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1.14.1.3 Draft Labeling Text

The draft package insert for generic drug product, Bortezomib for Injection, 3.5 mg per vial is provided in this section.

The SPL is also provided electronically in the corresponding section.

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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 per mL, or subcutaneously at a concentration of 2.5 mg per 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 Table1. 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) Prednisone (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest 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 $\times 10^9$/L and the absolute neutrophil count (ANC) should be at least 1 $\times 10^9$/L

Nonhematological 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 $\times 10^9$/L or ANC is not above 0.75 $\times 10^9$/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 nonhematological 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

Table 4: Dose Modifications on Days 4, 8, and 11 During Cycles of Combination Bortezomib for Injection, 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 $\times 10^9$/L	Withhold bortezomib for injection therapy for up to 2 weeks until the patient has an ANC at or above 0.75 $\times 10^9$/L and a platelet count at or above 25 $\times 10^9$/L. If, after bortezomib for injection has been withheld, the toxicity does not resolve, discontinue bortezomib for injection. If toxicity resolves such that the patient has an ANC at or above 0.75 $\times 10^9$/L and a platelet count at or above 25 $\times 10^9$/L, bortezomib for injection 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 for injection therapy until symptoms of the toxicity have resolved to Grade 2 or better. 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 rituximab, cyclophosphamide, doxorubicin and prednisone, see 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 nonhematological 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*	**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	Reduce bortezomib for injection to 1 mg/m^2
Grade 2 with pain or Grade 3 (severe	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

* Grading based on NCI Common Terminology Criteria CTCAE v4.0

managing money, etc.

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 Leve (e)

reconstituted concentration, use caution when calculating the volume to be administered [see Dosage and Administration (2.9)].

For each 3.5 mg single-dose vial of bortezomib, reconstitute with the following volume of 0.9% sodium chloride based on route of administration (Table 7):

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

Route of Administration	Bortezomib (mg per vial)	Diluent (0.9% Sodium Chloride)	Final Bortezomib Concentration (mg per mL)
Intravenous	3.5 mg	3.5 mL	1 mg per mL
Subcutaneous	3.5 mg	1.4 mL	2.5 mg per 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 per mL concentration]

$$\frac{\text{Patient BSA (m}^2\text{)} \times 1.3 \text{ mg/m}^2}{1 \text{ mg/mL}} = \text{Total bortezomib for injection volume (mL) to be administered}$$

Subcutaneous Administration [2.5 mg per mL concentration]

$$\frac{\text{Patient BSA (m}^2\text{)} \times 1.3 \text{ mg/m}^2}{2.5 \text{ mg/mL}} = \text{Total bortezomib for injection volume (mL) to be administered}$$

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 25 ℃ (77 ℉). 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.

Bortezomib

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 shoc
reaction in the bortezomib
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 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. The safety of reinitiating bortezomib 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 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. Measure platelet counts prior to each dose of bortezomib. 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 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*	Number of Patients (N=331) Á	Number (%) of Patients with Platelet Count /	Number (%) of Patients with Platelet Count W R
	309	8 (3%)	36 (12%)
to	14	2 (14%)	11 (79%)
to	7	1 (14%)	5 (71%)

*
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

vincristine, and prednisone (R-CHOP) arm as shown in Table 12 The incidence of bleeding events -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.

-CAP arm and was 52% in the R-CHOP arm. The incidence of febrile -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 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 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 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 postimplantation loss and a decreased number of live fetuses [see Use in Specific Populations (8.1)].

