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Prescribing Information

Bortezomib Teva 1.0 mg Powder for Solution for Injection
Bortezomib Teva 2.5 mg Powder for Solution for Injection
Bortezomib Teva 3.5 mg Powder for Solution for Injection

1. INDICATIONS AND USAGE

1.1 Multiple Myeloma

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

1.2 Mantle Cell Lymphoma

Bortezomib Teva is indicated for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.
Bortezomib Teva 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.

2. DOSAGE AND ADMINISTRATION

General Dosing Guidelines

The recommended starting dose of Bortezomib Teva is 1.3 mg/m². Bortezomib Teva 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 2.10). When administered intravenously, Bortezomib Teva is administered as a 3 to 5 second bolus intravenous injection.
Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered.
Bortezomib Teva 1 mg and 2.5 mg are for intravenous use only.
Bortezomib Teva 3.5 mg is for intravenous or subcutaneous use only.
Bortezomib Teva must not be administered by any other route. Intrathecal administration has resulted in death.

2.1 Dosage in Previously Untreated Multiple Myeloma

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

Table 1 - Dose Regimen for Patients with Previously Untreated Multyple Myeloma

Twice Weekly Bortezomib Teva (Cycles 1-4)

Week	1				2		3	4		5		6
Bortezomib Teva (1.3 mg/m²)	Day 1	--	--	Day 4	Day 8	Day 11	rest period	Day 22	Day 25	Day 29	Day 32	rest period
Melphalan (9 mg/m²) Prednisone (60 mg/m²)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period

Once Weekly Bortezomib Teva (Cycles 5-9 when used in combination with Melphalan and Prednisone)

Week	1				2		3	4		5		6
Bortezomib Teva (1.3 mg/m²)	Day 1	--	--		Day 8		rest period	Day 22		Day 29		rest period
Melphalan (9 mg/m²) Prednisone (60 mg/m²)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period

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

Prior to initiating any cycle of therapy with Bortezomib Teva in combination with melphalan and prednisone:
- Platelet count should be ≥ 70 x 10⁹/L and the absolute neutrophil count (ANC) should be ≥ 1.0 x 10⁹/L
- Non-hematological toxicities should have resolved to Grade 1 or baseline

Table 2 - Dose Modifications During Cycles of Combination Bortezomib Teva, 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 10⁹/L or ANC≤0.75 x 10⁹/L on a Bortezomib Teva dosing day (other than day 1)	Withhold Bortezomib Teva dose
If several Bortezomib Teva doses in consecutive cycles are withheld due to toxicity	Reduce Bortezomib Teva dose by 1 dose level (from 1.3 mg/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²)
Grade ≥ 3 non-hematological toxicities	Withhold Bortezomib Teva therapy until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, Bortezomib Teva may be reinitiated with one dose level reduction (from 1.3 mg/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²). For Bortezomib Teva-related neuropathic pain and/or peripheral neuropathy, hold or modify Bortezomib Teva as outlined in Table 5.

For information concerning melphalan and prednisone, see manufacturer's prescribing information.
For dose modifications guidelines for peripheral neuropathy see Management of peripheral neuropathy section (2.6).

2.3 Posology for patients with previously untreated mantle cell lymphoma (MCL)

Combination therapy with rituximab, cyclophosphamide, doxorubicin and prednisone (VcR-CAP)
Bortezomib Teva powder for solution for injection is administered via intravenous injection at the recommended dose of 1.3 mg/m² 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 Teva cycles are recommended, although for patients with a response first documented at cycle 6, two additional Bortezomib Teva cycles may be given. At least 72 hours should elapse between consecutive doses of Bortezomib Teva.
The following medicinal products are administered on day 1 of each Bortezomib Teva 3-week treatment cycle as intravenous infusions: rituximab at 375 mg/m², cyclophosphamide at 750 mg/m² and doxorubicin at 50 mg/m².
Prednisone is administered orally at 100 mg/m² on days 1, 2, 3, 4 and 5 of each Bortezomib Teva 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 Teva 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 Teva 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 Teva has been held, the toxicity does not resolve, as defined above, then Bortezomib Teva must be discontinued. • If toxicity resolves i.e., patient has an ANC ≥ 750 cells/μL and a platelet count ≥ 25,000 cells/μL, Bortezomib Teva may be reinitiated at a dose reduced by one dose level (from 1.3 mg/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²).
• If platelet counts < 25,000 cells/μL or ANC < 750 cells/μL on a Bortezomib Teva dosing day (other than Day 1 of each cycle)	Bortezomib Teva therapy should be withheld
Grade ≥ 3 non-haematological toxicities considered to be related to Bortezomib Teva	Bortezomib Teva therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, Bortezomib Teva may be reinitiated at a dose reduced by one dose level (from 1.3 mg/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²). For Bortezomib Teva-related neuropathic pain and/or peripheral neuropathy, hold and/or modify Bortezomib Teva as outlined in Table 1.

