

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

Table 9: Most Commonly Reported Adverse Reactions (≥10% in the Bortezomib, Melphalan and Prednisone Arm) with Grades 3 and ≥4 Intensity in the Previously Untreated Multiple Myeloma Study

	Bortezomib, Melphalan and Prednisone (n = 340)			**Melphalan and Prednisone** (n = 337)		
Body System	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
Adverse Reaction	n (%)	3	≥4	n (%)	3	≥4
Blood and Lymphatic System Disorders						
Thrombocytopenia	164 (48)	60 (18)	57 (17)	140 (42)	48 (14)	39 (12)
Neutropenia	160 (47)	101 (30)	33 (10)	143 (42)	77 (23)	42 (12)
Anemia	109 (32)	41 (12)	4 (1)	156 (46)	61 (18)	18 (5)
Leukopenia	108 (32)	64 (19)	8 (2)	93 (28)	53 (16)	11 (3)
Lymphopenia	78 (23)	46 (14)	17 (5)	51 (15)	26 (8)	7 (2)
Gastrointestinal Disorders						
Nausea	134 (39)	10 (3)	0	70 (21)	1 (<1)	0
Diarrhea	119 (35)	19 (6)	2 (1)	20 (6)	1 (<1)	0
Vomiting	87 (26)	13 (4)	0	41 (12)	2 (1)	0
Constipation	77 (23)	2 (1)	0	14 (4)	0	0
Abdominal pain upper	34 (10)	1 (<1)	0	20 (6)	0	0
Nervous System Disorders						
Peripheral neuropathy*	156 (46)	42 (12)	2 (1)	4 (1)	0	0
Neuralgia	117 (34)	27 (8)	2 (1)	1 (<1)	0	0
Paresthesia	42 (12)	6 (2)	0	4 (1)	0	0
General Disorders and Administration Site Conditions						
Fatigue	85 (25)	19 (6)	2 (1)	48 (14)	4 (1)	0
Asthenia	54 (16)	18 (5)	0	23 (7)	3 (1)	0
Pyrexia	53 (16)	4 (1)	0	19 (6)	1 (<1)	1 (<1)
Infections and Infestations	39 (11)	11 (3)	0	9 (3)	4 (1)	0

Body System Adverse Reaction	Bortezomib, Melphalan and Prednisone (n = 340)			Melphalan and Prednisone (n = 337)		
	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
	n (%)	3	≥4	n (%)	3	≥4
Herpes Zoster						
Metabolism and Nutrition Disorders						
Anorexia	64 (19)	6 (2)	0	19 (6)	0	0
Skin and Subcutaneous Tissue Disorders						
Rash	38 (11)	2 (1)	0	7 (2)	0	0
Psychiatric Disorders						
Insomnia	35 (10)	1 (<1)	0	21 (6)	0	0

* Represents High Level Term Peripheral Neuropathies NEC

Relapsed Multiple Myeloma Randomized Study of Bortezomib vs Dexamethasone

The safety data described below and in *Table 10* reflect exposure to either bortezomib (n=331) or dexamethasone (n=332) in a study of patients with relapsed multiple myeloma. Bortezomib was administered intravenously at doses of 1.3 mg/m^2 twice weekly for two out of three weeks (21 day cycle). After eight 21 day cycles patients continued therapy for three 35 day cycles on a weekly schedule. Duration of treatment was up to 11 cycles (nine months) with a median duration of six cycles (4.1 months). For inclusion in the trial, patients must have had measurable disease and one to three prior therapies. There was no upper age limit for entry. Creatinine clearance could be as low as 20 mL/min and bilirubin levels as high as 1.5 times the upper limit of normal. The overall frequency of adverse reactions was similar in men and women, and in patients <65 and ≥65 years of age. Most patients were Caucasian *[see Clinical Studies (14.1)]*.

Among the 331 bortezomib-treated patients, the most commonly reported (>20%) adverse reactions overall were nausea (52%), diarrhea (52%), fatigue (39%), peripheral neuropathies (35%), thrombocytopenia (33%), constipation (30%), vomiting (29%), and anorexia (21%). The most commonly reported (>20%) adverse reaction reported among the 332 patients in the dexamethasone group was fatigue (25%). Eight percent (8%) of patients in the bortezomib-treated arm experienced a Grade 4 adverse reaction; the most common reactions were thrombocytopenia (4%) and neutropenia (2%). Nine percent (9%) of dexamethasone-treated patients experienced a Grade 4 adverse reaction. All individual dexamethasone-related Grade 4 adverse reactions were less than 1%.

Serious Adverse Reactions and Adverse Reactions Leading to Treatment Discontinuation in the Relapsed Multiple Myeloma Study of Bortezomib vs Dexamethasone

Serious adverse reactions are defined as any reaction that results in death, is life-threatening, requires hospitalization or prolongs a current hospitalization, results in a significant disability, or is deemed to be an important medical event. A total of 80 (24%) patients from the bortezomib treatment arm experienced a serious adverse reaction during the study, as did 83 (25%) dexamethasone-treated patients. The most commonly reported serious adverse reactions in the bortezomib treatment arm were diarrhea (3%), dehydration, herpes zoster, pyrexia, nausea, vomiting, dyspnea, and thrombocytopenia (2% each). In the dexamethasone treatment group, the most commonly reported serious adverse reactions were pneumonia (4%), hyperglycemia (3%), pyrexia, and psychotic disorder (2% each).