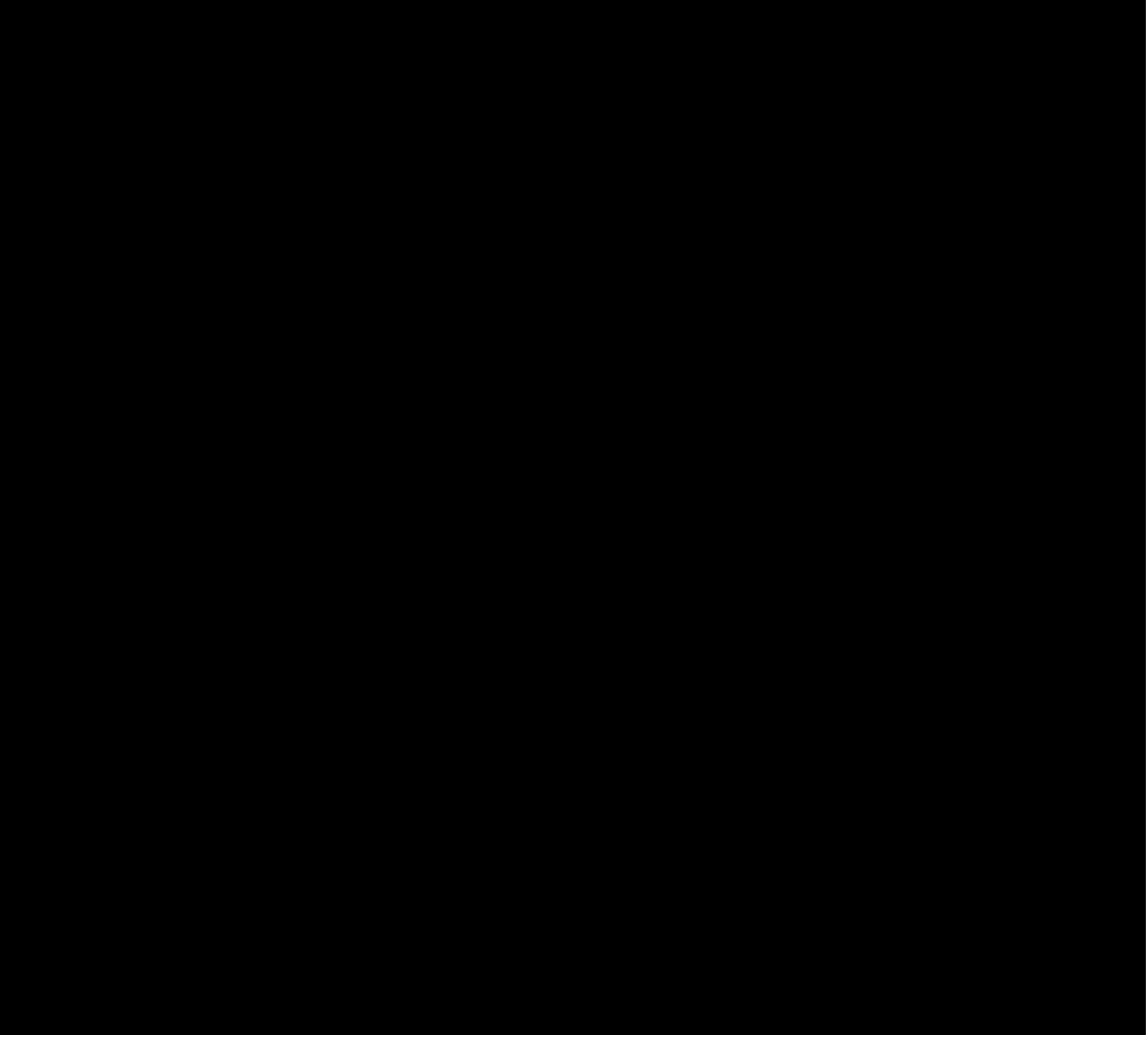
Advise females of reproductive potential to use effective contraception during treatment with bortezomib and for seven months following treatment. Advise males with female partners of reproductive potential to use effective contraception during treatment with bortezomib and for four months following treatment. If bortezomib is used during pregnancy or if the patient becomes pregnant during bortezomib 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)]



VcR-CAP arm and three patients in the R-
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 1,163 patients with previously-treated multiple myeloma (N=1,008) 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

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
are included. In the absence of a randomized comparator arm, it is often not possible to distinguish between adverse events that are drug-
underlying disease. Please see the discussion of specific adverse reactions that follows.

7DEOH 0RVW &RPPRQO\ 5HSRUWHG • 2YHUDOO
Analyses of Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma Studies Using the 1.3 mg/m^2 Dose (N=1,163)

	All Patients (N=1,163)		Multiple Myeloma (N=1,008)		Mantle Cell Lymphoma (N=155)	
Adverse Reactions	**All**	• * U D C **3**	**All**	• * U D C **3**	**All**	• * U D **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 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

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. Thrombocyto
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

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 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-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 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 <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 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%) 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 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 (>38 ℃) was reported as an adverse reaction for 21% of patients. The reaction was Grade 3 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 patients with mantle cell lymphoma.