In addition, when Bortezomib Teva 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.

2.4 Dosage in Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma

Bortezomib Teva (1.3 mg/m²/dose) is administered twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12-21).
For extended therapy of more than 8 cycles, Bortezomib Teva may be administered on the standard schedule or, for relapsed multiple myeloma, on a maintenance schedule of once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35) **[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 Teva.

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

Bortezomib Teva therapy should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematological toxicities excluding neuropathy as discussed below **[see Warnings and Precautions (5)]**. Once the symptoms of the toxicity have resolved, Bortezomib Teva therapy may be reinitiated at a 25% reduced dose (1.3 mg/m²/dose reduced to 1 mg/m²/dose; 1 mg/m²/dose reduced to 0.7 mg/m²/dose).
For dose modifications guidelines for peripheral neuropathy see Management of peripheral neuropathy section (2.6).

2.6 Dose Modifications of Peripheral Neuropathy

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

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

Sterility or 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 Teva to 1 mg/m² OR Change Bortezomib Teva treatment schedule to 1.3 mg/m² once per week
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL***)	Withhold Bortezomib Teva therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of Bortezomib Teva at 0.7 mg/m² once per week.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue Bortezomib Teva

* 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

2.7 Dosage in Patients with Hepatic Impairment

Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended Bortezomib Teva dose. Patients with moderate or severe hepatic impairment should be started on Bortezomib Teva at a reduced dose of 0.7 mg/m² per injection during the first cycle, and a subsequent dose escalation to 1.0 mg/m² or further dose reduction to 0.5 mg/m² may be considered based on patient tolerance (see Table 5).
[See Warnings and Precautions (5.10), Use in Specific Populations (8.6) and Clinical Pharmacology (11.3)].

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

	Bilirubin Level	SGOT (AST) Levels	Modification of Starting dose
Mild	≤ 1.0x ULN	> ULN	None
	> 1.0x-1.5x ULN	Any	None
Moderate	> 1.5x-3x ULN	Any	Reduce Bortezomib Teva to 0.7 mg/m² in the first cycle. Consider dose escalation to 1.0 mg/m² or further dose reduction to 0.5 mg/m² in subsequent cycles based on patient tolerability.
Severe	> 3x ULN	Any	

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

2.8 Administration Precautions

The drug quantity contained in one vial of Bortezomib Teva 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 2.9).
Bortezomib Teva 1 mg and Bortezomib Teva 2.5 mg:
Are authorized for intravenous use only.
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 Teva 3.5 mg administration subcutaneously, a less concentrated Bortezomib Teva solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously [see reconstitution/preparation for intravenous and subcutaneous administration section 2.9) 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 2.9]**.
Bortezomib Teva is an antineoplastic. Procedures for proper handling and disposal should be considered. **[See How Supplied/Storage and Handling (14)].**

2.9 Reconstitution/Preparation for Intravenous and Subcutaneous Administration

Proper aseptic technique should be used. Reconstitute **only with 0.9% sodium chloride**. The reconstituted product should be a clear and colorless solution.
Bortezomib Teva 1 mg and Bortezomib Teva 2.5 mg powder for solution for injection is for intravenous use only, while Bortezomib Teva 3.5 mg powder for solution for injection is for intravenous or subcutaneous use. Bortezomib Teva should not be administered intrathecally.
Instructions for reconstitution for intravenous injection only:
Bortezomib Teva 1 mg:
Each vial of Bortezomib Teva 1 mg must be reconstituted with 1 mL of sodium chloride 9 mg/ml (0.9%) solution for injection, by using appropriate syringe, without stopper removal. Dissolution of the lyophilized powder is completed in less than 2 minutes.
After reconstitution, each ml solution contains 1 mg bortezomib. The reconstituted solution is clear and colorless, with a final pH of 4 to 7.
The reconstituted solution must be inspected visually for particulate matter and discoloration prior to administration. If any discoloration or particulate matter is observed, the reconstituted solution must be discarded.
Bortezomib Teva 2.5 mg:
Each vial of Bortezomib Teva 2.5 mg must be reconstituted with 2.5 mL of sodium chloride 9 mg/ml (0.9%) solution for injection, by using appropriate syringe, without stopper removal. Dissolution of the lyophilized powder is completed in less than 2 minutes.
After reconstitution, each ml solution contains 1 mg bortezomib. The reconstituted solution is clear and colorless, with a final pH of 4 to 7.
The reconstituted solution must be inspected visually for particulate matter and discoloration prior to administration. If any discoloration or particulate matter is observed, the reconstituted solution must be discarded.
Instructions for reconstitution for intravenous or subcutaneous injection:
Bortezomib Teva 3.5 mg:
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, caution should be used when calculating the volume to be administered (see Administration Precautions section 2.8).

