Bortezomib Teva 3.5 mg Powder for Solution for Injection

32068544-03

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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
BORTEZOMIB TEVA 3.5 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 3.5 mg of bortezomib (as a mannitol boronic ester).
After reconstitution, 1 ml of solution for subcutaneous injection contains 2.5 mg bortezomib.
After reconstitution, 1 ml of solution for intravenous injection contains 1 mg bortezomib.
For the full list of excipients, see section 6.
Powder for Solution for Injection I.V., S.C.

3. THERAPUETIC INDICATIONS

3.1 Multiple Myeloma

Bortezomib Teva 3.5 mg is indicated for the treatment of patients with multiple myeloma.

3.2 Mantle Cell Lymphoma

Bortezomib Teva 3.5 mg is indicated for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.
Bortezomib Teva 3.5 mg in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.

4. DOSAGE AND ADMINISTRATION

General Dosing Guidelines

Bortezomib Teva 3.5 mg is for intravenous or subcutaneous use only.
Bortezomib Teva 3.5 mg must not be administered by any other route.
Intrathecal administration has resulted in death.
Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered.
The recommended starting dose of Bortezomib Teva 3.5 mg (bortezomib) is 1.3 mg/m^2. Bortezomib Teva 3.5 mg may be administered intravenously at a concentration of 1 mg/mL, or subcutaneously at a concentration of 2.5 mg/mL (see reconstitution/preparation for intravenous and subcutaneous administration (section 4.8)). When administered intravenously, Bortezomib Teva 3.5 mg is administered as a 3 to 5 second bolus intravenous injection.

4.1 Dosage in Previously Untreated Multiple Myeloma

Bortezomib Teva 3.5 mg is administered in combination with oral melphalan and oral prednisone for 9, 6-week treatment cycles as shown in Table 1. In Cycles 1-4, Bortezomib Teva 3.5 mg is administered twice weekly (Days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5 to 9, Bortezomib Teva 3.5 mg is administered once weekly (Days 1, 8, 22 and 29).
At least 72 hours should elapse between consecutive doses of Bortezomib Teva 3.5 mg.

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

Twice Weekly Bortezomib Teva 3.5 mg (Cycles 1 to 4)												
Week	1				2		3	4		5		6
Bortezomib (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 Teva 3.5 mg (Cycles 5 to 9 when used in combination with Melphalan and Prednisone)												
Week	1				2		3	4		5		6
Bortezomib (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

4.2 Dose Modification Guidelines for Combination Therapy with Bortezomib, Melphalan and Prednisone

Prior to initiating any cycle of therapy with bortezomib in combination with melphalan and prednisone:
- Platelet count should be ≥ 70 x 10^9/L and the absolute neutrophil count (ANC) should be ≥ 1.0 x 10^9/L.
- Non-hematological toxicities should have resolved to Grade 1 or baseline.

Table 2: Dose Modifications During Cycles of Combination Bortezomib, 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 ≤ 30 x 10^9/L or ANC ≤ 0.75 x 10^9/L on a bortezomib dosing day (other than day 1).	Withhold bortezomib dose
If several bortezomib doses in consecutive cycles are withheld due to toxicity	Reduce bortezomib dose by 1 dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2.
Grade ≥ 3 non-hematological toxicities	Withhold bortezomib therapy until symptoms of the toxicity have resolved to Grade 1 or baseline. 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 4.

For information concerning melphalan and prednisone, see manufacturer's prescribing information.
Dose modifications guidelines for peripheral neuropathy are provided [see Dosage and administration [4.6].

4.3 Posology for Patients with Previously Untreated Mantle Cell Lymphoma (MCL)

Combination therapy with rituximab, cyclophosphamide, doxorubicin and prednisone (VcR-CAP)
Bortezomib Teva 3.5 mg powder for solution for injection is administered via intravenous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11, followed by a 10-day rest period on days 12-21. This 3-week period is considered a treatment cycle. Six bortezomib cycles are recommended, although for patients with a response first documented at cycle 6, two additional bortezomib cycles may be given. At least 72 hours should elapse between consecutive doses of bortezomib.
The following medicinal products are administered on day 1 of each bortezomib 3-week treatment cycle as intravenous infusions: rituximab at 375 mg/m^2, cyclophosphamide at 750 mg/m^2 and doxorubicin at 50 mg/m^2.
Prednisone is administered orally at 100 mg/m^2 on days 1, 2, 3, 4 and 5 of each bortezomib treatment cycle.
Dose adjustments during treatment for patients with previously untreated mantle cell lymphoma
Prior to initiating a new cycle of therapy:
- Platelet counts should be ≥ 100,000 cells/μL and the absolute neutrophils count (ANC) should be ≥ 1,500 cells/μL.
- Platelet counts should be ≥ 75,000 cells/μL in patients with bone marrow infiltration or splenic sequestration.
- Haemoglobin ≥ 8 g/dL.
- Non-haematological toxicities should have resolved to Grade 1 or baseline.

Bortezomib treatment must be withheld at the onset of any ≥ Grade 3 bortezomib-related non-haematological toxicities (excluding neuropathy) or ≥ Grade 3 haematological toxicities. For dose adjustments, see Table 3 below.
Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration. Platelet transfusion for the treatment of thrombocytopenia should be considered when clinically appropriate.

Table 3: Dose Adjustments During Treatment for Patients with Previously Untreated Mantle Cell lymphoma

Toxicity	Posology modification or delay
Haematological toxicity	
≥ Grade 3 neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, a platelet count < 10,000 cells/μL	Bortezomib therapy should be withheld for up to 2 weeks until the patient has an ANC ≥ 750 cells/μL and a platelet count ≥ 25,000 cells/μL. • If, after bortezomib has been held, the toxicity does not resolve, as defined above, then bortezomib must be discontinued. • If toxicity resolves i.e. patient has an ANC ≥ 750 cells/μL and a platelet count ≥ 25,000 cells/μL, bortezomib may be reinitiated at a dose reduced 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).
If platelet counts < 25,000 cells/μL or ANC < 750 cells/μL on a bortezomib dosing day (other than Day 1 of each cycle)	Bortezomib therapy should be withheld
If several bortezomib doses in consecutive cycles are withheld due to toxicity	Reduce bortezomib 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 non-haematological toxicities considered to be related to bortezomib	Bortezomib therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, bortezomib may be reinitiated at a dose reduced 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). For bortezomib-related neuropathic pain and/or peripheral neuropathy, hold and/or modify bortezomib as outlined in Table 1.

In addition, when bortezomib is given **in** combination **with** other chemotherapeutic medicinal products, appropriate dose reductions for these medicinal products should be considered in the event of toxicities, according to the recommendations in the respective Summary of Product Characteristics.

4.4 Dosage in Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma

Bortezomib (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 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 section (13) for a description of dose administration during the trials). At least 72 hours should elapse between consecutive doses of bortezomib.

4.5 Dose Modification Guidelines for Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma

Bortezomib 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 (7)). Once the symptoms of the toxicity have resolved, bortezomib 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 Management of peripheral neuropathy section (4.5)).

4.6 Dose Modifications of Peripheral Neuropathy

Starting bortezomib 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 only after careful risk-benefit assessment.
Patients experiencing new or worsening peripheral neuropathy during bortezomib 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 -related neuropathic pain and/or peripheral neuropathy (see Table 4).

Table 4: Recommended Dose Modification for Bortezomib-related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms*	Modification of Dose and Regimen
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL))**	Reduce bortezomib to 1 mg/m^2 OR Change bortezomib treatment schedule to 1.3 mg/m^2 once per week
Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care ADL ***)	Withhold bortezomib therapy until toxicity resolves. When toxicity resolves, reinitiate with a reduced dose of Bortezomib Teva 3.5 mg at 0.7 mg/m^2 once per week.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue bortezomib

*Grading based on NCI Common Toxicity Criteria CTCAE v 4.0
** Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc;
*** Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

4.7 Dosage in Patients with Hepatic Impairment

Patients with mild hepatic impairment do not require a dose adjustment and should be treated per the recommended bortezomib dose. Patients with moderate or severe hepatic impairment should be started on bortezomib at a reduced dose of 0.7 mg/m^2 per injection during the first cycle, and a subsequent dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 may be considered based on patient tolerance (see Table 5) (see Warnings and Precautions (7.8), Use in Specific Populations (10.7) and Clinical Pharmacology (13.3)).