A total of 145 patients, including 84 (25%) of 331 patients in the bortezomib treatment group and 61 (18%) of 332 patients in the dexamethasone treatment group were discontinued from treatment due to adverse reactions. Among the 331 bortezomib-treated patients, the most commonly reported adverse

reaction leading to discontinuation was peripheral neuropathy (8%). Among the 332 patients in the dexamethasone group, the most commonly reported adverse reactions leading to treatment discontinuation were psychotic disorder and hyperglycemia (2% each).

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

Most Commonly Reported Adverse Reactions in the Relapsed Multiple Myeloma Study of Bortezomib vs Dexamethasone

The most common adverse reactions from the relapsed multiple myeloma study are shown in *Table 10*. All adverse reactions with incidence ≥10% in the bortezomib arm are included.

Table 10: Most Commonly Reported Adverse Reactions (≥10% in Bortezomib Arm), with Grades 3 and 4 Intensity in the Relapsed Multiple Myeloma Study of Bortezomib vs Dexamethasone (N=663)

	Bortezomib (N = 331)			**Dexamethasone (N = 332)**		
Adverse Reactions	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Any Adverse Reactions	324 (98)	193 (58)	28 (8)	297 (89)	110 (33)	29 (9)
Nausea	172 (52)	8 (2)	0	31 (9)	0	0
Diarrhea NOS	171 (52)	22 (7)	0	36 (11)	2 (<1)	0
Fatigue	130 (39)	15 (5)	0	82 (25)	8 (2)	0
Peripheral neuropathies*	115 (35)	23 (7)	2 (<1)	14 (4)	0	1 (<1)
Thrombocytopenia	109 (33)	80 (24)	12 (4)	11 (3)	5 (2)	1 (<1)
Constipation	99 (30)	6 (2)	0	27 (8)	1 (<1)	0
Vomiting NOS	96 (29)	8 (2)	0	10 (3)	1 (<1)	0
Anorexia	68 (21)	8 (2)	0	8 (2)	1 (<1)	0
Pyrexia	66 (20)	2 (<1)	0	21 (6)	3 (<1)	1 (<1)
Paresthesia	64 (19)	5 (2)	0	24 (7)	0	0
Anemia NOS	63 (19)	20 (6)	1 (<1)	21 (6)	8 (2)	0
Headache NOS	62 (19)	3 (<1)	0	23 (7)	1 (<1)	0
Neutropenia	58 (18)	37 (11)	8 (2)	1 (<1)	1 (<1)	0
Rash NOS	43 (13)	3 (<1)	0	7 (2)	0	0
Appetite decreased NOS	36 (11)	0	0	12 (4)	0	0
Dyspnea NOS	35 (11)	11 (3)	1 (<1)	37 (11)	7 (2)	1 (<1)
Abdominal pain NOS	35 (11)	5 (2)	0	7 (2)	0	0
Weakness	34 (10)	10 (3)	0	28 (8)	8 (2)	0

* Represents High Level Term Peripheral Neuropathies NEC

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

In the Phase 2 extension study of 63 patients, no new cumulative or new long-term toxicities were observed with prolonged bortezomib treatment. These patients were treated for a total of 5.3 to 23 months, including time on bortezomib in the prior bortezomib study *[see Clinical Studies (14.1)]*.

Safety Experience from the Phase 3 Open-Label Study of Bortezomib Subcutaneous vs Intravenous in Relapsed Multiple Myeloma

The safety and efficacy of bortezomib administered subcutaneously were evaluated in one Phase 3 study at the recommended dose of 1.3 mg/m^2. This was a randomized, comparative study of bortezomib subcutaneous vs intravenous in 222 patients with relapsed multiple myeloma. The safety data described below and in *Table 11* reflect exposure to either bortezomib subcutaneous (N=147) or bortezomib intravenous (N=74) *[see Clinical Studies (14.1)]*.

Table 11: Most Commonly Reported Adverse Reactions (≥10%), with Grade 3 and ≥4 Intensity in the Relapsed Multiple Myeloma Study (N=221) of Bortezomib Subcutaneous vs Intravenous

	Subcutaneous (N = 147)			Intravenous (N = 74)		
Body System	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
Adverse Reaction	n (%)	3	≥4	n (%)	3	≥4
Blood and Lymphatic System Disorders						
Anemia	28 (19)	8 (5)	0	17 (23)	3 (4)	0
Leukopenia	26 (18)	8 (5)	0	15 (20)	4 (5)	1 (1)
Neutropenia	34 (23)	15 (10)	4 (3)	20 (27)	10 (14)	3 (4)
Thrombocytopenia	44 (30)	7 (5)	5 (3)	25 (34)	7 (9)	5 (7)
Gastrointestinal Disorders						
Diarrhea	28 (19)	1 (1)	0	21 (28)	3 (4)	0
Nausea	24 (16)	0	0	10 (14)	0	0
Vomiting	13 (9)	3 (2)	0	8 (11)	0	0
General Disorders and Administration Site Conditions						
Asthenia	10 (7)	1 (1)	0	12 (16)	4 (5)	0
Fatigue	11 (7)	3 (2)	0	11 (15)	3 (4)	0
Pyrexia	18 (12)	0	0	6 (8)	0	0
Nervous System Disorders						
Neuralgia	34 (23)	5 (3)	0	17 (23)	7 (9)	0
Peripheral neuropathies*	55 (37)	8 (5)	1 (1)	37 (50)	10 (14)	1 (1)

Note: Safety population: 147 patients in the subcutaneous treatment group and 74 patients in the intravenous treatment group who received at least one dose of study medication

* Represents High Level Term Peripheral Neuropathies NEC

In general, safety data were similar for the subcutaneous and intravenous treatment groups. Differences were observed in the rates of some Grade ≥3 adverse reactions. Differences of ≥5% were reported in neuralgia (3% subcutaneous vs 9% intravenous), peripheral neuropathies (6% subcutaneous vs 15% intravenous), neutropenia (13% subcutaneous vs 18% intravenous), and thrombocytopenia (8% subcutaneous vs 16% intravenous).