For each 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

The reconstituted solution is clear and colorless, with a final pH of 4 to 7.
The reconstituted solution must be inspected visually for particulate matter and discoloration prior to administration. If any discoloration or particulate matter is observed, the reconstituted solution must be discarded.
Dose must be individualized to prevent overdose. 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]**

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

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

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

Stability: Unopened vials of Bortezomib Teva are stable until the date indicated on the package when stored in the original package protected from light.
Store below 25°C.
Bortezomib Teva contains no antimicrobial preservative.
The reconstituted solution should be used immediately after preparation. If the reconstituted solution is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. However, the chemical and physical in-use stability of the reconstituted solution has been demonstrated for 8 hours at 25°C stored in the original vial and/or a syringe prior to administration, the total storage time for the reconstituted medicinal product should not exceed 8 hours prior to administration.

3. DOSAGE FORMS AND STRENGTHS

Each single-use vial of Bortezomib Teva 1 mg contains 1 mg of bortezomib as a sterile lyophilized white to off-white powder.
Each single-use vial of Bortezomib Teva 2.5 mg contains 2.5 mg of bortezomib as a sterile lyophilized white to off-white powder.
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.

4. CONTRAINDICATIONS

Bortezomib Teva is contraindicated in patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol. Reactions have included anaphylactic reactions **[see adverse events (6)]**.
Bortezomib Teva is contraindicated in acute diffuse infiltrative pulmonary and pericardial disease. When Bortezomib Teva is given in combination with other medicinal products, refer to their Physician insert for additional contraindications.
Bortezomib Teva is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of Bortezomib Teva. **DO NOT ADMINISTER BORTEZOMIB TEVA INTRATHECALLY.**

5. WARNINGS AND PRECAUTIONS

Bortezomib Teva should be administered under the supervision of a physician experienced in the use of antineoplastic therapy. Complete blood counts (CBC) should be monitored frequently during treatment with Bortezomib Teva.
There have been fatal cases of inadvertent intrathecal administration of bortezomib.
Bortezomib Teva is authorized for IV or subcutaneous use only.
DO NOT ADMINISTER BORTEZOMIB TEVA INTRATHECALLY.

5.1 Peripheral Neuropathy

Bortezomib treatment causes a peripheral neuropathy that is predominantly sensory. However, cases of severe sensory and motor peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral neuropathy (including ≥Grade 3) during treatment with Bortezomib. 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 events 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 Teva therapy may require a decrease in the dose and/or a less dose-intense schedule **[see Dosage and Administration (2)]**.
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 **[see Adverse Events (6)]**. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

5.2 Hypotension

The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 8%. These events are observed throughout therapy. Caution should be used when treating patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetics. **[See Adverse Events (6)]**.

5.3 Cardiac Toxicity

Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have occurred during Bortezomib therapy, including reports in patients with no risk factors for decreased left ventricular ejection fraction. Fluid retention may be a predisposing factor for signs and symptoms of heart failure. Patients with risk factors for, or existing heart disease should be closely 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 events suggestive of heart failure (acute pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock, pulmonary edema) was ≤ 1% for each individual event in the Bortezomib group. In the dexamethasone group the incidence was ≤ 1% for cardiac failure and congestive cardiac failure; there were no reported events of acute pulmonary edema, pulmonary edema, or cardiogenic shock. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.

5.4 Pulmonary Toxicity

There have been reports of acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration, lung and Acute Respiratory Distress Syndrome (ARDS) in patients receiving Bortezomib. Some of these events have been fatal. A pre-treatment chest radiograph is recommended to serve as a baseline for potential post-treatment pulmonary changes.
In a clinical trial, the first two patients given high-dose cytarabine (2 g/m² per day) by continuous infusion with daunorubicin and Bortezomib for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy, and the study was terminated. Therefore, this specific regimen with concomitant administration with high-dose cytarabine (2 g/m² per day) by continuous infusion over 24 hours is not recommended.
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 Teva until a prompt and comprehensive diagnostic evaluation is conducted.

5.5 Posterior Reversible Encephalopathy Syndrome (PRES)

Posterior Reversible Encephalopathy Syndrome (PRES; formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS)) has occurred in patients receiving Bortezomib. PRES is a rare, reversible, neurological disorder which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably MRI (Magnetic Resonance Imaging), is used to confirm the diagnosis. In patients developing PRES, discontinue Bortezomib Teva. The safety of reinitiating Bortezomib therapy in patients previously experiencing PRES is not known.