Table 5: Recommended Starting Dose Modification for Bortezomib in Patients with Hepatic Impairment

Grade of hepatic impairment*	Bilirubin Level	SGOT (AST) Levels	Modification of Starting Dose
Mild	≤ 1.0 x ULN	> ULN	None
	> 1.0 x – 1.5 x ULN	Any	None
Moderate	> 1.5x – 3 x ULN	Any	Reduce bortezomib to 0.7 mg/m^2 in the first treatment cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	> 3 x ULN	Any	

Abbreviations: SGOT = serum glutamic oxaloacetic transaminase;
AST = aspartate aminotransferase; ULN = upper limit of the normal range
***Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe).**

4.8 Administration Precautions

The drug quantity contained in one vial of Bortezomib Teva 3.5 mg may exceed the usual dose required. Caution should be used in calculating the dose to prevent overdose (see reconstitution/preparation for intravenous and subcutaneous administration (section 4.8)).
Bortezomib Teva 3.5 mg is authorized for intravenous or subcutaneous use only. Intrathecal administration has resulted in death.
When administered subcutaneously, sites for each injection (thigh or abdomen) should be rotated. New injections should be given 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 administration subcutaneously, a less concentrated bortezomib solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously (see reconstitution/preparation for intravenous and subcutaneous administration (section 4.8) and follow reconstitution instructions for 1 mg/mL). Alternatively, the intravenous route of administration should be considered (see reconstitution/preparation for intravenous and subcutaneous administration (section 4.9)).
Bortezomib Teva 3.5 mg is a cytotoxic drug. Follow applicable special handling and disposal procedures [See How Supplied/Storage and Handling (16)].

4.9 Reconstitution/Preparation for Intravenous and Subcutaneous Administration

Use proper aseptic technique. Reconstitute **only with 0.9% sodium chloride.**
The reconstituted solution is clear and colourless, with a final pH of 4 to 7.
Different volumes of 0.9% sodium chloride 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 Administration Precautions section 4.8).
For each 3.5 mg single-dose vial of Bortezomib Teva 3.5 mg reconstitute with the following volume of 0.9% sodium chloride based on route of administration (Table 6):

Table 6: Reconstitution Volumes and Final Concentration for Intravenous and Subcutaneous Administration

Route of administration	Bortezomib (mg/vial)	Diluent (0.9% Sodium Chloride)	Final bortezomib Concentration (mg/mL)
Intravenous	3.5 mg	3.5 mL	1 mg/mL
Subcutaneous	3.5 mg	1.4 mL	2.5 mg/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 Teva to be administered:

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

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

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

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

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:
The expiry date of the product is indicated on the packaging materials.
Unopened vials:
Store below 25°C.
Keep container in the outer carton in order to protect from light.
Bortezomib Teva contains no antimicrobial preservative.
Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 25°C (stored in the original vial and/or syringe).
From a microbiological point of view, unless the method of opening/reconstitution precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user.

5. DOSAGE FORMS AND STRENGTHS

Each single-use vial of Bortezomib Teva 3.5 mg contains 3.5 mg of bortezomib as a sterile lyophilized white to off-white powder.

6. CONTRAINDICATIONS

Bortezomib Teva is contraindicated in patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol or any of the excipients. Reactions have included anaphylactic reactions (see Adverse Reactions (8.1)).
Bortezomib Teva is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of bortezomib.
DO NOT ADMINISTER BORTEZOMIB TEVA 3.5 MG INTRATHECALLY.

7. WARNINGS AND PRECAUTIONS

7.1 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. 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 versus 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. Starting bortezomib 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 therapy may require a decrease in the dose and/or a less dose-intense schedule (see Dosage and Administration (4)).
In the bortezomib versus 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.

7.2 Hypotension

The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 8% [see Adverse Reactions (8.1)]. 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.

7.3 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 (8.1)]. 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.

7.4 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.

7.5 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.

7.6 Gastrointestinal Toxicity

Bortezomib treatment can cause nausea, diarrhea, constipation, and vomiting (see Adverse Reactions (8.1)) 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.

7.7 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 Tables 6 and 7 Dosage and Administration (5.6)).
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 versus 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 7. The incidence of bleeding (≥ Grade 3) was 2% on the bortezomib arm and was < 1% in the dexamethasone arm.

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

* A baseline platelet count of 50,000/μL was required for study eligibility.
Data were missing at baseline for 1 patient.

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% versus 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 patient) and was 1.2% in the R- CHOP arm (three patient).
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.

7.8 Hepatic impairment

Bortezomib is metabolised by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with Bortezomib at reduced doses and closely monitored for toxicities (see sections 4.6 and 13.3).

7.9 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.

7.10 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 re-challenge information in these patients.

7.11 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.

7.12 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 (10.1)].
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 (10.1, 10.3), Nonclinical Toxicology (14.1)].

7.13 Herpes Zoster Virus Reactivation

Antiviral prophylaxis is recommended in patients being treated with Bortezomib.
In patients with MCL (study LYM-3002), the incidence of herpes zoster infection was 6.7% in the VcR-CAP arm and 1.2% in the R-CHOP arm.

7.14 Progressive multifocal leukoencephalopathy (PML)

Very rare cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with bortezomib. Patients diagnosed with PML had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their first dose of bortezomib.
Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of CNS problems. If a diagnosis of PML is suspected, patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. Discontinue bortezomib if PML is diagnosed.

7.15 Seizures

Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.

7.16 Renal impairment

Renal complications are frequent in patients with multiple myeloma. Patients with renal impairment should be monitored closely.

7.17 Concomitant medicinal products

Patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors. Caution should be exercised when bortezomib is combined with CYP3A4 or CYP2C19 substrates.
Normal liver function should be confirmed and caution should be exercised in patients receiving oral hypoglycemics.

7.18 Potentially immunocomplex-mediated reactions

Potentially immunocomplex-mediated reactions, such as serum-sickness-type reaction, polyarthritis with rash and proliferative glomerulonephritis have been reported uncommonly. Bortezomib should be discontinued if serious reactions occur.

7.19 Hepatitis B Virus (HBV) reactivation and infection

When rituximab is used in combination with bortezomib, HBV screening must always be performed in patients at risk of infection with HBV before initiation of treatment. Carriers of hepatitis B and patients with a history of hepatitis B must be closely monitored for clinical and laboratory signs of active HBV infection during and following rituximab combination treatment with bortezomib. Antiviral prophylaxis should be considered. Refer to the Summary of Product Characteristics of rituximab for more information.