A local reaction was reported in 6% of patients in the subcutaneous group, mostly redness. Only two (1%) patients were reported as having severe reactions, one case of pruritus and one case of redness. Local reactions led to reduction in injection concentration in one patient and drug discontinuation in one patient. Local reactions resolved in a median of six days.

Dose reductions occurred due to adverse reactions in 31% of patients in the subcutaneous treatment group compared with 43% of the intravenously-treated patients. The most common adverse reactions leading to a dose reduction included peripheral sensory neuropathy (17% in the subcutaneous treatment group compared with 31% in the intravenous treatment group); and neuralgia (11% in the subcutaneous treatment group compared with 19% in the intravenous treatment group).

Serious Adverse Reactions and Adverse Reactions Leading to Treatment Discontinuation in the Relapsed Multiple Myeloma Study of Bortezomib Subcutaneous vs Intravenous

The incidence of serious adverse reactions was similar for the subcutaneous treatment group (20%) and the intravenous treatment group (19%). The most commonly reported serious adverse reactions in the subcutaneous treatment arm were pneumonia and pyrexia (2% each). In the intravenous treatment

group, the most commonly reported serious adverse reactions were pneumonia, diarrhea, and peripheral sensory neuropathy (3% each).

In the subcutaneous treatment group, 27 patients (18%) discontinued study treatment due to an adverse reaction compared with 17 patients (23%) in the intravenous treatment group. Among the 147 subcutaneously-treated patients, the most commonly reported adverse reactions leading to discontinuation were peripheral sensory neuropathy (5%) and neuralgia (5%). Among the 74 patients in the intravenous treatment group, the most commonly reported adverse reactions leading to treatment discontinuation were peripheral sensory neuropathy (9%) and neuralgia (9%).

Two patients (1%) in the subcutaneous treatment group and one (1%) patient in the intravenous treatment group died due to an adverse reaction during treatment. In the subcutaneous group the causes of death were one case of pneumonia and one case of sudden death. In the intravenous group the cause of death was coronary artery insufficiency.

Safety Experience from the Clinical Trial in Patients with Previously Untreated Mantle Cell Lymphoma

Table 12 describes safety data from 240 patients with previously untreated mantle cell lymphoma who received bortezomib (1.3 mg/m^2) administered intravenously in combination with rituximab (375 mg/m^2), cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2), and prednisone (100 mg/m^2) (VcR-CAP) in a prospective randomized study.

Infections were reported for 31% of patients in the VcR-CAP arm and 23% of the patients in the comparator (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) arm, including the predominant preferred term of pneumonia (VcR-CAP 8% vs R-CHOP 5%).

Table 12: Most Commonly Reported Adverse Reactions (≥5%) with Grades 3 and ≥4 Intensity in the Previously Untreated Mantle Cell Lymphoma Study

	VcR-CAP (N = 240)			R-CHOP (N = 242)		
Body System Adverse Reactions	All n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)	All n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)
Blood and Lymphatic System Disorders						
Neutropenia	209 (87)	32 (13)	168 (70)	172 (71)	31 (13)	125 (52)
Leukopenia	116 (48)	34 (14)	69 (29)	87 (36)	39 (16)	27 (11)
Anemia	106 (44)	27 (11)	4 (2)	71 (29)	23 (10)	4 (2)
Thrombocytopenia	172 (72)	59 (25)	76 (32)	42 (17)	9 (4)	3 (1)
Febrile neutropenia	41 (17)	24 (10)	12 (5)	33 (14)	17 (7)	15 (6)
Lymphopenia	68 (28)	25 (10)	36 (15)	28 (12)	15 (6)	2 (1)
Nervous System Disorders						
Peripheral neuropathy*	71 (30)	17 (7)	1 (<1)	65 (27)	10 (4)	0
Hypoesthesia	14 (6)	3 (1)	0	13 (5)	0	0
Paresthesia	14 (6)	2 (1)	0	11 (5)	0	0
Neuralgia	25 (10)	9 (4)	0	1 (<1)	0	0
General Disorders and Administration Site Conditions						
Fatigue	43 (18)	11 (5)	1 (<1)	38 (16)	5 (2)	0
Pyrexia	48 (20)	7 (3)	0	23 (10)	5 (2)	0
Asthenia	29 (12)	4 (2)	1 (<1)	18 (7)	1 (<1)	0
Edema peripheral	16 (7)	1 (<1)	0	13 (5)	0	0
Gastrointestinal Disorders						
Nausea	54 (23)	1 (<1)	0	28 (12)	0	0
Constipation	42 (18)	1 (<1)	0	22 (9)	2 (1)	0
Stomatitis	20 (8)	2 (1)	0	19 (8)	0	1 (<1)
Diarrhea	59 (25)	11 (5)	0	11 (5)	3 (1)	1 (<1)
Vomiting	24 (10)	1 (<1)	0	8 (3)	0	0
Abdominal distension	13 (15)	0	0	4 (2)	0	0
Infections and Infestations						
Pneumonia	20 (8)	8 (3)	5 (2)	11 (5)	5 (2)	3 (1)
Skin and Subcutaneous Tissue Disorders						
Alopecia	31 (13)	1 (<1)	1 (<1)	33 (14)	4 (2)	0
Metabolism and Nutrition Disorders						
Hyperglycemia	10 (4)	1 (<1)	0	17 (7)	10 (4)	0
Decreased appetite	36 (15)	2 (1)	0	15 (6)	1 (<1)	0
Vascular Disorders						
Hypertension	15 (6)	1 (<1)	0	3 (1)	0	0
Psychiatric Disorders						
Insomnia	16 (7)	1 (<1)	0	8 (3)	0	0

Key: R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; VcR-CAP = bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.
* Represents High Level Term Peripheral Neuropathies NEC.