Herpes Virus Infection

Consider using antiviral prophylaxis in subjects being treated with bortezomib. 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 Table 10, Table 11, and Table 13; no cumulative toxicities were observed upon retreatment. The most common adverse drug reaction was thrombocytopenia which occurred in 52% of the p

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),

Bortezomib

8.8 Patients with Diabetes

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

10 OVERDOSAGE

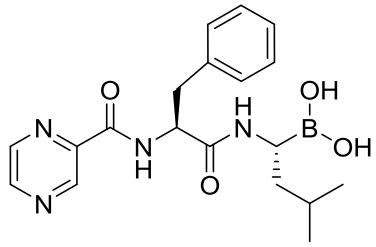
There is no known specific antidote for bortezomib overdosage. In humans, fatal outcomes following the administration of more than twice the recommended therapeutic dose have been reported, which were associated with the acute onset of symptomatic hypotension (5.2) and thrombocytopenia (5.7
and appropriate supportive care given.

Studies in monkeys and dogs showed that intravenous bortezomib doses as low as two times the recommended clinical dose on a mg/m^2 basis were associated with increases in heart rate, decreases in contractility, hypotension, and death. In dog studies, a slight increase in the corrected QT interval was observed at doses resulting in death. In monkeys, doses of 3 mg/m^2 and greater (approximately twice the recommended clinical dose) resulted in hypotension starting at one hour postadministration, with progression to death in 12 to 14 hours following drug administration.

11 DESCRIPTION

Bortezomib for injection, a proteasome inhibitor, contains bortezomib which is an antineoplastic agent. Bortezomib is a modified dipeptidyl boronic acid. The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) amino]propyl]amino]butyl] boronic acid.

Bortezomib has the following chemical structure:



The molecular weight is 384.24. The molecular formula is $C_{19}H_{25}BN_4O_4$. The solubility of bortezomib, as the monomeric boronic acid, in water is 3.3 to 3.8 mg/mL in a pH range of 2 to 6.5.

Bortezomib for injection is available for intravenous injection or subcutaneous use. Each single-dose vial contains 3.5 mg of bortezomib as a sterile lyophilized powder. It also contains the inactive ingredient: 35 mg mannitol, USP. 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Following twice weekly administration of 1 mg/m^2 and 1.3 mg/m^2 bortezomib doses, the maximum inhibition of 20S proteasome activity (relative to baseline) in whole blood was observed five minutes after drug administration. Comparable maximum inhibition of 20S proteasome activity was observed between 1 mg/m^2 and 1.3 mg/m^2 doses. Maximal inhibition ranged from 70% to 84% and from 73% to 83% for the 1 mg/m^2 and 1.3 mg/m^2 dose regimens, respectively.

12.3 Pharmacokinetics

Following intravenous administration of 1 mg/m^2 and 1.3 mg/m^2 doses, the mean maximum plasma concentrations of bortezomib (C_{max}) after the first dose (Day 1) were 57 and 112 ng/mL, respectively. When administered twice weekly, the mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1 mg/m^2 dose and 89 to 120 ng/mL for the 1.3 mg/m^2 dose.

Following an intravenous bolus or subcutaneous injection of a 1.3 mg/m^2 dose to patients with multiple myeloma, the total systemic exposure after repeat dose administration (AUC_{last}) was equivalent for subcutaneous and intravenous administration. The AUC_{last} geometric mean ratio (90%, confidence interval) was 0.99 (0.8 to

Bortezomib is primarily oxidatively metabolized to several inactive metabolites in vitro via cytochrome P450 (CYP) enzymes 3A4, CYP2C19, and CYP1A2, and to a lesser extent by CYP2D6 and CYP2C9.

Excretion

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

Specific Populations

No clinically significant differences in the pharmacokinetics of bortezomib were observed based on age, sex, or renal impairment (including patients administered bortezomib after dialysis). The effect of race on bortezomib pharmacokinetics is unknown.

Patients with Hepatic Impairment

Following administration of bortezomib doses ranging from 0.5 mg/m^2 to 1.3 mg/m^2, mild (total

impairment did not alter dose-normalized bortezomib AUC when compared to patients with normal hepatic function. Dose normalized mean bortezomib AUC increased by approximately 60% in patients with moderate (total bilirubin >1.5 to 3x ULN and any AST) or severe (total bilirubin >3x ULN and any AST) hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment.

Drug Interaction Studies

Clinical Studies

No clinically significant differences in bortezomib pharmacokinetics were observed when coadministered with dexamethasone (weak CYP3A4 inducer), omeprazole (strong CYP2C19 inhibitor), or melphalan in combination with prednisone.