5.6 Gastrointestinal Toxicity

Bortezomib Teva treatment can cause nausea, diarrhea, constipation, and vomiting **[see Adverse Events (6)]** sometimes requiring use of antiemetic and antidiarrheal medications. Ileus can occur. Fluid and electrolyte replacement should be administered to prevent dehydration.
Interrupt Bortezomib Teva for severe symptoms.

5.7 Thrombocytopenia/Neutropenia

Bortezomib is associated with thrombocytopenia and neutropenia that follow a cyclical pattern with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of the subsequent cycle. The cyclical pattern of platelet and neutrophil decreases and recovery remain consistent in the studies of multiple myeloma and mantle cell lymphoma, with no evidence of cumulative thrombocytopenia or neutropenia in the treatment regimens studied.
Monitor complete blood counts (CBC) frequently during treatment with Bortezomib. Measure platelet counts prior to each dose of Bortezomib Teva. Adjust dose/schedule for thrombocytopenia **[see Tables 2 and 3 and Dosage and Administration (2.5)]**. 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 11. The incidence of bleeding events (≥ Grade 3) was 1% in the VcR-CAP arm (3 patients) and was < 1% in the R-CHOP arm (1 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.

5.8 Tumor Lysis Syndrome

Because Bortezomib Teva is a cytotoxic agent and can rapidly kill malignant plasma cells and MCL cells, the complications of tumor lysis syndrome may occur. Tumor lysis syndrome has been reported with Bortezomib therapy. Patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor patients closely and take appropriate precautions.

5.9 Hepatic Toxicity

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

5.10 Hepatic Impairment

Bortezomib is metabolized by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with Bortezomib Teva at reduced starting doses and closely monitored for toxicities. **[See Dosage and Administration (2.7), Use in Specific Populations (8.6) and Clinical Pharmacology (11.3)].**

5.11 Embryo-fetal Risk

Women of reproductive potential should avoid becoming pregnant while being treated with Bortezomib. Bortezomib administered to rabbits during organogenesis at a dose approximately 0.5 times the clinical dose of 1.3 mg/m² based on body surface area caused post-implantation loss and a decreased number of live fetuses **[see Use in Specific Populations (8.1)].**

5.12 Herpes zoster virus reactivation

Antiviral prophylaxis should be considered in patients being treated with Bortezomib Teva.
In the Phase 3 study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in patients treated with Bortezomib+Melphalan+Prednisone compared with Melphalan+Prednisone (14% versus 4% respectively).
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.

5.13 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 Teva if PML is diagnosed.

5.14 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.

5.15 Renal impairment

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

5.16 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.

5.17 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.

5.18 Hepatitis B Virus (HBV) reactivation and infection

When rituximab is used in combination with Bortezomib Teva, 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 Teva. Antiviral prophylaxis should be considered. Refer to the Summary of Product Characteristics of rituximab for more information.

6. ADVERSE EVENTS

The following adverse events are also discussed in other sections of the labeling:
- Peripheral Neuropathy **[see Warnings and Precautions (5.1); Dosage and Administration (2.6) (Table 4)]**
- Hypotension **[see Warnings and Precautions (5.2)]**
- Cardiac Toxicity **[see Warnings and Precautions (5.3)]**
- Pulmonary Toxicity **[see Warnings and Precautions (5.4)]**
- Posterior Reversible Encephalopathy Syndrome (PRES) **[see Warnings and Precautions (5.5)]**
- Gastrointestinal Toxicity **[see Warnings and Precautions (5.6)]**
- Thrombocytopenia/Neutropenia **[see Warnings and Precautions (5.7)]**
- Tumor Lysis Syndrome **[see Warnings and Precautions (5.8)]**
- Hepatic Toxicity **[see Warnings and Precautions (5.9)]**

6.1 Clinical Trials Safety Experience

Because clinical trials are conducted under widely varying conditions, adverse events 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/m²) administered intravenously in combination with melphalan (9 mg/m²) and prednisone (60 mg/m²) 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 Events (>10% in Bortezomib IV, Melphalan and Prednisone arm) with Grades 3 and ≥ 4 Intensity in the Previously Untreated Multiple Myeloma Study

	Bortezomib, Melphalan and Prednisone			Melphalan and Prednisone		
System Organ Class Preferred Term	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
Diarrhoea	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 [a]	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

[a] Represents High Level Term Peripheral Neuropathies NEC

Relapsed Multiple Myeloma Randomized Study of Bortezomib vs. Dexamethasone
The safety data described below and in Table 10 reflect exposure to either Bortezomib (n=331) or dexamethasone (n=332) in a study of patients with multiple myeloma. Bortezomib was administered intravenously at doses of 1.3 mg/m² twice weekly for 2 out of 3 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 (9 months) with a median duration of 6 cycles (4.1 months). For inclusion in