The incidence of herpes zoster reactivation was 4.6% in the VcR-CAP arm and 0.8% in the R-CHOP arm. Antiviral prophylaxis was mandated by protocol amendment.

The incidences of Grade ≥3 bleeding events were similar between the two arms (four patients in the VcR-CAP arm and three patients in the R-CHOP arm). All of the Grade ≥3 bleeding events resolved without sequelae in the VcR-CAP arm.

Adverse reactions leading to discontinuation occurred in 8% of patients in VcR-CAP group and 6% of patients in R-CHOP group. In the VcR-CAP group, the most commonly reported adverse reaction leading to discontinuation was peripheral sensory neuropathy (1%; three patients). The most commonly reported adverse reaction leading to discontinuation in the R-CHOP group was febrile neutropenia (<1%; two patients).

Integrated Summary of Safety (Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma)
Safety data from Phase 2 and 3 studies of single agent bortezomib 1.3 mg/m^2/dose twice weekly for two weeks followed by a ten day rest period in 1163 patients with previously-treated multiple myeloma (N=1008) and previously-treated mantle cell lymphoma (N=155) were integrated and tabulated. This analysis does not include data from the Phase 3 open-label study of bortezomib subcutaneous vs intravenous in relapsed multiple myeloma. In the integrated studies, the safety profile of bortezomib was similar in patients with multiple myeloma and mantle cell lymphoma.

In the integrated analysis, the most commonly reported (>20%) adverse reactions were nausea (49%), diarrhea (46%), asthenic conditions including fatigue (41%) and weakness (11%), peripheral neuropathies (38%), thrombocytopenia (32%), vomiting (28%), constipation (25%), and pyrexia (21%). Eleven percent (11%) of patients experienced at least one episode of ≥Grade 4 toxicity, most commonly thrombocytopenia (4%) and neutropenia (2%).

In the Phase 2 relapsed multiple myeloma clinical trials of bortezomib administered intravenously, local skin irritation was reported in 5% of patients, but extravasation of bortezomib was not associated with tissue damage.

Serious Adverse Reactions and Adverse Reactions Leading to Treatment Discontinuation in the Integrated Summary of Safety
A total of 26% of patients experienced a serious adverse reaction during the studies. The most commonly reported serious adverse reactions included diarrhea, vomiting and pyrexia (3% each), nausea, dehydration, and thrombocytopenia (2% each) and pneumonia, dyspnea, peripheral neuropathies, and herpes zoster (1% each).

Adverse reactions leading to discontinuation occurred in 22% of patients. The reasons for discontinuation included peripheral neuropathy (8%), and fatigue, thrombocytopenia, and diarrhea (2% each).

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

Most Commonly Reported Adverse Reactions in the Integrated Summary of Safety
The most common adverse reactions are shown in *Table 13*. All adverse reactions occurring at ≥10% are included. In the absence of a randomized comparator arm, it is often not possible to distinguish between adverse events that are drug-caused and those that reflect the patient's underlying disease. Please see the discussion of specific adverse reactions that follows.

Table 13: Most Commonly Reported (≥ 10% Overall) Adverse Reactions in Integrated Analyses of Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma Studies Using the 1.3 mg/m^2 Dose (N=1163)

	All Patients (N=1163)		Multiple Myeloma (N=1008)		Mantle Cell Lymphoma (N=155)	
Adverse Reactions	All	≥Grade 3	All	≥Grade 3	All	≥Grade 3
Nausea	567 (49)	36 (3)	511 (51)	32 (3)	56 (36)	4 (3)
Diarrhea NOS	530 (46)	83 (7)	470 (47)	72 (7)	60 (39)	11 (7)
Fatigue	477 (41)	86 (7)	396 (39)	71 (7)	81 (52)	15 (10)
Peripheral neuropathies*	443 (38)	129 (11)	359 (36)	110 (11)	84 (54)	19 (12)
Thrombocytopenia	369 (32)	295 (25)	344 (34)	283 (28)	25 (16)	12 (8)
Vomiting NOS	321 (28)	44 (4)	286 (28)	40 (4)	35 (23)	4 (3)
Constipation	296 (25)	17 (1)	244 (24)	14 (1)	52 (34)	3 (2)
Pyrexia	249 (21)	16 (1)	233 (23)	15 (1)	16 (10)	1 (<1)
Anorexia	227 (20)	19 (2)	205 (20)	16 (2)	22 (14)	3 (2)
Anemia NOS	209 (18)	65 (6)	190 (19)	63 (6)	19 (12)	2 (1)
Headache NOS	175 (15)	8 (<1)	160 (16)	8 (<1)	15 (10)	0
Neutropenia	172 (15)	121 (10)	164 (16)	117 (12)	8 (5)	4 (3)
Rash NOS	156 (13)	8 (<1)	120 (12)	4 (<1)	36 (23)	4 (3)
Paresthesia	147 (13)	9 (<1)	136 (13)	8 (<1)	11 (7)	1 (<1)
Dizziness (excl vertigo)	129 (11)	13 (1)	101 (10)	9 (<1)	28 (18)	4 (3)
Weakness	124 (11)	31 (3)	106 (11)	28 (3)	18 (12)	3 (2)

* Represents High Level Term Peripheral Neuropathies NEC

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

Gastrointestinal Toxicity

A total of 75% of patients experienced at least one gastrointestinal disorder. The most common gastrointestinal disorders included nausea, diarrhea, constipation, vomiting, and appetite decreased. Other gastrointestinal disorders included dyspepsia and dysgeusia. Grade 3 adverse reactions occurred in 14% of patients; ≥Grade 4 adverse reactions were ≤1%. Gastrointestinal adverse reactions were considered serious in 7% of patients. Four percent (4%) of patients discontinued due to a gastrointestinal adverse reaction. Nausea was reported more often in patients with multiple myeloma (51%) compared to patients with mantle cell lymphoma (36%).