7.20 Haematological toxicity

Bortezomib treatment is very commonly associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia). In studies in patients with relapsed multiple myeloma treated with bortezomib and in patients with previously untreated MCL treated with bortezomib in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR CAP), one of the most common haematologic toxicity was transient thrombocytopenia. Platelets were lowest at Day 11 of each cycle of bortezomib treatment and typically recovered to baseline by the next cycle. There was no evidence of cumulative thrombocytopenia. The mean platelet count nadir measured was approximately 40% of baseline in the single agent multiple myeloma studies and 50% in the MCL study. In patients with advanced myeloma the severity of thrombocytopenia was related to pre- treatment platelet count: for baseline platelet counts < 75,000/μl, 90% of 21 patients had a count ≤ 25,000/μl during the study, including 14% < 10,000/μl; in contrast, with a baseline platelet count > 75,000/μl, only 14% of 309 patients had a count ≤ 25,000/μl during the study.
In patients with MCL (study LYM 3002), there was a higher incidence (56.7% versus 5.8%) of Grade ≥ 3 thrombocytopenia in the bortezomib treatment group (VcR CAP) as compared to the non bortezomib treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R CHOP]). The two treatment groups were similar with regard to the overall incidence of all grade bleeding events (6.3% in the VcR CAP group and 5.0% in the R CHOP group) as well as Grade 3 and higher bleeding events (VcR CAP: 4 patients [1.7%]; R CHOP: 3 patients [1.2%]). In the VcR CAP group, 22.5% of patients received platelet transfusions compared to 2.9% of patients in the R CHOP group.
Gastrointestinal and intracerebral haemorrhage, have been reported in association with bortezomib treatment. Therefore, platelet counts should be monitored prior to each dose of bortezomib. Bortezomib therapy should be withheld when the platelet count is < 25,000/μl or, in the case of combination with melphalan and prednisone, when the platelet count is ≤ 30,000/μl (see section 5.3). Potential benefit of the treatment should be carefully weighed against the risks, particularly in case of moderate to severe thrombocytopenia and risk factors for bleeding.
Complete blood counts (CBC) with differential and including platelet counts should be frequently monitored throughout treatment with bortezomib. Platelet transfusion should be considered when clinically appropriate (see section 4.3).
In patients with MCL, transient neutropenia that was reversible between cycles was observed, with no evidence of cumulative neutropenia. Neutrophils were lowest at Day 11 of each cycle of bortezomib treatment and typically recovered to baseline by the next cycle. In study LYM 3002, colony stimulating factor support was given to 78% of patients in the VcR CAP arm and 61% of patients in the R CHOP arm. Since patients with neutropenia are at increased risk of infections, they should be monitored for signs and symptoms of infection and treated promptly. Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration (see section 4.3).

7.21 Intrathecal administration

There have been fatal cases of inadvertent intrathecal administration of bortezomib. bortezomib 1 mg powder for solution for injection is for intravenous use only, while bortezomib 3.5 mg powder for solution for injection is for intravenous or subcutaneous use. Bortezomib should not be administered intrathecally.

7.22 Electrocardiogram investigations

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

8. ADVERSE REACTIONS

The following clinically significant adverse reactions are also discussed in other sections of the labeling:
- Peripheral Neuropathy (see Warnings and Precautions (7.1);
- Hypotension (see Warnings and Precautions (7.2))
- Cardiac Toxicity (see Warnings and Precautions (7.3))
- Pulmonary Toxicity (see Warnings and Precautions (7.4))
- Posterior Reversible Encephalopathy Syndrome (PRES) (see Warnings and Precautions (7.5))
- Gastrointestinal Toxicity (see Warnings and Precautions (7.6))
- Thrombocytopenia/Neutropenia (see Warnings and Precautions (7.7))
- Hepatic impairment *[see Warnings and Precautions (7.8)]*
- Tumor Lysis Syndrome (see Warnings and Precautions (7.9))
- Hepatic Toxicity (see Warnings and Precautions (7.10))
- Thrombotic Microangiopathy *[see Warnings and Precautions (7.11)]*

8.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions 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 8 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 8: Most Commonly Reported Adverse Reactions (≥ 10% in 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 Adverse reaction	**Total** n (%)	**Toxicity Grade, n (%)** 3	≥ 4	**Total** n (%)	**Toxicity Grade, 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)
Anaemia	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
Paraesthesia	42 (12)	6 (2)	0	4 (1)	0	0
General Disorders and Administration Site Conditions						
Fatigue	85 (25)	19 (6)	2 (1)	48 (14)	4 (1)	0
Asthenia	54 (16)	18 (5)	0	23 (7)	3 (1)	0
Pyrexia	53 (16)	4 (1)	0	19 (6)	1 (< 1)	1 (< 1)
Infections and Infestations						
Herpes Zoster	39 (11)	11 (3)	0	9 (3)	4 (1)	0
Metabolism and Nutrition Disorders						
Anorexia	64 (19)	6 (2)	0	19 (6)	0	0
Skin and Subcutaneous Tissue Disorders						
Rash	38 (11)	2 (1)	0	7 (2)	0	0
Psychiatric Disorders						
Insomnia	35 (10)	1 (< 1)	0	21 (6)	0	0

* Represents High Level Term Peripheral Neuropathies NEC

See next page

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/m² 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 (15.1)].
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 1 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 9. All adverse reactions with incidence ≥ 10% in the bortezomib arm are included.

Table 9: Most Commonly Reported Adverse Reactions (≥ 10% in Bortezomib arm), with Grades 3 and 4 Intensity in 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 (15.1)].
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/m². This was a randomized, comparative study of bortezomib subcutaneous versus intravenous in 222 patients with relapsed multiple myeloma. The safety data described below and in Table 10 reflect exposure to either bortezomib subcutaneous (n=147) or bortezomib intravenous (n=74) (see Clinical Studies (15.1)).

Table 10: 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 Adverse Reaction	**Total n (%)**	**Toxicity grade, n (%) 3**	**≥ 4**	**Total n (%)**	**Toxicity grade, 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 NEC*	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 1 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 versus 9% intravenous), peripheral neuropathies NEC (6% subcutaneous versus 15% intravenous), neutropenia (13% subcutaneous versus 18% intravenous), and thrombocytopenia (8% subcutaneous versus 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 6 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 versus 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 11 describes safety data from 240 patients with previously untreated mantle cell lymphoma who received Bortezomib (1.3 mg/m²) administered intravenously in combination with rituximab (375 mg/m²), cyclophosphamide (750 mg/m²), doxorubicin (50 mg/m²), and prednisone (100 mg/m²) (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% versus R-CHOP 5%).

Table 11: 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 (5)	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).
Mantle Cell Lymphoma (MCL)
The safety profile of bortezomib in 240 MCL patients treated with bortezomib at 1.3 mg/m² in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR CAP) versus 242 patients treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R CHOP] was relatively consistent to that observed in patients with multiple myeloma with main differences described below. Additional adverse drug reactions identified associated with the use of the combination therapy (VcR CAP) were hepatitis B infection (< 1%) and myocardial ischaemia (1.3%). The similar incidences of these events in both treatment arms, indicated that these adverse drug reactions are not attributable to bortezomib alone. Notable differences in the MCL patient population as compared to patients in the multiple myeloma studies were a ≥ 5% higher incidence of the haematological adverse reactions (neutropenia, thrombocytopenia, leukopenia, anemia, lymphopenia), peripheral sensory neuropathy, hypertension, pyrexia, pneumonia, stomatitis, and hair disorders.
Adverse drug reactions identified as those with a ≥ 1% incidence, similar or higher incidence in the VcR CAP arm and with at least a possible or probable causal relationship to the components of the VcR CAP arm, are listed in Table 8 below. Also included are adverse drug reactions identified in the VcR CAP arm that were considered by investigators to have at least a possible or probable causal relationship to bortezomib based on historical data in the multiple myeloma studies.
Adverse reactions are listed below by system organ class and frequency grouping. Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Table 12 has been generated using Version 16 of the MedDRA.

Table 12: Adverse reactions in patients with Mantle Cell Lymphoma treated with VcR CAP in a clinical trial