Hypotension
The incidence of hypotension (postural hypotension, orthostatic hypotension 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 an SAE, 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 event.
Neutropenia
Neutrophil counts decreased during the Bortezomib dosing period (days 1 to 11) and returned toward baseline during the 10-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 event 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 event for 21% of patients. The event was Grade 3 in 1% and ≥ Grade 4 in <1%. Pyrexia was reported as a serious adverse event 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 Teva. In the randomized studies in previously untreated and relapsed multiple myeloma, herpes zoster reactivation was more common in subjects treated with Bortezomib (ranging between 6-11%) than in the control groups (3-4%). Herpes simplex was seen in 1-3% in subjects treated with Bortezomib and 1-3% 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%).
Additional Serious Adverse Events from Clinical Studies
The following clinically important SAEs that are not described above have been reported in clinical trials in patients treated with Bortezomib administered as monotherapy or in combination with other chemotherapeutics. These studies were conducted in patients with hematological malignancies and in solid tumors.
Blood and lymphatic system disorders: Anemia, disseminated intravascular coagulation, febrile neutropenia, lymphopenia, leukopenia.
Cardiac disorders: Angina pectoris, atrial fibrillation aggravated, atrial flutter, bradycardia, sinus arrest, cardiac amyloidosis, complete atrioventricular block, myocardial ischemia, myocardial infarction, pericarditis, pericardial effusion, Torsades de pointes, ventricular tachycardia.
Ear and labyrinth disorders: Hearing impaired, vertigo.
Eye disorders: Diplopia and blurred vision, conjunctival infection, irritation.
Gastrointestinal disorders: Abdominal pain, ascites, dysphagia, fecal impaction, gastroenteritis, gastritis hemorrhagic, hematemesis, hemorrhagic duodenitis, ileus paralytic, large intestinal obstruction, paralytic intestinal obstruction, peritonitis, small intestinal obstruction, large intestinal perforation, stomatitis, melena, pancreatitis acute, oral mucosal petechiae, gastroesophageal reflux.
General disorders and administration site conditions: Chills, edema, edema peripheral, injection site erythema, neuralgia, injection site pain, irritation, malaise, phlebitis.
Hepatobiliary disorders: Cholestasis, hepatic hemorrhage, hyperbilirubinemia, portal vein thrombosis, hepatitis, liver failure.
Immune system disorders: Anaphylactic reaction, drug hypersensitivity, immune complex mediated hypersensitivity, angioedema, laryngeal edema.
Infections and infestations: Aspergillosis, bacteremia, bronchitis, urinary tract infection, herpes viral infection, listeriosis, nasopharyngitis, pneumonia, respiratory tract infection, septic shock, toxoplasmosis, oral candidiasis, sinusitis, catheter related infection.
Injury, poisoning and procedural complications: Catheter related complication, skeletal fracture, subdural hematoma.
Investigations: Weight decreased.
Metabolism and nutrition disorders: Dehydration, hypocalcemia, hyperuricemia, hypokalemia, hyperkalemia, hyponatremia, hypernatremia.
Musculoskeletal and connective tissue disorders: Arthralgia, back pain, bone pain, myalgia, pain in extremity.
Nervous system disorders: Ataxia, coma, dizziness, dysarthria, dysesthesia, dysautonomia, encephalopathy, cranial palsy, grand mal convulsion, headache, hemorrhagic stroke, motor dysfunction, neuralgia, spinal cord compression, paralysis, postherpetic neuralgia, transient ischemic attack.
Psychiatric disorders: Agitation, anxiety, confusion, insomnia, mental status change, psychotic disorder, suicidal ideation.
Renal and urinary disorders: Calculus renal, bilateral hydronephrosis, bladder spasm, hematuria, hemorrhagic cystitis, urinary incontinence, urinary retention, renal failure (acute and chronic), glomerular nephritis proliferative.
Respiratory, thoracic and mediastinal disorders: Acute respiratory distress syndrome, aspiration pneumonia, atelectasis, chronic obstructive airways disease exacerbated, cough, dysphagia, dyspnea, dyspnea exertional, epistaxis, hemoptysis, hypoxia, lung infiltration, pleural effusion, pneumonitis, respiratory distress, pulmonary hypertension.
Skin and subcutaneous tissue disorders: Urticaria, face edema, rash (which may be pruritic), leukocytoclastic vasculitis, pruritus.
Vascular disorders: Cerebrovascular accident, cerebral hemorrhage, deep venous thrombosis, hypertension, peripheral embolism, pulmonary embolism, pulmonary hypertension.