Strong CYP3A4 Inhibitor

Coadministration with ketoconazole (strong CYP3A4 inhibitor) increased bortezomib exposure by 35%.

Strong CYP3A4 Inducer

Coadministration with rifampin (strong CYP3A4 inducer) decreased bortezomib exposure by approximately 45%.

In Vitro Studies

Bortezomib may inhibit CYP2C19 activity and increase exposure to drugs that are substrates for this enzyme.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with bortezomib.

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

Fertility studies with bortezomib were not performed but evaluation of reproductive tissues has been performed in the general toxicity studies. In the six month rat toxicity study, degenerative effects in

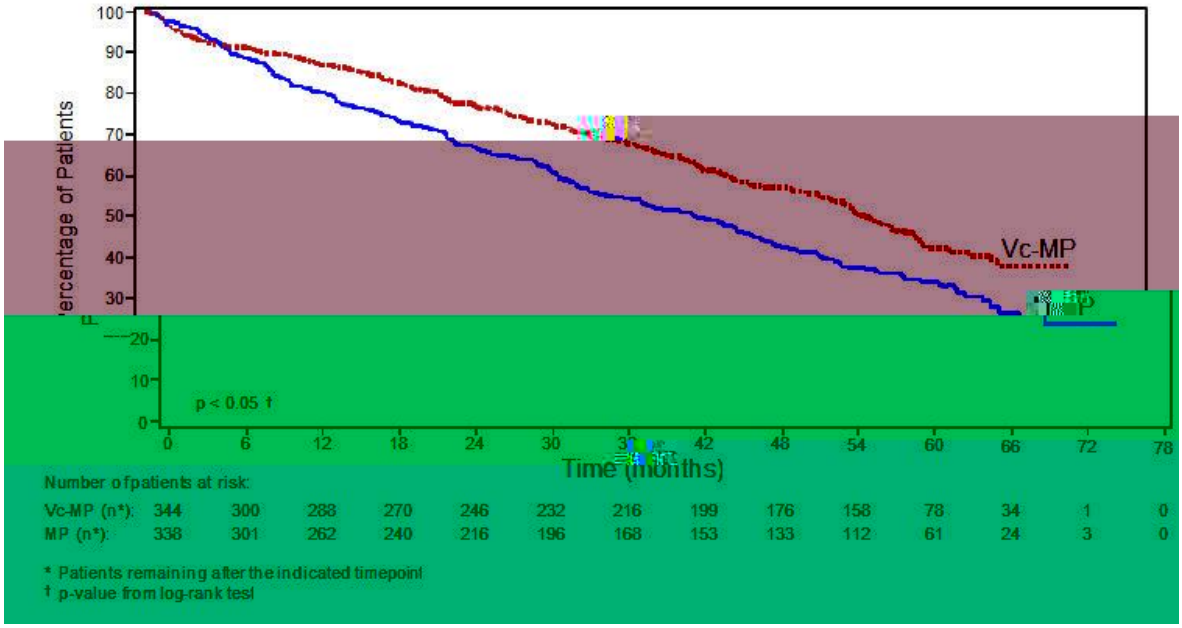
treatment arm despite subsequent therapies including bortezomib based regimens. In an updated analysis of overall survival based on 387 deaths (median follow-up 60.1 months), the median overall survival for the bortezomib, melphalan and prednisone treatment arm was 56.4 months and
ılan and prednisone treatment arm was 43.1 months, with a hazard ratio of 0.695 (95%
).

Table 14: Summary of Efficacy Analyses in the Previously Untreated Multiple Myeloma Study

Efficacy Endpoint	Bortezomib, Melphalan and Prednisone (n=344)	Melphalan and Prednisone (n=338)

%* EM)<</MCID 28 244.85 5834. /TT EM.0294.828 re f* EM/MC5 >>BDC 0 1434.21337.673.5497 138.77 41.4 re

Figure 2: Overall Survival Bortezomib, Melphalan and Prednisone vs Melphalan and Prednisone



Randomized, Clinical Study in Relapsed Multiple Myeloma of Bortezomib vs Dexamethasone

A prospective Phase 3, international, randomized (1:1), stratified, open-label clinical study (NCT00048230) enrolling 669 patients was designed to determine whether bortezomib resulted in improvement in time to progression (TTP) compared to high-dose dexamethasone in patients with progressive multiple myeloma following 1 to 3 prior therapies. Patients considered to be refractory to prior high-
neuropathy or platelet counts <50,000/μL. A total of 627 patients were evaluable for response.