System Organ Class	Incidence	Adverse reaction
Infections and infestations	Very Common	Pneumonia*
	Common	Sepsis (inc septic shock)*, Herpes zoster (inc disseminated & ophthalmic), Herpes virus infection*, Bacterial infections*, Upper/lower respiratory tract infection*, Fungal infection*, Herpes simplex*
	Uncommon	Hepatitis B, Infection*, Bronchopneumonia
Blood and lymphatic system disorders	Very Common	Thrombocytopenia*, Febrile neutropenia, Neutropenia*, Leukopenia*, Anaemia*, Lymphopenia*
	Uncommon	Pancytopenia*
Immune system disorders	Common	Hypersensitivity*
	Uncommon	Anaphylactic reaction
Metabolism and nutrition disorders	Very Common	Decreased appetite
	Common	Hypokalaemia*, Blood glucose abnormal*, Hyponatraemia*, Diabetes mellitus*, Fluid retention
	Uncommon	Tumour lysis syndrome
Psychiatric disorders	Common	Sleep disorders and disturbances*
Nervous system disorders	Very Common	Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia*
	Common	Neuropathies*, Motor neuropathy*, Loss of consciousness (inc syncope), Encephalopathy*, Peripheral sensorimotor neuropathy, Dizziness*, Dysgeusia*, Autonomic neuropathy
	Uncommon	Autonomic nervous system imbalance
Eye disorders	Common	Vision abnormal*
Ear and labyrinth disorders	Common	Dysacusis (inc tinnitus)*
	Uncommon	Vertigo*, Hearing impaired (up to and inc deafness)
Cardiac disorders	Common	Cardiac fibrillation (inc atrial), Arrhythmia*, Cardiac failure (inc left and right ventricular)*, Myocardial ischaemia, Ventricular dysfunction*
	Uncommon	Cardiovascular disorder (inc cardiogenic shock)
Vascular disorders	Common	Hypertension*, Hypotension*, Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea*, Cough*, Hiccups
	Uncommon	Acute respiratory distress syndrome, Pulmonary embolism, Pneumonitis, Pulmonary hypertension, Pulmonary oedema (inc acute)
Gastrointestinal disorders	Very Common	Nausea and vomiting symptoms*, Diarrhoea*, Stomatitis*, Constipation
	Common	Gastrointestinal haemorrhage (inc mucosal)*, Abdominal distension, Dyspepsia, Oropharyngeal pain*, Gastritis*, Oral ulceration*, Abdominal discomfort, Dysphagia, Gastrointestinal inflammation*, Abdominal pain (inc gastrointestinal and splenic pain)*, Oral disorder*
	Uncommon	Colitis (inc clostridium difficile)*
Hepatobiliary disorders	Common	Hepatotoxicity (inc liver disorder)
	Uncommon	Hepatic failure
Skin and subcutaneous tissue disorders	Very Common	Hair disorder*
	Common	Pruritus*, Dermatitis*, Rash*
Musculoskeletal and connective tissue disorders	Common	Muscle spasms*, Musculoskeletal pain*, Pain in extremity
Renal and urinary disorders	Common	Urinary tract infection*
General disorders and administration site conditions	Very Common	Pyrexia*, Fatigue, Asthenia
	Common	Oedema (inc peripheral), Chills, Injection site reaction*, Malaise*
Investigations	Common	Hyperbilirubinaemia*, Protein analyses abnormal*, Weight decreased, Weight increased

* Grouping of more than one MedDRA preferred term.

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/m²/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 [see Clinical Studies (15)].
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 reactions 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/m² 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 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 (7.7)].
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 neuropathy 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 versus 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 (> 38°C) 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. 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 (3-4%). Herpes simplex was seen in 1-3% 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.
Mantle cell lymphoma
Antiviral prophylaxis was administered to 137 of 240 patients (57%) in the VcR CAP arm. The incidence of herpes zoster among patients in the VcR CAP arm was 10.7% for patients not administered antiviral prophylaxis compared to 3.6% for patients administered antiviral prophylaxis (see section 7.13).
Hepatitis B Virus (HBV) reactivation and infection
Mantle cell lymphoma
HBV infection with fatal outcomes occurred in 0.8% (n=2) of patients in the non bortezomib treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R CHOP) and 0.4% (n=1) of patients receiving bortezomib in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR CAP). The overall incidence of hepatitis B infections was similar in patients treated with VcR CAP or with R CHOP (0.8% vs 1.2% respectively).
Mantle cell lymphoma
In study LYM 3002 in which bortezomib was administered with rituximab, cyclophosphamide, doxorubicin, and prednisone (R CAP), the incidence of peripheral neuropathy in the combination regimens is presented in the table below:

Table 14: Incidence of peripheral neuropathy in study LYM 3002 by toxicity and treatment discontinuation due to peripheral neuropathy

	VcR-CAP (N=240)	R-CHOP (N=242)
Incidence of PN (%)		
All Grade PN	30	29
≥ Grade 2 PN	18	9
≥ Grade 3 PN	8	4
Discontinuation due to PN (%)	2	< 1

VcR-CAP= bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone;
R-CHOP= rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
PN=peripheral neuropathy
Peripheral neuropathy included the preferred terms: peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensorimotor neuropathy

Elderly MCL patients
42.9% and 10.4% of patients in the VcR CAP arm were in the range 65-74 years and ≥ 75 years of age, respectively. Although in patients aged ≥ 75 years, both VcR-CAP and R-CHOP were less tolerated, the serious adverse event rate in the VcR-CAP groups was 68%, compared to 42% in the R-CHOP group.

8.2 Post-marketing Experience

The following adverse drug reactions have been identified from the worldwide post-marketing 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-Barre 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)
Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

See next page

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Bortezomib
Teva 3.5 mg
Powder for
Solution for
Injection

32086309-03

9. DRUG INTERACTIONS

9.1 Effects of Other Drugs on Bortezomib

Strong CYP3A4 inducers

Coadministration with a strong CYP3A4 inducer decreases the exposure of bortezomib [see Clinical Pharmacology (13.3)] which may decrease bortezomib efficacy. Avoid coadministration with strong CYP3A4 inducers.

Strong CYP3A4 Inhibitors

Coadministration with a strong CYP3A4 inhibitor increases the exposure of bortezomib [see Clinical Pharmacology (13.3)] which may increase the risk of bortezomib 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.

9.2 Drugs Without Clinically Significant Interactions with bortezomib

No clinically significant drug interactions have been observed when bortezomib was coadministered with dexamethasone, omeprazole, or melphalan in combination with prednisone [see Clinical Pharmacology (13.3)].
During clinical trials, hypoglycemia and hyperglycemia were uncommonly and commonly 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 antidiabetics.

10. USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (13.1)]* findings in animals, Bortezomib can cause fetal harm when administered to a pregnant woman. There are no studies with the use of Bortezomib in pregnant women to inform drug-associated risks. Bortezomib caused embryo-fetal lethality in rabbits at doses lower than the clinical dose (see Data). Advise pregnant women of the potential risk to the fetus.
Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits at the highest dose tested (0.075 mg/kg; 0.5 mg/m^2 in the rat and 0.05 mg/kg; 0.6 mg/m^2 in the rabbit) when administered during organogenesis. These dosages are approximately 0.5 the clinical dose of 1.3 mg/m^2 based on body surface area.
Bortezomib caused embryo-fetal lethality in rabbits at doses lower than the clinical dose (approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area). Pregnant rabbits given bortezomib during organogenesis at a dose of 0.05mg/kg (0.6 mg/m^2) experienced significant post-implantation loss and decreased number of live fetuses. Live fetuses from these litters also showed significant decreases in fetal weight.

10.2 Lactation

Risk Summary

There are no data on the presence of bortezomib or its metabolites in human milk, the effects of the drug on the breastfed child, or the effects of the drug on milk production. Because many drugs are excreted in human milk and because the potential for serious adverse reactions in a breastfed child from bortezomib is unknown, advise nursing women not to breastfeed during treatment with bortezomib and for two months after treatment.

10.3 Females and Males of Reproductive Potential

Based on its mechanism of action and findings in animals, bortezomib can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (10.1)].

Pregnancy Testing

Conduct pregnancy testing in females of reproductive potential prior to initiating bortezomib treatment.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with bortezomib and for seven months after the last dose.

Males

Males with female partners of reproductive potential should use effective contraception during treatment with bortezomib and for four months after the last dose.

Infertility

Based on the mechanism of action and findings in animals, bortezomib may have an effect on either male or female fertility [see Nonclinical Toxicology (14.1)].