Thrombocytopenia

Across the studies, bortezomib-associated thrombocytopenia was characterized by a decrease in platelet count during the dosing period (Days 1 to 11) and a return toward baseline during the ten day rest period during each treatment cycle. Overall, thrombocytopenia was reported in 32% of patients. Thrombocytopenia was Grade 3 in 22%, ≥Grade 4 in 4%, and serious in 2% of patients, and the reaction resulted in bortezomib discontinuation in 2% of patients *[see Warnings and Precautions (5.7)]*. Thrombocytopenia was reported more often in patients with multiple myeloma (34%) compared to patients with mantle cell lymphoma (16%). The incidence of ≥Grade 3 thrombocytopenia also was higher in patients with multiple myeloma (28%) compared to patients with mantle cell lymphoma (8%).

Peripheral Neuropathy

Overall, peripheral neuropathies occurred in 38% of patients. Peripheral neuropathy was Grade 3 for 11% of patients and ≥Grade 4 for <1% of patients. Eight percent (8%) of patients discontinued

bortezomib due to peripheral neuropathy. The incidence of peripheral neuropathy was higher among patients with mantle cell lymphoma (54%) compared to patients with multiple myeloma (36%).

In the bortezomib vs dexamethasone Phase 3 relapsed multiple myeloma study, among the 62 bortezomib-treated patients who experienced ≥Grade 2 peripheral neuropathy and had dose adjustments, 48% had improved or resolved with a median of 3.8 months from first onset.

In the Phase 2 relapsed multiple myeloma studies, among the 30 patients who experienced Grade 2 peripheral neuropathy resulting in discontinuation or who experienced ≥Grade 3 peripheral neuropathy, 73% reported improvement or resolution with a median time of 47 days to improvement of one grade or more from the last dose of bortezomib.

Hypotension
The incidence of hypotension (postural, orthostatic and hypotension NOS) was 8% in patients treated with bortezomib. Hypotension was Grade 1 or 2 in the majority of patients and Grade 3 in 2% and ≥Grade 4 in <1%. Two percent (2%) of patients had hypotension reported as a serious adverse reaction, and 1% discontinued due to hypotension. The incidence of hypotension was similar in patients with multiple myeloma (8%) and those with mantle cell lymphoma (9%). In addition, <1% of patients experienced hypotension associated with a syncopal reaction.

Neutropenia
Neutrophil counts decreased during the bortezomib dosing period (Days 1 to 11) and returned toward baseline during the ten day rest period during each treatment cycle. Overall, neutropenia occurred in 15% of patients and was Grade 3 in 8% of patients and ≥Grade 4 in 2%. Neutropenia was reported as a serious adverse reaction in <1% of patients and <1% of patients discontinued due to neutropenia. The incidence of neutropenia was higher in patients with multiple myeloma (16%) compared to patients with mantle cell lymphoma (5%). The incidence of ≥Grade 3 neutropenia also was higher in patients with multiple myeloma (12%) compared to patients with mantle cell lymphoma (3%).

Asthenic Conditions (Fatigue, Malaise, Weakness, Asthenia)
Asthenic conditions were reported in 54% of patients. Fatigue was reported as Grade 3 in 7% and ≥Grade 4 in <1% of patients. Asthenia was reported as Grade 3 in 2% and ≥Grade 4 in <1% of patients. Two percent (2%) of patients discontinued treatment due to fatigue and <1% due to weakness and asthenia. Asthenic conditions were reported in 53% of patients with multiple myeloma and 59% of patients with mantle cell lymphoma.

Pyrexia
Pyrexia (>38ºC) was reported as an adverse reaction for 21% of patients. The reaction was Grade 3 in 1% and ≥Grade 4 in <1%. Pyrexia was reported as a serious adverse reaction in 3% of patients and led to bortezomib discontinuation in <1% of patients. The incidence of pyrexia was higher among patients with multiple myeloma (23%) compared to patients with mantle cell lymphoma (10%). The incidence of ≥Grade 3 pyrexia was 1% in patients with multiple myeloma and <1% in patients with mantle cell lymphoma.

Herpes Virus Infection
Consider using antiviral prophylaxis in subjects being treated with Bortezomib for Injection. In the randomized studies in previously untreated and relapsed multiple myeloma, herpes zoster reactivation was more common in subjects treated with bortezomib (ranging between 6% to 11%) than in the control

groups (3% to 4%). Herpes simplex was seen in 1% to 3% in subjects treated with bortezomib and 1% to 3% in the control groups. In the previously untreated multiple myeloma study, herpes zoster virus reactivation in the bortezomib, melphalan and prednisone arm was less common in subjects receiving prophylactic antiviral therapy (3%) than in subjects who did not receive prophylactic antiviral therapy (17%).