Stratification factors were based on the number of lines of prior therapy the patient had previously received (one previous line vs more than one line of therapy), time of progression relative to prior treatment (progression during or within six months of stopping their most recent therapy vs relapse >6 months after receiving their most recent therapy), and screening beta$_2$-microglobulin mg/L vs >2.5 mg/L).

Baseline patient and disease characteristics are summarized in Table 15

Table 15: Summary of Baseline Patient and Disease Characteristics in the Relapsed Multiple Myeloma Study

Patient Characteristics	Bortezomib (N=333)	Dexamethasone (N=336)
Median age in years (range)	62 (33, 84)	61 (27, 86)
Gender: Male/female	56%/44%	60%/40%
Race: Caucasian/black/other	90%/6%/4%	88%/7%/5%
	13%	17%
Hemoglobin <100 g/L	32%	28%
Platelet count <75 $\times 10^9$/L	6%	4%

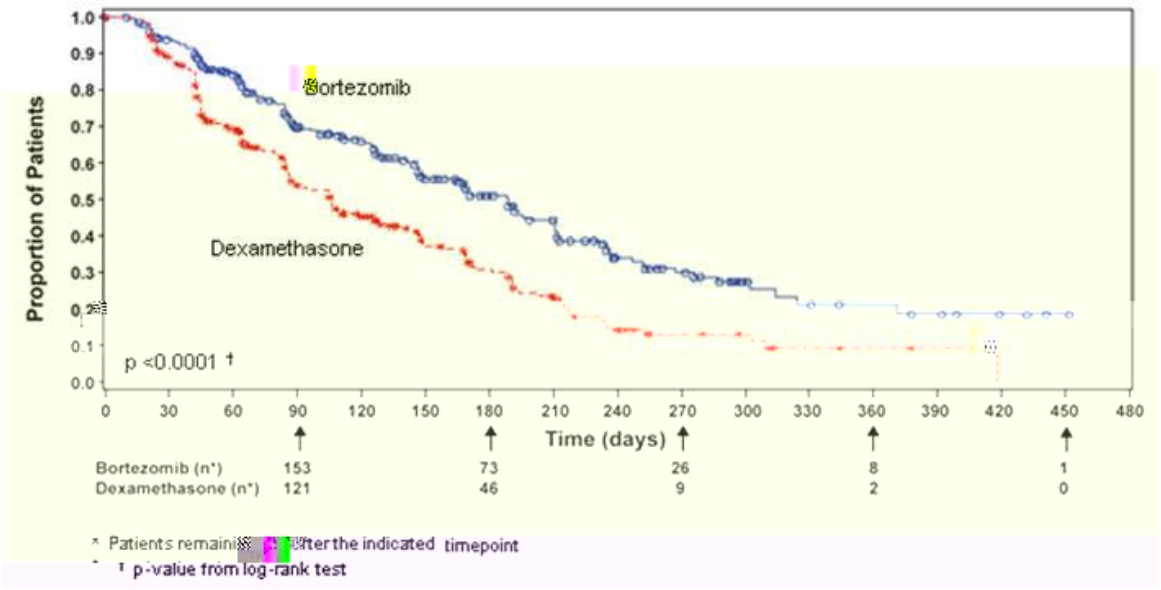
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	60%/23%/12%	59%/24%/13%
Median beta$_2$-microglobulin (mg/L)	3.7	3.6
Median albumin (g/L)	39	39
	17 (5%)	11 (3%)
Median Duration of Multiple Myeloma Since Diagnosis (Years)	3.5	3.1
Number of Prior Therapeutic Lines of Treatment		
Median	2	2
1 prior line	40%	35%
>1 prior line	60%	65%
Previous Therapy		

cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test (IF^-). Partial response (PR) requires
myeloma protein on at least two occasions for a minimum of at least six 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 16: Summary of Efficacy Analyses in the Relapsed Multiple Myeloma Study