10.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.
The activity and safety of Bortezomib in combination with intensive re-induction chemotherapy was evaluated in pediatric and young adult patients with lymphoid malignancies (pre-B cell ALL 77%, 16% with T-cell ALL, and 7% T-cell lymphoblastic lymphoma (LL)), all of whom relapsed within 36 months of initial diagnosis in a single-arm multicenter, non-randomized cooperative group trial. An effective re-induction multiagent chemotherapy regimen was administered in Three blocks. Block 1 included vincristine, prednisone, doxorubicin and pegaspargase; Block 2 included cyclophosphamide, etoposide and methotrexate; Block 3 included high dose cytosine arabinoside and asparaginase.
Bortezomib was administered at a dose of 1.3 mg/m^2 as a bolus intravenous injection on Days 1, 4, 8 and 11 of block 1 and days 1, 4, and 8 of block 2. There were 140 patients with ALL or LL enrolled and evaluated for safety. The median age was ten years (range 1 to 26), 57% were male, 70% were white, 14% were black, 4% were Asian, 2% were American Indian/ Alaska Native, 1% were Pacific Islander.
The activity was evaluated in a pre-specified subset of the first 60 evaluable patients enrolled on the study with pre-B ALL ≤ 21 years and relapsed < 36 months from diagnosis. The complete remission (CR) rate at day 36 was compared to that in a historical control set of patients who had received the identical backbone therapy without Bortezomib. There was no evidence that the addition of Bortezomib had any impact on the CR rate.
No new safety concerns were observed when bortezomib was added to a chemotherapy backbone regimen as compared with a historical control group in which the backbone regimen was given without Bortezomib.
The BSA-normalized clearance of bortezomib in pediatric patients was similar to that observed in adults.

10.5 Geriatric Use

Of the 669 patients enrolled in the relapsed multiple myeloma study, 245 (37%) were 65 years of age or older: 125 (38%) on the bortezomib arm and 120 (36%) on the dexamethasone arm. Median time to progression and median duration of response for patients ≥ 65 were longer on bortezomib compared to dexamethasone [5.5 mo versus 4.3 mo, and 8.0 mo versus 4.9 mo, respectively]. On the bortezomib arm, 40% (n=46) of evaluable patients aged ≥ 65 experienced response (CR+PR) versus 18% (n=21) on the dexamethasone arm. The incidence of Grade 3 and 4 events was 64%, 78% and 75% for Bortezomib patients ≤ 50, 51-64 and ≤ 65 years old, respectively [see Adverse Reactions (9.1); Clinical Studies (15)].
No overall differences in safety or effectiveness were observed between patients ≥ age 65 and younger patients receiving Bortezomib; but greater sensitivity of some older individuals cannot be ruled out.

10.6 Renal Impairment

No starting dosage adjustment of Bortezomib is recommended for patients with renal impairment. In patients requiring dialysis, Bortezomib should be administered after the dialysis procedure [see Clinical Pharmacology (13.3)].

10.7 Hepatic Impairment

No starting dosage adjustment of Bortezomib is recommended for patients with mild hepatic impairment (total bilirubin ≤ 1x ULN and AST > ULN, or total bilirubin > 1 to 1.5x ULN and any AST). The exposure of bortezomib is increased in patients with moderate (total bilirubin ≥ 1.5 to 3x ULN and any AST) and severe (total bilirubin > 3x ULN and any AST) hepatic impairment. Reduce the starting dose in patients with moderate or severe hepatic impairment [see Dosage and Administration (4.6), Clinical Pharmacology (13.3)].

10.8 Patients with Diabetes

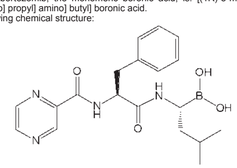
During clinical trials, hypoglycemia and hyperglycemia were reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their anti-diabetic medication.

11. 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 (7.2) and thrombocytopenia (7.7). In the event of an overdosage, the patient's vital signs should be monitored and appropriate supportive care given.
Studies in monkeys and dogs showed that 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 3.0 mg/m^2 and greater (approximately twice the recommended clinical dose) resulted in hypotension starting at one hour post-administration, with progression to death in 12 to 14 hours following drug administration.

12. DESCRIPTION

Bortezomib Teva 3.5 mg powder 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 Teva 3.5 mg 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.
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.

13. CLINICAL PHARMACOLOGY

13.1 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 signalling 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.

13.2 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 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.

13.3 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 (0.80 to 1.23). The C_{max} after subcutaneous administration (20.4 ng/mL) was lower than after intravenous administration (223 ng/mL) with repeat dose administration.
Distribution
The mean distribution volume of bortezomib ranged from approximately 498 to 1884 L/m^2 following single- or repeat-dose administration of 1 mg/m^2 or 1.3 mg/m^2 to patients with multiple myeloma. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100 to 1000 ng/mL.
Elimination
The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours after the 1 mg/m^2 dose and 76 to 108 hours after the 1.3 mg/m^2 dose. The mean total body clearances were 102 and 112 L/h following the first dose for doses of 1 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1 and 1.3 mg/m^2, respectively.
Metabolism
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 to 1.3 mg/m^2, mild (total bilirubin ≤ 1x ULN and AST > ULN, or total bilirubin > 1 to 1.5x ULN and any AST) hepatic 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 hepatic impairment. A lower starting dose is recommended in patients with moderate 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.
Renal Impairment:
A pharmacokinetic study was conducted in patients with various degrees of renal impairment who were classified according to their creatinine clearance values (CrCl) into the following groups: Normal (CrCl ≥ 60 mL/min/1.73 m^2, N=12), Mild (CrCl=40-59 mL/min/1.73 m^2, N=10), Moderate (CrCl=20-39 mL/min/1.73 m^2, N=9), and Severe (CrCl < 20 mL/min/1.73 m^2, N=3). A group of dialysis patients who were dosed after dialysis was also included in the study (N=8). Patients were administered intravenous doses of 0.7 to 1.3 mg/m^2 of bortezomib twice weekly. Exposure of bortezomib (dose-normalized AUC and C_{max}) was comparable among all the groups (see Use in Specific Populations (10.6)).
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.
In vitro studies indicate that bortezomib is a weak inhibitor of the cytochrome P450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6 and 3A4. Based on the limited contribution (7%) of CYP2D6 to the metabolism of bortezomib, the CYP2D6 poor metaboliser phenotype is not expected to affect the overall disposition of bortezomib.
A drug drug interaction study assessing the effect of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC increase of 35% (CI90% [1.032 to 1.772]) based on data from 12 patients. Therefore, patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).
In a drug drug interaction study assessing the effect of omeprazole, a potent CYP2C19 inhibitor, on the pharmacokinetics of bortezomib (injected intravenously), there was no significant effect on the pharmacokinetics of bortezomib based on data from 17 patients.
A drug drug interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC reduction of 45% based on data from 6 patients. Therefore, the concomitant use of bortezomib with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort) is not recommended, as efficacy may be reduced.
In the same drug drug interaction study assessing the effect of dexamethasone, a weaker CYP3A4 inducer, on the pharmacokinetics of bortezomib (injected intravenously), there was no significant effect on the pharmacokinetics of bortezomib based on data from 7 patients.
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.

14. NONCLINICAL TOXICOLOGY

14.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with bortezomib.
Bortezomib showed clastogenic activity (structural chromosomal aberrations) in the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells. Bortezomib was not genotoxic when tested in the *in vitro* mutagenicity assay (Ames test) and *in vivo* micronucleus assay in mice.
Fertility studies with bortezomib were not performed but evaluation of reproductive tissues has been performed in the general toxicity studies. In the 6-month rat toxicity study, degenerative effects in the ovary were observed at doses ≥ 0.3 mg/m^2 (one-fourth of the recommended clinical dose), and degenerative changes in the testes occurred at 1.2 mg/m^2.

14.2 Animal Toxicology and/or Pharmacology

Cardiovascular Toxicity:

Studies in monkeys showed that administration of dosages approximately twice the recommended clinical dose resulted in heart rate elevations, followed by profound progressive hypotension, bradycardia, and death 12 to 14 hours post dose. Doses ≥ 1.2 mg/m^2 induced dose-proportional changes in cardiac parameters. Bortezomib has been shown to distribute to most tissues in the body, including the myocardium. In a repeated dosing toxicity study in the monkey, myocardial hemorrhage, inflammation, and necrosis were also observed.

Chronic Administration:

In animal studies at a dose and schedule similar to that recommended for patients (twice weekly dosing for two weeks followed by one week rest), toxicities observed included severe anemia and thrombocytopenia, and gastrointestinal, neurological and lymphoid system toxicities. Neurotoxic effects of bortezomib in animal studies included axonal swelling and degeneration in peripheral nerves, dorsal spinal roots, and tracts of the spinal cord. Additionally, multifocal hemorrhage and necrosis in the brain, eye, and heart were observed.