Retreatment in Relapsed Multiple Myeloma

A single-arm trial was conducted in 130 patients with relapsed multiple myeloma to determine the efficacy and safety of retreatment with intravenous bortezomib. The safety profile of patients in this trial is consistent with the known safety profile of bortezomib-treated patients with relapsed multiple myeloma as demonstrated in *Tables 10, 11, and 13*; no cumulative toxicities were observed upon retreatment. The most common adverse drug reaction was thrombocytopenia which occurred in 52% of the patients. The incidence of ≥Grade 3 thrombocytopenia was 24%. Peripheral neuropathy occurred in 28% of patients, with the incidence of ≥Grade 3 peripheral neuropathy reported at 6%. The incidence of serious adverse reactions was 12.3%. The most commonly reported serious adverse reactions were thrombocytopenia (3.8%), diarrhea (2.3%), and herpes zoster and pneumonia (1.5% each).

Adverse reactions leading to discontinuation occurred in 13% of patients. The reasons for discontinuation included peripheral neuropathy (5%) and diarrhea (3%).

Two deaths considered to be bortezomib-related occurred within 30 days of the last bortezomib dose; one in a patient with cerebrovascular accident and one in a patient with sepsis.

Additional Adverse Reactions from Clinical Studies

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

Blood and Lymphatic System Disorders: Anemia, disseminated intravascular coagulation, febrile neutropenia, lymphopenia, leukopenia

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

Ear and Labyrinth Disorders: Hearing impaired, vertigo

Eye Disorders: Diplopia and blurred vision, conjunctival infection, irritation

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

General Disorders and Administration Site Conditions: Chills, edema, edema peripheral, injection site erythema, neuralgia, injection site pain, irritation, malaise, phlebitis

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

Immune System Disorders: Anaphylactic reaction, drug hypersensitivity, immune complex mediated hypersensitivity, angioedema, laryngeal edema

Infections and Infestations: Aspergillosis, bacteremia, bronchitis, urinary tract infection, herpes viral infection, listeriosis, nasopharyngitis, pneumonia, respiratory tract infection, septic shock, toxoplasmosis, oral candidiasis, sinusitis, catheter-related infection

Injury, Poisoning and Procedural Complications: Catheter-related complication, skeletal fracture, subdural hematoma

Investigations: Weight decreased

Metabolism and Nutrition Disorders: Dehydration, hypocalcemia, hyperuricemia, hypokalemia, hyperkalemia, hyponatremia, hypernatremia

Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain, bone pain, myalgia, pain in extremity

Nervous System Disorders: Ataxia, coma, dizziness, dysarthria, dysesthesia, dysautonomia, encephalopathy, cranial palsy, grand mal convulsion, headache, hemorrhagic stroke, motor dysfunction, neuralgia, spinal cord compression, paralysis, postherpetic neuralgia, transient ischemic attack

Psychiatric Disorders: Agitation, anxiety, confusion, insomnia, mental status change, psychotic disorder, suicidal ideation

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

Respiratory, Thoracic and Mediastinal Disorders: Acute respiratory distress syndrome, aspiration pneumonia, atelectasis, chronic obstructive airways disease exacerbated, cough, dysphagia, dyspnea, dyspnea exertional, epistaxis, hemoptysis, hypoxia, lung infiltration, pleural effusion, pneumonitis, respiratory distress, pulmonary hypertension

Skin and Subcutaneous Tissue Disorders: Urticaria, face edema, rash (which may be pruritic), leukocytoclastic vasculitis, pruritus

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

6.2 Postmarketing Experience

The following adverse reactions have been identified from the worldwide postmarketing experience with bortezomib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Cardiac Disorders: Cardiac tamponade

Ear and Labyrinth Disorders: Deafness bilateral

Eye Disorders: Optic neuropathy, blindness, chalazion/blepharitis

Gastrointestinal Disorders: Ischemic colitis

Infections and Infestations: Progressive multifocal leukoencephalopathy (PML), ophthalmic herpes, herpes meningoencephalitis

Nervous System Disorders: Posterior reversible encephalopathy syndrome (PRES, formerly RPLS), Guillain-Barré syndrome, demyelinating polyneuropathy

Respiratory, Thoracic and Mediastinal Disorders: Acute diffuse infiltrative pulmonary disease

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute febrile neutrophilic dermatosis (Sweet's syndrome)

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Bortezomib

Strong CYP3A4 Inducers
Coadministration with a strong CYP3A4 inducer decreases the exposure of bortezomib *[see Clinical Pharmacology (12.3)]* which may decrease Bortezomib for Injection efficacy. Avoid coadministration with strong CYP3A4 inducers.

Strong CYP3A4 Inhibitors
Coadministration with a strong CYP3A4 inhibitor increases the exposure of bortezomib *[see Clinical Pharmacology (12.3)]* which may increase the risk of Bortezomib for Injection toxicities. Monitor patients for signs of bortezomib toxicity and consider a bortezomib dose reduction if bortezomib must be given in combination with strong CYP3A4 inhibitors.

7.2 Drugs Without Clinically Significant Interactions with Bortezomib

No clinically significant drug interactions have been observed when Bortezomib for Injection was coadministered with dexamethasone, omeprazole, or melphalan in combination with prednisone *[see Clinical Pharmacology (12.3)]*.