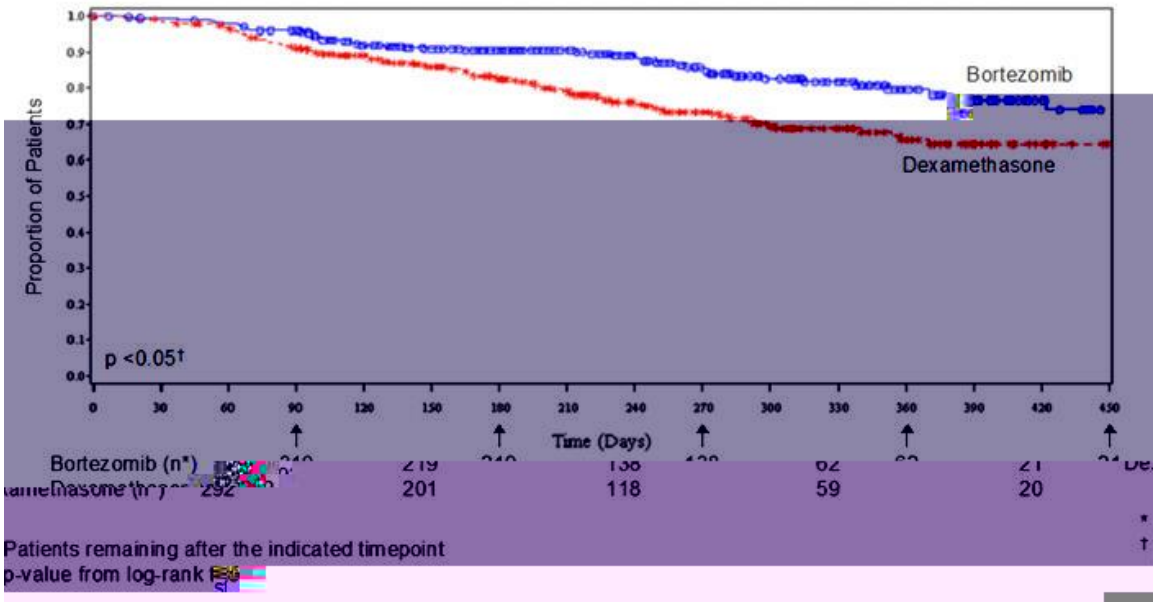
Efficacy Endpoint	All Patients		1 Prior Line of Therapy		>1 Prior Line of Therapy	
	Bortezomib	**Dex**	**Bortezomib**	**Dex**	**Bortezomib**	**Dex**
	(n=333)	**(n=336)**	**(n=132)**	**(n=119)**	**(n=200)**	**(n=217)**
Time to Progression Events n (%)	147 (44)	196 (58)	55 (42)	64 (54)	92 (46)	132 (61)
Median* (95% CI)	6.2 mo (4.9, 6.9)	3.5 mo (2.9, 4.2)	7 mo (6.2, 8.8)	5.6 mo (3.4, 6.3)	4.9 mo (4.2, 6.3)	2.9 mo (2.8, 3.5)
Hazard ratio (95% CI)	0.55 (0.44, 0.69)		0.55 (0.38, 0.81)		0.54 (0.41, 0.72)	

Figure 3: Time to Progression Bortezomib vs Dexamethasone (Relapsed Multiple Myeloma Study)



As shown in Figure 4, bortezomib had a significant survival advantage relative to dexamethasone (p <0.05). The median follow-up was 8.3 months.

Figure 4: Overall Survival Bortezomib vs Dexamethasone (Relapsed Multiple Myeloma Study)



For the 121 patients achieving a response (CR or PR) on the bortezomib arm, the median duration was 8 months (95% CI: 6.9, 11.5 months) compared to 5.6 months (95% CI: 4.8, 9.2 months) for

the 56 responders on the dexamethasone arm. The response rate was significantly higher on the bortezomib arm regardless of beta$_2$-microglobulin levels at baseline.

Randomized, Open-Label Clinical Study of Bortezomib Subcutaneous vs Intravenous in Relapsed Multiple Myeloma

An open-label, randomized, Phase 3 noninferiority study (NCT00722566) compared the efficacy and safety of the subcutaneous administration of bortezomib vs the intravenous administration. This

CR n (%)	17 (11)	9 (12)
PR n (%)	61 (41)	29 (39)
nCR n (%)	14 (9)	7 (9)
Median Time to Progression, months	10.4	9.4
Median Progression-Free Survival, months	10.2	8
1 Year Overall Survival (%)*	72.6	76.7

* Median duration of follow-up is 11.8 months

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

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

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

Patients from the two Phase
additional clinical benefit, continued to receive bortezomib beyond 8 cycles on an extension study. Sixty-three (63) patients from the Phase 2 multiple myeloma studies were enrolled and received a median of seven additional cycles of bortezomib 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 three week dosing schedule during the extension study. No new cumulative or new long-term toxicities were observed with prolonged bortezomib treatment [see Adverse Reactions (6.1)].