15. CLINICAL STUDIES

15.1 Multiple Myeloma

Randomized, Open-Label Clinical Study in Patients with Previously Untreated Multiple Myeloma:
A prospective, international, randomized (1:1), open-label clinical study of 682 patients was conducted to determine whether Bortezomib administered intravenously (1.3 mg/m^2) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) resulted in improvement in time to progression (TTP) when compared to melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in patients with previously untreated multiple myeloma. Treatment was administered for a maximum of nine cycles (approximately 54 weeks) and was discontinued early for disease progression or unacceptable toxicity.
Antiviral prophylaxis was recommended for patients on the Bortezomib study arm.
The median age of the patients in the study was 71 years (48; 91), 50% were male, 88% were Caucasian and the median Karnofsky performance status score for the patients was 80 (60; 100). Patients had IgG/IgA/Light chain myeloma in 63% / 25% / 8% instances, a median hemoglobin of 105 g/L (64; 165), and a median platelet count of 221,500 /microliter (33,000; 587,000).
Efficacy results for the trial are presented in Table 15. At a pre-specified interim analysis (with median follow-up of 16.3 months), the combination of bortezomib, melphalan and prednisone therapy resulted in significantly superior results for time to progression, progression-free survival, overall survival and response rate. Further enrollment was halted, and patients receiving melphalan and prednisone were offered bortezomib in addition. A later, pre-specified analysis of overall survival (with median follow-up of 36.7 months with a hazard ratio of 0.65, 95% CI: 0.51, 0.84) resulted in a statistically significant survival benefit for the bortezomib, melphalan and prednisone 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 for the melphalan and prednisone treatment arm was 43.1 months, with a hazard ratio of 0.695 (95% CI: 0.57, 0.85).

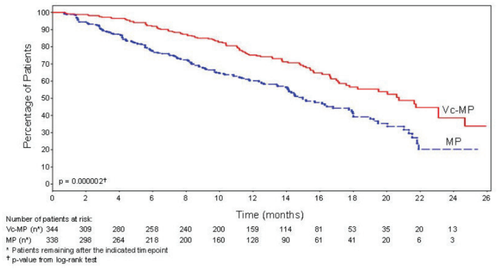
Table 15: Summary of Efficacy Analyses in the Previously Untreated Multiple Myeloma Study

Efficacy Endpoint	Bortezomib, Melphalan and Prednisone (n=344)	Melphalan and Prednisone (n=338)
Time to Progression		
Events n (%)	101 (29)	152 (45)
Median* (months)	20.7	15.0
(95% CI)	(17.6, 24.7)	(14.1, 17.9)
Hazard ratio†	0.54	
(95% CI)	(0.42, 0.70)	
p-value ‡ [c]	0.000002	
Progression-free Survival		
Events n (%)	135 (39)	190 (56)
Median* (months)	18.3	14.0
(95% CI)	(16.6, 21.7)	(11.1, 15.0)
Hazard ratio†	0.61	
(95% CI)	(0.49, 0.76)	
p-value ‡	0.00001	
Response Rate		
CR [§] n(%)	102 (30)	12 (4)
PR [§] n (%)	136 (40)	103 (30)
nCR n (%)	5 (1)	0
CR + PR [§] n (%)	238 (69)	115 (34)
p-value [¶]	< 10^{-10}	
Overall Survival at median follow-up of 36.7 months		
Events (deaths) n (%)	109 (32)	148 (44)
Median* (months)	Not Reached	43.1
(95% CI)	(46.2, NR)	(34.8, NR)
Hazard ratio†	0.65	
(95% CI)	(0.51, 0.84)	
p-value ‡	0.00084	

Note: All results are based on the analysis performed at a median follow-up duration of 16.3 months except for the overall survival analysis
* Kaplan-Meier estimate
† Hazard ratio estimate is based on a Cox proportional-hazard model adjusted for stratification factors: beta$_2$-microglobulin, albumin, and region. A hazard ratio less than 1 indicates an advantage for bortezomib, melphalan and prednisone
‡ p-value based on the stratified log-rank test adjusted for stratification factors: β_2-microglobulin, albumin, and region
§ EBMT criteria
¶ p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors

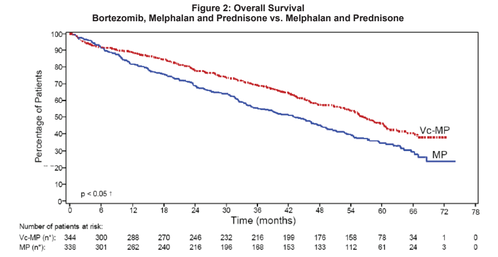
TTP was statistically significantly longer on the bortezomib, melphalan and prednisone arm (see Figure 1) (median follow-up 16.3 months).

Figure 1: Time to Progression
Bortezomib, Melphalan and Prednisone vs. Melphalan and Prednisone



Overall survival was statistically significantly longer on the Bortezomib, Melphalan and Prednisone arm (see Figure 2) (median follow-up 60.1 months).

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-dose dexamethasone were excluded as were those with baseline grade ≥ 2 peripheral neuropathy or platelet counts < 50,000/µL. A total of 627 patients were evaluable for response. Stratification factors were based on the number of lines of prior therapy the patient had previously received (one previous line versus 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 versus relapse > 6 months after receiving their most recent therapy), and screening β_2-microglobulin levels (≤ 2.5 mg/L versus > 2.5 mg/L).
Baseline patient and disease characteristics are summarized in Table 16.

Table 16: 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)	62.0 (33, 84)	61.0 (27, 86)
Gender: male/female	56% / 44%	60% / 40%
Race: Caucasian/black/other	90% / 6% / 4%	88% / 7% / 5%
Karnofsky performance status score ≤ 70	13%	17%
Hemoglobin < 100 g/L	32%	28%
Platelet count < 75 x 10^9/L	6%	4%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	60% / 23% / 12%	59% / 24% / 13%
Median β_2-microglobulin (mg/L)	3.7	3.6
Median albumin (g/L)	39.0	39.0
Creatinine clearance < 30 mL/min [n (%)]	17 (5%)	11 (3%)
Median Duration of Multiple Myeloma Since Diagnosis (Years)	3.5	3.1
Number of Prior Therapeutic Lines of Treatment		
Median	2	2
1 prior line	40%	35%
> 1 prior line	60%	65%
Previous Therapy		
Any prior steroids, e.g., dexamethasone, VAD	98%	99%
Any prior anthracyclines, e.g., VAD, mitoxantrone	77%	76%
Any prior alkylating agents, e.g., MP, VBMCP	91%	92%
Any prior thalidomide therapy	48%	50%
Vinca alkaloids	74%	72%
Prior stem cell transplant/other high-dose therapy	67%	68%
Prior experimental or other types of therapy	3%	2%

Patients in the Bortezomib treatment group were to receive eight 3-week treatment cycles followed by three 5-week treatment cycles of Bortezomib. Patients achieving a CR were treated for 4 cycles beyond first evidence of CR. Within each 3-week treatment cycle, Bortezomib 1.3 mg/m^2/dose alone was administered by intravenous bolus twice weekly for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). Within each 5-week treatment cycle, Bortezomib 1.3 mg/m^2 /dose alone was administered by intravenous bolus once weekly for 4 weeks on Days 1, 8, 15, and 22 followed by a 13-day rest period (Days 23 to 35) (see Dosage and administration (4.4)).
Patients in the dexamethasone treatment group were to receive four 5-week treatment cycles followed by five 4-week treatment cycles. Within each 5-week treatment cycle, dexamethasone 40 mg/day PO was administered once daily on Days 1 to 4, 9 to 12, and 17 to 20 followed by a 15-day rest period (Days 21-35). Within each 4-week treatment cycle, dexamethasone 40 mg/day PO was administered once daily on Days 1 to 4 followed by a 24-day rest period (Days 5 to 28). Patients with documented progressive disease on dexamethasone were offered Bortezomib at a standard dose and schedule on a companion study. Following a preplanned interim analysis of time to progression, the dexamethasone arm was halted and all patients randomized to dexamethasone were offered Bortezomib, regardless of disease status.
In the bortezomib arm, 34% of patients received at least one Bortezomib dose in all 8 of the 3- week cycles of therapy, and 13% received at least one dose in all 11 cycles. The average number of Bortezomib doses during the study was 22, with a range of 1 to 44. In the dexamethasone arm, 40% of patients received at least one dose in all 4 of the 5-week treatment cycles of therapy, and 6% received at least one dose in all 9 cycles.
The time to event analyses and response rates from the relapsed multiple myeloma study are presented in Table 17. Response and progression were assessed using the European Group for Blood and Marrow Transplantation (EBMT) criteria. Complete response (CR) required < 5% plasma cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test (IF-). Partial Response (PR) requires ≥ 50% reduction in serum myeloma protein and ≥ 90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks along with stable bone disease and normal calcium. Near complete response (nCR) was defined as meeting all the criteria for complete response including 100% reduction in M-protein by protein electrophoresis; however, M-protein was still detectable by immunofixation (IF-).