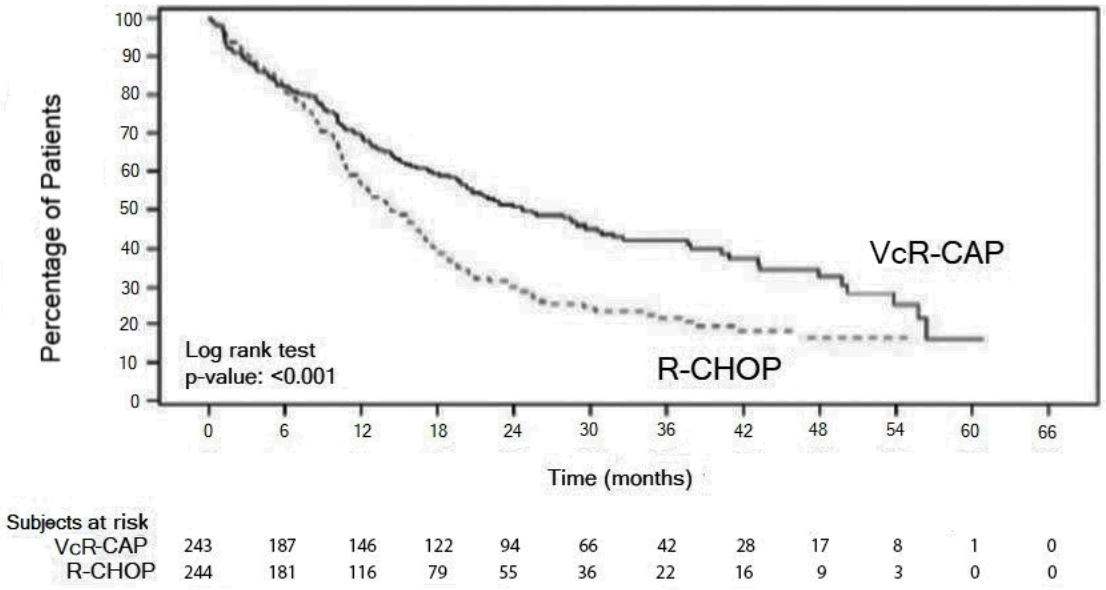
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Based on its mechanism of action *[see Clinical Pharmacology (12.1)]* and findings in animals, Bortezomib for Injection can cause fetal harm when administered to a pregnant woman. There are no

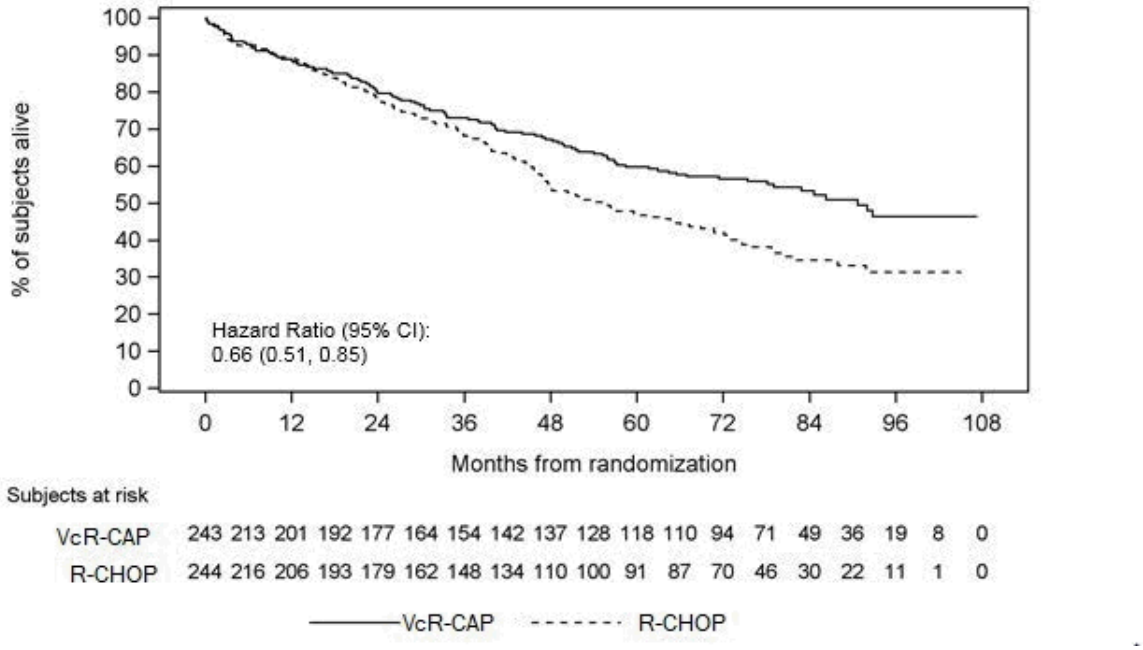
CI = Confidence Interval; IPI = International Prognostic Index; LDH = Lactate dehydrogenase
[a] Based on Kaplan-Meier product limit estimates.
[b] Hazard ratio estimate is based on a Cox's model stratified by IPI risk and stage of disease. A hazard ratio <1 indicates an advantage for VcR-CAP.
[c] Based on Log-rank test stratified with IPI risk and stage of disease.
[d] Includes CR by independent radiographic assessment, bone marrow, and LDH using ITT population.
[e] Includes CR + CRu + PR by independent radiographic assessment, regardless of the verification by bone marrow and LDH, using ITT population.