A Single-Arm Trial of Retreatment in Relapsed Multiple Myeloma

A single-arm, open-label trial (NCT00431769) was conducted to determine the efficacy and safety of retreatment with bortezomib
myeloma who previously had at least partial response on a bortezomib-containing regimen (median of two prior lines of therapy [range: 1 to 7]) were retreated upon progression with bortezomib

TC00572 <005 <0051 <0051

14.2 Mantle Cell Lymphoma

A Randomized, Open-Label Clinical Study in Patients with Previously Untreated Mantle Cell Lymphoma

A randomized, open-label, Phase 3 study (NCT00722137) was conducted in 487 adult patients with previously untreated mantle cell lymphoma (Stage II, III or IV) who were ineligible or not considered for bone marrow transplantation to determine whether bortezomib administered in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP) resulted in improvement in progression-free survival (PFS) when compared to the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). This clinical study utilized independent pathology confirmation and independent radiologic response assessment.

Patients in the VcR-CAP treatment arm received bortezomib (1.3 mg/m^2) administered intravenously on Days 1, 4, 8, and 11 (rest period Days 12 to 21); rituximab (375 mg/m^2) on Day 1; cyclophosphamide (750 mg/m^2) on Day 1; doxorubicin (50 mg/m^2) on Day 1; and prednisone (100 mg/m^2) on Day 1 through Day 5 of the 21 day treatment cycle. For patients with a response first documented at Cycle 6, two additional treatment cycles were allowed.

Median patient age was 66 years, 74% were male, 66% were Caucasian and 32% were Asian. Sixty-nine percent of patients had a positive bone marrow aspirate and/or a positive bone marrow biopsy for MCL, 54% of patients had an International Prognostic Index (IPI) score of three (high-intermediate) or higher and 76% had Stage IV disease.

The majority of the patients in both groups received six or more cycles of treatment, 84% in the VcR-CAP group and 83% in the R-CHOP group. Median number of cycles received by patients in both treatment arms was six with 17% of patients in the R-CHOP group and 14% of subjects in the VcR-CAP group receiving up to two additional cycles.

The efficacy results for PFS, CR and ORR with a median follow-up of 40 months are presented in Table 18. The response criteria used to assess efficacy were based on the International Workshop to Standardize Response Criteria for Non-
results at a median follow-up of 78.5 months are also presented in Table 18 and Figure 6. The combination of VcR-CAP resulted in statistically significant prolongation of PFS compared with R-CHOP (see Table 18; Figure 5).

Table 18: Summary of Efficacy Analyses in the Previously Untreated Mantle Cell Lymphoma Study

Efficacy Endpoint n: Intent to Treat patients	VcR-CAP (n=243)	R-CHOP (n=244)
Progression-Free Survival (by independent radiographic assessment)		
Events n (%)	133 (55)	165 (68)
Median* (months) (95% CI)	25 (20, 32)	14 (12, 17)
Hazard ratio (95% CI)	0.63 (0.5, 0.79)	
p-value	<0.001	
Complete Response Rate (CR)§		
n (%)	108 (44)	82 (34)

(95% CI)	(38, 51)	(28, 40)
Overall Response Rate (CR + Cru + PR)¶		
n (%)	214 (88)	208 (85)
(95% CI)	(83, 92)	(80, 89)
Overall Survival		
Events n (%)	103 (42)	138 (57)
Median* (months) (95% CI)	91 (71, NE)	56 (47, 69)
Hazard Ratio (95% CI)	0.66 (0.51, 0.85)	

Note: All results are based on the analysis performed at a median follow-up duration of 40 months except for the overall survival analysis, which was performed at a median follow-up of 78.5 months.