Table 17: 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)	7.0 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)	
p-value ‡	< 0.0001		0.0019		< 0.0001	
Overall Survival						
Events (deaths) n (%)	51 (15)	84 (25)	12 (9)	24 (20)	39 (20)	60 (28)
Hazard ratio † (95% CI)	0.57 (0.40, 0.81)		0.39 (0.19, 0.81)		0.65 (0.43, 0.97)	
p-value ‡ [§]	< 0.05		< 0.05		< 0.05	
Response Rate						
population [¶] n= 627	n=315	n=312	n=128	n=110	n=187	n=202
CR [#] n (%)	20 (6)	2 (< 1)	8 (6)	2 (2)	12 (6)	0 (0)
PR [#] n (%)	101 (32)	54 (17)	49 (38)	27 (25)	52 (28)	27 (13)
nCR[#] * n (%)	21 (7)	3 (< 1)	8 (6)	2 (2)	13 (7)	1 (< 1)
CR + PR [#] n (%)	121 (38)	56 (18)	57 (45)	29 (26)	64 (34)	27 (13)
p-value *	< 0.0001		0.0035		< 0.0001	

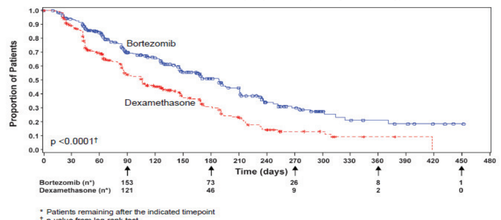
* Kaplan-Meier estimate
† Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable. A hazard ratio less than 1 indicates an advantage for bortezomib.
‡ p-value based on the stratified log-rank test including randomization stratification factors.
§ Precise p-value cannot be rendered
¶ Response population includes patients who had measurable disease at baseline and received at least 1 dose of study drug.
# EBMT criteria; nCR meets all EBMT criteria for CR but has positive IF. Under EBMT criteria nCR is in the PR category.
* In 2 patients, the IF was unknown.
* p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors

TTP was statistically significantly longer on the Bortezomib arm (see Figure 3).

See next page

Bortezomib / Israel / 590x400 mm (36x35 mm folded) / Side B

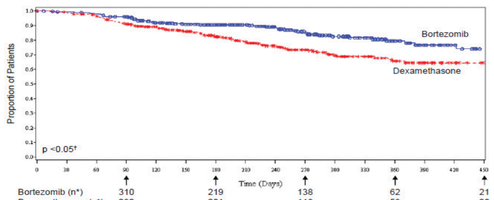
Figure 3: Time to Progression
Bortezomib vs. Dexamethasone (relapsed multiple meyeloma study)



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

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 meyeloma study)



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

For the 121 patients achieving a response (CR or PR) on the Bortezomib arm, the median duration was 8.0 months (95% CI: 6.9, 11.5 months) compared to 5.6 months (95% CI: 4.8, 9.2 months) for the 56 responders on the dexamethasone arm.
The response rate was significantly higher on the bortezomib arm regardless of β_2- microglobulin levels at baseline.

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

An open-label, randomized, phase 3 non-inferiority study (NCT00722566) compared the efficacy and safety of the subcutaneous administration of Bortezomib versus the intravenous administration. This study included 222 Bortezomib-naive patients with relapsed multiple myeloma, who were randomized in a 2:1 ratio to receive 1.3 mg/m^2 of Bortezomib by either the subcutaneous (n=148) or intravenous (n=74) route for eight cycles. Patients who did not obtain an optimal response (less than Complete Response (CR) to therapy with bortezomib alone after 4 cycles were allowed to receive oral dexamethasone 20 mg daily on the day of and after bortezomib administration (82 patients in subcutaneous treatment group and 39 patients in the intravenous treatment group). Patients with baseline Grade ≥ 2 peripheral neuropathy or neuropathic pain, or platelet counts < 50,000/µL were excluded. A total of 218 patients were evaluable for response.
Stratification factors were based on the number of lines of prior therapy the patient had received (one previous line versus more than one line of therapy), and International Staging System (ISS) stage (incorporating β_2-microglobulin and albumin levels; Stages I, II, or III).
The baseline demographic and others characteristics of the two treatment groups are summarized as follows: the median age of the patient population was approximately 64 years of age (range 38 to 88 years), primarily male (subcutaneous: 50%, intravenous: 64%); the primary type of myeloma is IgG (subcutaneous: 65% IgG, 26% IgA, 8% light chain; intravenous: 72% IgG, 19% IgA, 8% light chain), ISS staging I/II/III (%) was 27, 41, 32 for both subcutaneous and intravenous, Karnofsky performance status score was ≤ 70% in 22% of subcutaneous and 16% of intravenous, creatinine clearance was 67.5 mL/min in subcutaneous and 73 mL/min in intravenous, the median years from diagnosis was 2.68 and 2.93 in subcutaneous and intravenous, respectively, and the proportion of patients with more than one prior line of therapy was 38% in subcutaneous and 35% in intravenous.
This study met its primary (non-inferiority) objective that single agent subcutaneous bortezomib retains at least 60% of the overall response rate after four cycles relative to single agent intravenous bortezomib. The results are provided in Table 18.

Table 18: Summary of Efficacy Analyses in the Relapsed Multiple Myeloma Study of Bortezomib Subcutaneous vs. Intravenous

	Subcutaneous bortezomib	Intravenous bortezomib
Intent to Treat Population	(n=148)	(n=74)
Primary Endpoint		
Response Rate at 4 cycles		
ORR (CR + PR) n (%)	63 (43)	31 (42)
Ratio of Response Rates (95% CI)	1.01 (0.73, 1.40)	
CR n (%)	11 (7)	6 (8)
PR n (%)	52 (35)	25 (34)
nCR n (%)	9 (6)	4 (5)
Secondary Endpoints		
Response Rate at 8 Cycles		
ORR (CR + PR)	78 (53)	38 (51)
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	8.0
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 1.0 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 10- 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 1.0 mg/m^2 and 38% (10/26) at 1.3 mg/m^2.

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

Patients from the two phase 2 studies who in the investigators' opinion would experience additional clinical benefit continued to receive 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 7 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 3-week dosing schedule during the extension study. No new cumulative or new long-term toxicities were observed with prolonged Bortezomib treatment (see Adverse Events (8.1)).

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. One hundred and thirty patients (≥ 18 years of age) with multiple 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 administered intravenously. Patients were excluded from trial participation if they had peripheral neuropathy or neuropathic pain of Grade ≥ 2. At least six months after prior Bortezomib therapy, Bortezomib was restarted at the last tolerated dose of 1.3 mg/m^2 (n=93) or ≤ 1 mg/m^2 (n=37) and given on Days 1, 4, 8 and 11 every three weeks for maximum of eight cycles either as single agent or in combination with dexamethasone in accordance with the standard of care.
Dexamethasone was administered in combination with Bortezomib to 83 patients in Cycle 1 with an additional 11 patients receiving dexamethasone during the course of Bortezomib retreatment cycles.
The primary endpoint was best confirmed response to retreatment as assessed by European Group for Blood and Marrow Transplantation (EBMT) criteria. Fifty of the 130 patients achieved a best confirmed response of Partial Response or better for an overall response rate of 38.5% (95% CI: 30.1, 47.4). One patient achieved a Complete Response and 49 achieved Partial Response. In the 50 responding patients, the median duration of response was 6.5 months and the range was 0.6 to 19.3 months.