6.2 Post-marketing Experience
The following adverse drug events have been identified from the worldwide post-marketing experience with Bortezomib. Because these events 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: atrioventricular block complete, cardiac tamponade, ischemic colitis, encephalopathy, dysautonomia, deafness bilateral, disseminated intravascular coagulation, hepatitis, acute pancreatitis, progressive multifocal leukoencephalopathy (PML), acute diffuse infiltrative pulmonary disease, PRES (formerly RPLS), toxic epidermal necrolysis, acute febrile neutrophilic dermatosis (Sweet's syndrome), herpes meningoencephalitis, optic neuropathy, blindness and ophthalmic herpes, Stevens-Johnson Syndrome, septic shock, Angioedema, Anaphylactic reaction, autonomic neuropathy, decubitus ulcer, intestinal obstruction.

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:
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

7. DRUG INTERACTIONS
Bortezomib is a substrate of cytochrome P450 enzyme 3A4, 2C19 and 1A2.

7.1 CYP3A4 inhibitors
Co-administration of ketoconazole, a strong CYP3A4 inhibitor, increased the exposure of bortezomib by 35% in 12 patients. Monitor patients for signs of bortezomib toxicity and consider a bortezomib dose reduction if bortezomib must be given in combination with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir).

7.2 CYP2C19 inhibitors
Co-administration of omeprazole, a strong inhibitor of CYP2C19, had no effect on the exposure of bortezomib in 17 patients.

7.3 CYP3A4 inducers
Co-administration of rifampin, a strong CYP3A4 inducer, is expected to decrease the exposure of bortezomib by at least 45%. Because the drug interaction study (n=6) was not designed to exert the maximum effect of rifampin on bortezomib PK, decreases greater than 45% may occur. Efficacy may be reduced when Bortezomib is used in combination with strong CYP3A4 inducers; therefore, concomitant use of strong CYP3A4 inducers is not recommended in patients receiving Bortezomib Teva (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital).
St. John's Wort *(Hypericum perforatum)* may decrease bortezomib exposure unpredictably and should be avoided.

7.4 Dexamethasone: Co-administration of dexamethasone, a weak CYP3A4 inducer, had no effect on the exposure of bortezomib in 7 patients.

7.5 5-Melphalan-Prednisone: Co-administration of melphalan-prednisone increased the exposure of bortezomib by 17% in 21 patients. However, this increase is unlikely to be clinically relevant.
During clinical trials, hypoglycemia and hyperglycemia were uncommonly and commonly reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving Bortezomib Teva treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category D **[see Warnings and Precautions (5.11)]**.
Risk Summary
Bortezomib Teva may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If Bortezomib Teva is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Bortezomib caused embryo-fetal lethality in rabbits at doses lower than the clinical dose.
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 half the clinical dose of 1.3 mg/m^2 based on body surface area.
Pregnant rabbits given bortezomib during organogenesis at a dose of 0.05 mg/kg (0.6 mg/m^2) experienced significant post-implantation loss and decreased number of live fetuses. Live fetuses from these litters also showed significant decreases in fetal weight. The dose is approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area.

8.2 Nursing Mothers
It is not known whether bortezomib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse events in nursing infants from Bortezomib Teva, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.3 Pediatric Use
The effectiveness of Bortezomib Teva in pediatric patients with relapsed pre-B acute lymphoblastic leukemia (ALL) has not been established.
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 3 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 10 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.

8.4 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 Events (6.1); Clinical Studies (13)]**.
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.

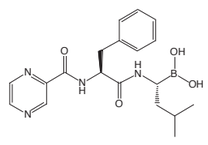
8.5 Patients with Renal Impairment
The pharmacokinetics of Bortezomib are not influenced by the degree of renal impairment. Therefore, dosing adjustments of Bortezomib Teva are not necessary for patients with renal insufficiency. Since dialysis may reduce Bortezomib concentrations, Bortezomib Teva should be administered after the dialysis procedure **[see Clinical Pharmacology (12.3)]**.

8.6 Patients with Hepatic Impairment
The exposure of bortezomib is increased in patients with moderate (bilirubin > 1.5 - 3x ULN) and severe (bilirubin > 3 x ULN) hepatic impairment. Starting dose should be reduced in those patients. **[See Dosage and Administration (2.7), Warnings and Precautions (5.10), and Pharmacokinetics (12.3)]**.

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

9. OVERDOSAGE
There is no known specific antidote for Bortezomib overdosage. In humans, fatal outcomes following the administration of more than twice the recommended therapeutic dose have been reported, which were associated with the acute onset of symptomatic hypotension (5.2) and thrombocytopenia (5.7). In the event of an overdosage, the patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or inotropic agents) and body temperature.
Studies in monkeys and dogs showed that intravenous bortezomib as low as 2 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 1 hour post-administration, with progression to death in 12 to 14 hours following drug administration.