CI = Confidence Interval; IPI = International Prognostic Index; LDH = Lactate dehydrogenase

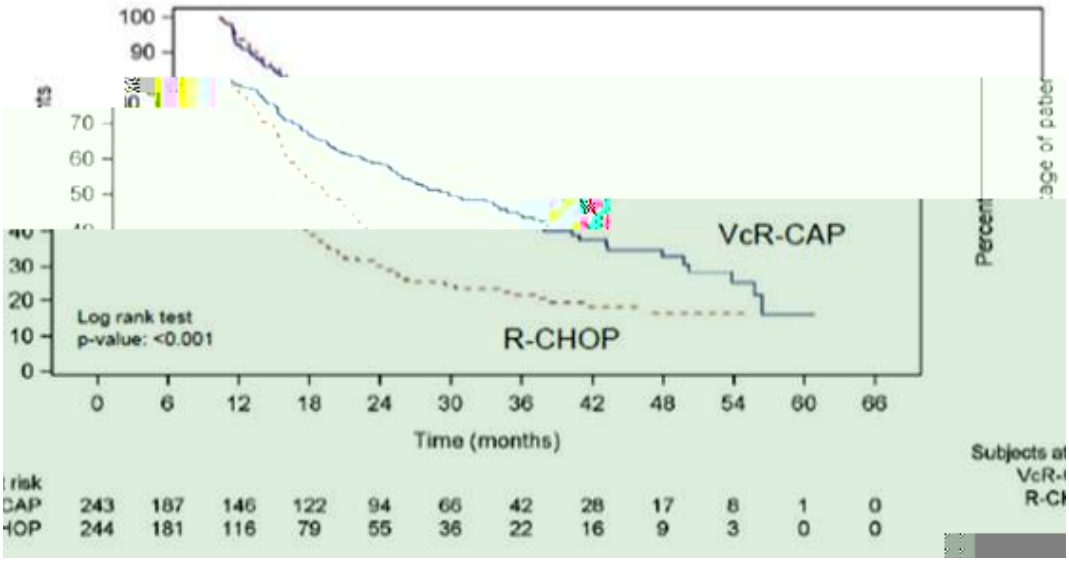
* Based on Kaplan-Meier product limit estimates.

hazard ratio <1 indicates an advantage for VcR-CAP.

§ Includes CR by independent radiographic assessment, bone marrow, and LDH using ITT population.

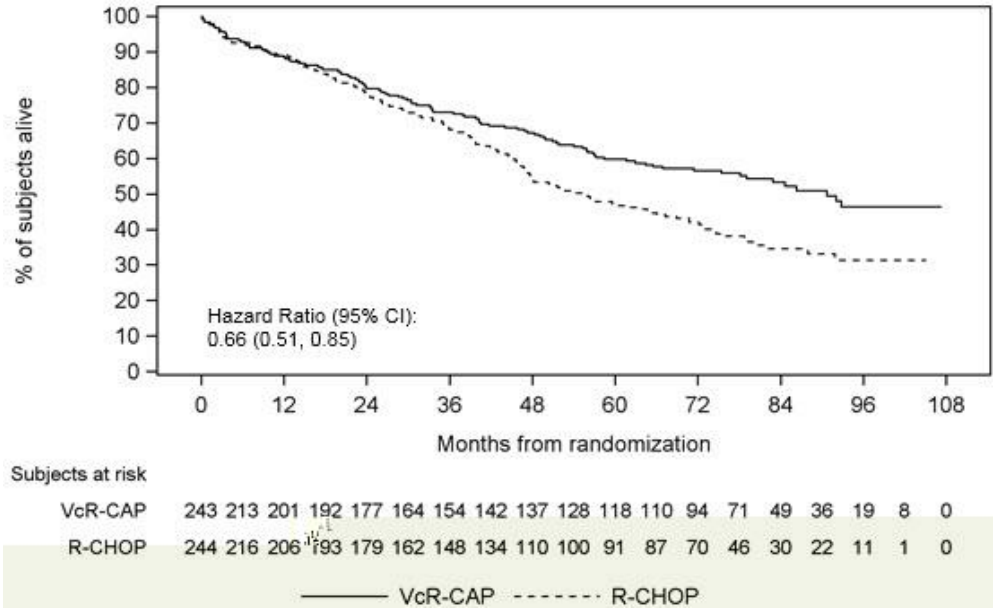
¶ Includes CR + Cru + PR by independent radiographic assessment, regardless of the verification by bone marrow and LDH, using ITT population.

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)

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 thtfmtracia-3 im[(premedie)4 (aelnstru-15 (y)i-10 (f)12 i)-5 (y)nstruor10 (f thio)3 4ose male psk tr

Other

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

Manufactured by:
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Lianyungang, Jiangsu 222069, China

Distributed by:
eVenus Pharmaceutical Laboratories, Inc.
506 Carnegie Center, Suite 100
Princeton, NJ 08540 USA

Revised: March 2022

Rev. 02