15.2 Mantle Cell Lymphoma

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

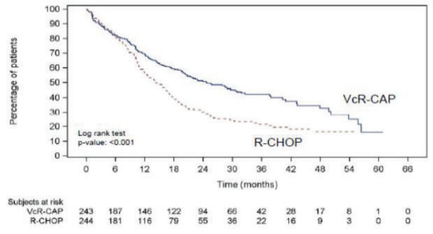
A randomized, open-label, Phase 3 study (NCT00722137) was conducted in 487 adult patients with previously untreated mantle cell lymphoma (Stage II, III or IV) who were ineligible or not considered for bone marrow transplantation to determine whether Bortezomib administered in combination with rituximab, 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. 69% 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 6 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 19. The response criteria used to assess efficacy were based on the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma (IWRC). Final overall survival results at a median follow up of 78.5 months are also presented in Table 19 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 19: 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)	25	14
(95% CI)	(20, 32)	(12, 17)
Hazard ratio †	0.63	
(95% CI)	(0.50, 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)	

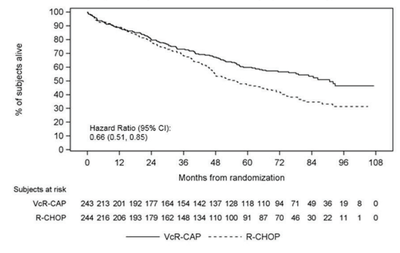
Note: All results are based on the analysis performed at a median follow-up duration of 40 months except for the overall survival analysis, which was performed at a median follow-up of 78.5 months.
˙ Based on Kaplan-Meier product limit estimates.
† Hazard ratio estimate is based on a Cox's model stratified by IPI risk and stage of disease. A hazard ratio < 1 indicates an advantage for VcR-CAP.
‡ Based on log-rank test stratified with IPI risk and stage of disease.
§ 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.
CI=Confidence Interval; IPI= International Prognostic Index; LDH=Lactate Dehydrogenase.

Figure 5: Progression-Free Survival
VcR-CAP versus 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 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 2 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 (4.3,4.4)].
Responses to Bortezomib are shown in Table 20. 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 20: 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)

Clinical efficacy in previously untreated mantle cell lymphoma (MCL)

Study LYM 3002 was a Phase III, randomised, open label study comparing the efficacy and safety of the combination of Bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR CAP; n=243) to that of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R CHOP; n=244) in adult patients with previously untreated MCL (Stage II, III or IV). Patients in the VcR CAP treatment arm received Bortezomib (1.3 mg/m^2; on days 1, 4, 8, 11, rest period days 12 21), rituximab 375 mg/m^2 IV on day 1; cyclophosphamide 750 mg/m^2 IV on day 1; doxorubicin 50 mg/m^2 IV on day 1; and prednisone 100 mg/m^2 orally on day 1 through day 5 of the 21 day Bortezomib treatment cycle. For patients with a response first documented at cycle 6, two additional treatment cycles were given. The primary efficacy endpoint was progression free survival based on Independent Review Committee (IRC) assessment. Secondary endpoints included, time to progression (TTP), time to next anti lymphoma treatment (TNT), duration of treatment free interval (TFI), overall response rate (ORR) and complete response (CR/CRu) rate, overall survival (OS) and response duration.
The demographic and baseline disease characteristics were generally well balanced between the two treatment arms: median patient age was 66 years, 74% were male, 66% were Caucasian and 32% Asian, 69% 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 ≥ 3, and 76% had Stage IV disease. Treatment duration (median=17 weeks) and duration of follow up (median=40 months) were comparable in both treatment arms. A median of 6 cycles was received by patients in both treatment arms with 14% of subjects in the VcR CAP group and 17% of patients in the R CHOP group receiving 2 additional cycles. The majority of the patients in both groups completed treatment, 80% in the VcR CAP group and 82% in the R CHOP group. Efficacy results are presented in Table 21:

Table 21: Efficacy results from study LYM 3002

Efficacy endpoint	**VcR-CAP**	**R-CHOP**	
n: ITT patients	243	244	
Progression free survival (IRC)[a]			
Events n (%)	133 (54.7%)	165 (67.6%)	HR[b] (95% CI)=0.63 (0.50; 0.79) p-value[d] < 0.001
Median[c] (95% CI) (months)	24.7 (19.8; 31.8)	14.4 (12; 16.9)	
Response rate			
n: response-evaluable patients	229	228	
Overall complete response (CR+CRu)[f] n (%)	122 (53.3%)	95 (41.7%)	OR[e] (95% CI)=1.688 (1.148; 2.481) p-value[d]=0.007
Overall response (CR+CRu+PR)[h] n (%)	211 (92.1%)	204 (89.5%)	OR[e] (95% CI)=1.428 (0.749; 2.722) p-value[d]=0.275

a. Based on Independent Review Committee (IRC) assessment (radiological data only).
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 Kaplan-Meier product limit estimates.
d. Based on Log rank test stratified with IPI risk and stage of disease.
e. Mantel-Haenszel estimate of the common odds ratio for stratified tables is used, with IPI risk and stage of disease as stratification factors. An odds ratio (OR) > 1 indicates an advantage for VcR-CAP.
f. Include all CR+CRu, by IRC, bone marrow and LDH.
g. P-value from the Cochran Mantel-Haenszel chi-square test, with IPI and stage of disease as stratification factors.
h. Include all radiological CR+CRu+PR by IRC regardless the verification by bone marrow and LDH.
CR=Complete Response; CRu=Complete Response unconfirmed; PR=Partial Response; CI=Confidence Interval, HR=Hazard Ratio; OR=Odds Ratio; ITT=Intent to Treat

Median PFS by investigator assessment was 30.7 months in the VcR CAP group and 16.1 months in the R CHOP group (Hazard Ratio [HR]=0.51; p < 0.001). A statistically significant benefit (p < 0.001) in favour of the VcR CAP treatment group over the R CHOP group was observed for TTP (median 30.5 versus 16.1 months), TNT (median 44.5 versus 24.8 months) and TFI (median 40.6 versus 20.5 months). The median duration of complete response was 42.1 months in the VcR CAP group compared with 18 months in the R CHOP group. The duration of overall response was 21.4 months longer in the VcR CAP group (median 36.5 months versus 15.1 months in the R CHOP group). The final analysis for OS was performed after a median follow-up of 82 months. Median OS was 90.7 months for the VcR-CAP group compared with 55.7 months for the R-CHOP group (HR=0.66; p=0.001). The observed final median difference in the OS between the 2 treatment groups was 35 months.

16. HOW SUPPLIED/STORAGE AND HANDLING

Type I clear glass 10 ml capacity vial, closed with a grey bromobutyl stopper and grey aluminium cap, with a red flip-off disc containing 3.5 mg bortezomib.
The vials are "sleeved" (provided with a transparent cover) and placed into a carton.
Each pack contains 1 single use vial.

DO NOT ADMINISTER BORTEZOMIB TEVA INTRATHECALLY

Unopened vials:
Store below 25°C.
Keep container in the outer carton in order to protect from light.
Consider handling and disposal of Bortezomib Teva according to guidelines issued for cytotoxic drugs, including the use of gloves and other protective clothing to prevent skin contact.

Reconstituted solution:
Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 25°C (stored in the original vial and/or syringe).
From a microbiological point of view, unless the method of opening/reconstitution precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user.

17. NAME AND ADDRESS OF LICENSE HOLDER AND MANUFACTURER

Teva Israel Ltd.
124 Dvora HaNevi'a St., Tel Aviv 6944020, Israel

18. MARKETING REGISTRATION NUMBER

158.86.34239
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