10. DESCRIPTION
Bortezomib Teva powder for solution for injection 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 1.0 mg is available for intravenous injection use only. Each single-use vial contains 1.0 mg of bortezomib as a sterile lyophilized powder. It also contains the inactive ingredient: 10 mg mannitol, Ph.Eur.
Bortezomib Teva 2.5 mg is available for intravenous injection only. Each single-use vial contains 2.5 mg of bortezomib as a sterile lyophilized powder. It also contains the inactive ingredient: 25 mg mannitol, Ph.Eur.
Bortezomib Teva 3.5 mg is available for intravenous injection or subcutaneous use. Each single-use vial contains 3.5 mg of bortezomib as a sterile lyophilized powder. It also contains the inactive ingredient: 35 mg mannitol, Ph.Eur.
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.

11. CLINICAL PHARMACOLOGY

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

11.2 Pharmacodynamics
Following twice weekly administration of 1 mg/m^2 and 1.3 mg/m^2 bortezomib doses (n=12 per each dose level), the maximum inhibition of 20S proteasome activity (relative to baseline) in whole blood was observed 5 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.

11.3 Pharmacokinetics
Following intravenous administration of 1 mg/m^2 and 1.3 mg/m^2 doses to 24 patients with multiple myeloma (n=12, per each dose level), the mean maximum plasma concentrations of bortezomib (C_{max}) after the first dose (Day 1) were 57 and 112 ng/mL, respectively. In subsequent doses, 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. 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 was 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.
Following an intravenous bolus or subcutaneous injection of a 1.3 mg/m^2 dose to patients (n=14 for intravenous, n=17 for subcutaneous) with multiple myeloma, the total systemic exposure after repeat dose administration (AUC_{last}) was equivalent for subcutaneous and intravenous administration. The C_{max} after subcutaneous administration (20.4 ng/mL) was lower than intravenous (223 ng/mL). The AUC_{last} geometric mean ratio was 0.99 and 90% confidence intervals were 80.18% - 122.80%.
Distribution: The mean distribution volume of bortezomib ranged from 1659 liters to 3294 liters (498 to 1884 L/m^2) following single- or repeat-dose IV administration of 1.0 mg/m^2 or 1.3 mg/m^2 to patients with multiple myeloma. This suggests bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100 to 1000 ng/mL.
Metabolism: In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes 3A4, 2C19, and 1A2. Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor. The major metabolic pathway is deboronation to form 2 deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent drug.
Elimination:
The pathways of elimination of bortezomib have not been characterized in humans.
Age: Analyses of data after the first dose of Cycle 1 (Day 1) in 39 multiple myeloma patients who had received intravenous doses of 1 mg/m^2 and 1.3 mg/m^2 showed that both dose-normalized AUC and C_{max} tend to be less in younger patients. Patients < 65 years of age (n=26) had about 25% lower mean dose-normalized AUC and C_{max} than those ≥ 65 years of age (n=13).
Gender: Mean dose-normalized AUC and C_{max} values were comparable between male (n=22) and female (n=17) patients after the first dose of Cycle 1 for the 1 and 1.3 mg/m^2 doses.
Race: The effect of race on exposure to bortezomib could not be assessed as most of the patients were Caucasian.
Hepatic Impairment:
The effect of hepatic impairment (see Table 5 for definition of hepatic impairment) on the pharmacokinetics of IV bortezomib was assessed in 60 patients with cancer at bortezomib doses ranging from 0.5 to 1.3 mg/m^2. When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-normalized bortezomib AUC. However, the dose-normalized mean AUC values were increased by approximately 60% in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients should be monitored closely **[see Dosage and Administration (2.7), Warnings and Precautions (5.10) and Use in Specific Populations (8.6)]**.
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 (8.5)]**.
Pediatric:
See use in specific population 8.3.
Cytochrome P450: Bortezomib is a poor inhibitor of human liver microsome cytochrome P450 1A2, 2C9, 2D6, and 3A4, with IC50 values of >30pM (>11.5 pg/mL). Bortezomib may inhibit 2C19 activity (IC_{50} = 18 pM, 6.9 pg/mL) and increase exposure to drugs that are substrates for this enzyme. Bortezomib did not induce the activities of cytochrome P450 3A4 and 1A2 in primary cultured human hepatocytes.

12. NONCLINICAL TOXICOLOGY

12.1 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. Bortezomib could have a potential effect on either male or female fertility.

12.2 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 2 weeks followed by 1-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.

13. CLINICAL STUDIES

13.1 Multiple Myeloma
Randomized, Open-Label Clinical Study in Patients with Previously Untreated Multiple Myeloma:
A prospective Phase 3, international, randomized (1:1), open-label clinical study of 682 patients was conducted to determine whether 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 9 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 13. 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).