Figure 5: Progression-Free Survival VcR-CAP vs R-CHOP (previously Untreated Mantle Cell Lymphoma Study)



Key: R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; VcR-CAP = bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Figure 6: Overall Survival VcR-CAP vs R-CHOP (previously Untreated Mantle Cell Lymphoma Study)



Key: R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; VcR-CAP = bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

A Phase 2 Single-Arm Clinical Study in Relapsed Mantle Cell Lymphoma after Prior Therapy

The safety and efficacy of bortezomib in relapsed or refractory mantle cell lymphoma were evaluated in an open-label, single-arm, multicenter study (NCT00063713) of 155 patients with progressive disease who had received at least one prior therapy. The median age of the patients was 65 years (42, 89), 81% were male, and 92% were Caucasian. Of the total, 75% had one or more extra-nodal sites of disease, and 77% were Stage 4. In 91% of the patients, prior therapy included all of the following: an anthracycline or mitoxantrone, cyclophosphamide, and rituximab. A total of thirty-seven percent (37%) of patients were refractory to their last prior therapy. An intravenous bolus injection of bortezomib 1.3 mg/m^2/dose was administered twice weekly for two weeks on Days 1, 4, 8, and 11 followed by a ten day rest period (Days 12 to 21) for a maximum of 17 treatment cycles. Patients achieving a CR or CRu were treated for four cycles beyond first evidence of CR or CRu. The study employed dose modifications for toxicity *[see Dosage and Administration (2.6, 2.7)]*.

Responses to bortezomib are shown in *Table 19*. Response rates to bortezomib were determined according to the International Workshop Response Criteria (IWRC) based on independent radiologic review of CT scans. The median number of cycles administered across all patients was four; in responding patients the median number of cycles was eight. The median time to response was 40 days (range: 31 to 204 days). The median duration of follow-up was more than 13 months.

Table 19: Response Outcomes in a Phase 2 Relapsed Mantle Cell Lymphoma Study

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

15 REFERENCES

1. "OSHA Hazardous Drugs" (refer to antineoplastic weblinks including OSHA Technical Manual). *OSHA*. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

Bortezomib for Injection is supplied as individually cartoned 5 mL or 10 mL vials containing 1 mg or 2.5 mg of bortezomib, respectively, as a white to off-white cake or powder.

Unit of Sale	**Strength**
NDC 0409-1704-01 1 Single-dose vial in a carton	1 mg/vial
NDC 0409-1703-01 1 Single-dose vial in a carton	2.5 mg/vial

Unopened vials may be stored at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Retain in original package to protect from light.

Follow guidelines for handling and disposal for hazardous drugs, including the use of gloves and other protective clothing to prevent skin contact[1].

17 PATIENT COUNSELING INFORMATION

Discuss the following with patients prior to treatment with Bortezomib for Injection:

Peripheral Neuropathy
Advise patients to report the development or worsening of sensory and motor peripheral neuropathy to their healthcare provider *[see Warnings and Precautions (5.1)]*.

Hypotension
Advise patients to drink adequate fluids to avoid dehydration and to report symptoms of hypotension to their healthcare provider *[see Warnings and Precautions (5.2)]*.

Instruct patients to seek medical advice if they experience symptoms of dizziness, light headedness or fainting spells, or muscle cramps.

Cardiac Toxicity
Advise patients to report signs or symptoms of heart failure to their healthcare provider *[see Warnings and Precautions (5.3)]*.

Pulmonary Toxicity
Advise patients to report symptoms of ARDS, pulmonary hypertension, pneumonitis, and pneumonia immediately to their healthcare provider *[see Warnings and Precautions (5.4)]*.

Posterior Reversible Encephalopathy Syndrome (PRES)
Advise patients to seek immediate medical attention for signs or symptoms of PRES *[see Warnings and Precautions (5.5)]*.

Gastrointestinal Toxicity
Advise patients to report symptoms of gastrointestinal toxicity to their healthcare provider and to drink adequate fluids to avoid dehydration. Instruct patients to seek medical advice if they experience symptoms of dizziness, light headedness or fainting spells, or muscle cramps *[see Warnings and Precautions (5.6)]*.

Thrombocytopenia/Neutropenia
Advise patients to report signs or symptoms of bleeding or infection immediately to their healthcare provider *[see Warnings and Precautions (5.7)]*.

Tumor Lysis Syndrome
Advise patients of the risk of tumor lysis syndrome and to drink adequate fluids to avoid dehydration *[see Warnings and Precautions (5.8)]*.

Hepatic Toxicity
Advise patients to report signs or symptoms of hepatic toxicity to their healthcare provider *[see Warnings and Precautions (5.9)]*.

Thrombotic Microangiopathy
Advise patients to seek immediate medical attention if any signs or symptoms of thrombotic microangiopathy occur *[see Warnings and Precautions (5.10)]*.

Ability to Drive or Operate Machinery or Impairment of Mental Ability
Bortezomib for Injection may cause fatigue, dizziness, syncope, orthostatic/postural hypotension. Advise patients not to drive or operate machinery if they experience any of these symptoms *[see Warnings and Precautions (5.2, 5.5)]*.

Embryo-Fetal Toxicity
Advise females of the potential risk to the fetus and to use effective contraception during treatment with Bortezomib for Injection and for seven months following the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with Bortezomib for Injection and for four months following the last dose. Instruct patients to report pregnancy to their

physicians immediately if they or their female partner becomes pregnant during treatment or within seven months following last dose *[see Warnings and Precautions (5.11)]*.

Lactation
Advise women not to breastfeed while receiving Bortezomib for Injection and for two months after last dose *[see Use in Specific Populations (8.2)]*.

Concomitant Medications
Advise patients to speak with their physicians about any other medication they are currently taking.

Diabetic Patients
Advise patients to check their blood sugar frequently if using an oral antidiabetic medication and to notify their physicians of any changes in blood sugar level.

Dermal
Advise patients to contact their physicians if they experience rash, severe injection site reactions *[see Dosage and Administration (2.9)]*, or skin pain. Discuss with patients the option for antiviral prophylaxis for herpes virus infection *[see Adverse Reactions (6.1)]*.

Other
Instruct patients to contact their physicians if they develop an increase in blood pressure, bleeding, fever, constipation, or decreased appetite.

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Manufactured for:
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