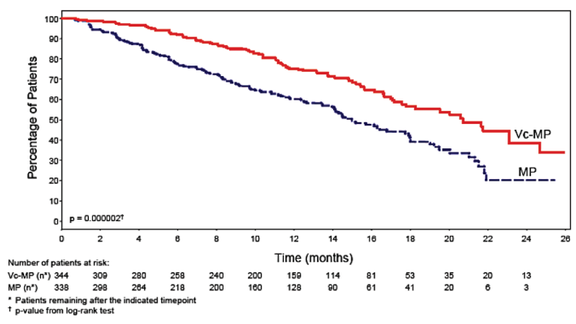
Table 13: Summary of Efficacy Analyses in the Previously Untreated Multiple Myeloma Study

Efficacy Endpoint	Bortezomib, Melphalan and Prednisone n=344	Melphalan and Prednisone n=338
Time to Progression		
Events n (%)	101 (29)	152 (45)
Median [a] (months)	20.7	15.0
(95% CI)	(17.6, 24.7)	(14.1, 17.9)
Hazard ratio [b]	0.54	
(95% CI)	(0.42, 0.70)	
p-value [c]	0.000002	
Progression-free Survival		
Events n (%)	135 (39)	190 (56)
Median [a] (months)	18.3	14.0
(95% CI)	(16.6, 21.7)	(11.1, 15.0)
Hazard ratio [b]	0.61	
(95% CI)	(0.49, 0.76)	
p-value c	0.00001	
Response Rate		
CR [d] n (%)	102 (30)	12 (4)
PR [d] n (%)	136 (40)	103 (30)
nCR n (%)	5 (1)	0
CR + PR [d] n (%)	238 (69)	115 (34)
p-value [e]	<10-10	
Overall Survival at median follow-up of 36.7 months		
Events (deaths) n (%)	109 (32)	148 (44)
Median [a] (months)	Not Reached	43.1
(95% CI)	(46.2, NR)	(34.8, NR)
Hazard ratio [b]	0.65	
(95% CI)	(0.51, 0.84)	
p-value [c]	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 that was performed at a median follow-up duration of 60.1 months.
[a] Kaplan-Meier estimate
[b] Hazard ratio estimate is based on a Cox proportional-hazard model adjusted for stratification factors: β_2-microglobulin, albumin, and region. A hazard ratio less than 1 indicates an advantage for bortezomib, melphalan and prednisone
[c] p-value based on the stratified log-rank test adjusted for stratification factors: β_2-microglobulin, albumin, and region
[d] EBMT criteria
[e] p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors
NE: Not estimable

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

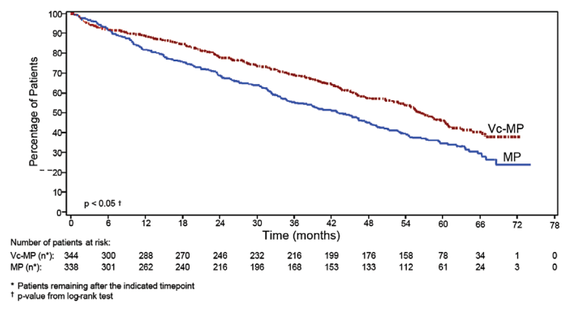
Figure 1: Time to Progression
Bortezomib, Melphalan and Prednisone versus Melphalan and Prednisone



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

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 versus Melphalan and Prednisone



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

Randomized, Clinical Study in Relapsed Multiple Myeloma of Bortezomib vs. Dexamethasone
A prospective Phase 3, international, randomized (1:1), stratified, open-label clinical study 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 (1 previous line versus more than 1 line of therapy), time of progression relative to prior treatment (progression during or within 6 months of stopping their most recent therapy versus relapse >6 months after receiving their most recent therapy), and screening β_2-microglobulin levels (≤2.5 mg/L versus >2.5 mg/L).
Baseline patient and disease characteristics are summarized in Table 14.

Table 14: 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 IV bolus twice weekly for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). Within each 5-week treatment cycle, Bortezomib 1.3 mg/m^2 /dose alone was administered by IV bolus once weekly for 4 weeks on Days 1, 8, 15, and 22 followed by a 13-day rest period (Days 23 to 35) **[see Dosage and administration (2.1)]**.
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 15**. 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[e]).

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

	All Patients		1 Prior Line of Therapy		> 1 Prior Line of Therapy	
	Bortezomib	Dex	Bortezomib	Dex	Bortezomib	Dex
Efficacy Endpoint	n=333	n=336	n=132	n=119	n=200	n=217
Time to Progression Events n (%)	147 (44)	196 (58)	55 (42)	64 (54)	92 (46)	132 (61)
Median [a] (95% CI)	6.2 mo (4.9, 6.9)	3.5 mo (2.9, 4.2)	7.0 mo (6.2, 8.8)	5.6 mo (3.4, 6.3)	4.9 mo (4.2, 6.