Prescribing Information

BORTEZOMIB S.K. 3.5mg

Powder for Solution for Injection
Each vial contains 3.5 mg bortezomib (as a mannitol boronic ester).

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma
BORTEZOMIB S.K. is indicated for the treatment of patients with multiple myeloma.

1.2 Mantle Cell Lymphoma
BORTEZOMIB S.K. is indicated for the treatment of patients with mantle cell Lymphoma who have received at least one prior therapy. -

BORTEZOMIB S.K. 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 S.K. is 1.3mg/m^2. BORTEZOMIB S.K. may be administered intravenously at a concentration of 1mg/ml, or subcutaneously at a concentration of 2.5 mg/ml (see reconstitution /preparation for intravenous and subcutaneous administration section 2.9). When administered intravenously, BORTEZOMIB S.K. 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 S.K. IS FOR INTRAVENOUS OR SUBCUTANEOUS USE ONLY.
BORTEZOMIB S.K. must not be administered by any other route. Intrathecal administration has resulted in death.

2.1 Dosage in Previously Untreated Multiple Myeloma
BORTEZOMIB S.K. (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 S.K. is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, BORTEZOMIB S.K. is administered once weekly (days 1, 8, 22 and 29).
At least 72 hours should elapse between consecutive doses of BORTEZOMIB S.K.

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

Twice Weekly BORTEZOMIB S.K. (Cycles 1-4)

Week	**1**				**2**		**3**	**4**		**5**		**6**
BORTEZOMIB S.K. (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 S.K. (Cycles 5-9 when used in combination with Melphalan and Prednisone)

Week	**1**				**2**		**3**	**4**		**5**		**6**
BORTEZOMIB S.K. (1.3 mg/m^2)	Day 1	--	--		Day 8		rest period	Day 22		Day 29		rest period
Melphalan (9 mg/m^2) Prednisone (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period

2.2 Dose Modification Guidelines for Combination Therapy with BORTEZOMIB S.K., Melphalan and Prednisone

Prior to initiating any cycle of therapy with BORTEZOMIB S.K. 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 S.K., 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 $\leq$30 x 10^9/L or ANC$\leq$ 0.75 x 10^9/L on a BORTEZOMIB S.K. dosing day (other than day 1)	Withhold Bortezomib S.K. dose
If several BORTEZOMIB S.K. doses in consecutive cycles are withheld due to toxicity	Reduce BORTEZOMIB S.K. 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 $\geq$3 non-hematological toxicities	Withhold BORTEZOMIB S.K. therapy until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, BORTEZOMIB S.K. 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 S.K.-related neuropathic pain and/or peripheral neuropathy, hold or modify BORTEZOMIB S.K. 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 S.K. 3.5mg 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 S.K. cycles are recommended, although for patients with a response first documented at cycle 6, two additional BORTEZOMIB S.K. cycles may be given. At least 72 hours should elapse between consecutive doses of BORTEZOMIB S.K.

The following medicinal products are administered on day 1 of each BORTEZOMIB S.K. 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 S.K. 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 S.K. treatment must be withheld at the onset of any ≥ Grade 3 BORTEZOMIB S.K.-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 S.K. 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 S.K. has been held, the toxicity does not resolve, as defined above, then BORTEZOMIB S.K. must be discontinued. • If toxicity resolves i.e. patient has an ANC ≥ 750 cells/µL and a platelet count ≥ 25,000 cells/µL, BORTEZOMIB S.K. 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 S.K. dosing day (other than Day 1 of each cycle)	BORTEZOMIB S.K. therapy should be withheld
Grade ≥ 3 non-haematological toxicities considered to be related to BORTEZOMIB S.K.	BORTEZOMIB S.K. therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, BORTEZOMIB S.K. 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 S.K.-related neuropathic pain and/or peripheral neuropathy, hold and/or modify BORTEZOMIB S.K. as outlined in Table 1.

In addition, when BORTEZOMIB S.K. 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 S.K. (1.3 mg/m^2/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 S.K. 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 S.K.

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

BORTEZOMIB S.K. 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 S.K. 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 (2.6)

2.6 Dose Modifications of Peripheral Neuropathy

Starting BORTEZOMIB S.K. 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 S.K. only after careful risk-benefit assessment.

Patients experiencing new or worsening peripheral neuropathy during BORTEZOMIB S.K. 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 S.K.-related neuropathic pain and/or peripheral neuropathy see Table 4.

Table 4 – Recommended Dose Modification for BORTEZOMIB S.K. 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 S.K. to 1 mg/m^2 OR Change BORTEZOMIB S.K. 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 S.K. therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of BORTEZOMIB S.K. at 0.7 mg/m^2 once per week.
Grade 4 (life threatening consequences; urgent intervention indicated)	Discontinue BORTEZOMIB S.K.

*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 S.K. dose. Patients with moderate or severe hepatic impairment should be started on BORTEZOMIB S.K. 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 (5.10), Use in Specific Populations (8.6) and Clinical Pharmacology (11.3)]***

Table 5: Recommended Starting Dose Modification for BORTEZOMIB S.K. 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 S.K. to 0.7 mg/m^2 in the first 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	> 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 (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 2.9).

BORTEZOMIB S.K. 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 S.K. administration subcutaneously, a less concentrated BORTEZOMIB S.K. 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 S.K. 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.

Dissolution of the lyophilised powder is completed in less than 2 minutes.

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 3.5 mg single-use vial of bortezomib 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 overdose. After determining patient body surface area (BSA) in square meters, use the following equations to calculate the total volume (ml) of reconstituted BORTEZOMIB S.K. to be administered:

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

$$\frac{\text{BORTEZOMIB S.K. dose (mg/m}^2\text{) x patient BSA (m}^2\text{)}}{\text{1 mg/mL}} = \text{Total BORTEZOMIB S.K. volume (ml) to be administered}$$

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

$$\frac{\text{BORTEZOMIB S.K. dose (mg/m}^2\text{) x patient BSA (m}^2\text{)}}{\text{2.5 mg/mL}} = \text{Total BORTEZOMIB S.K. volume (ml) to be administered}$$

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: Unopened vials of BORTEZOMIB S.K. are stable until the date indicated on the package when stored in the original package protected from light. Do not store above 25°C.

BORTEZOMIB S.K. 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 S.K. contains 3.5 mg of bortezomib as a white to off-white cake or powder.

4 CONTRAINDICATIONS

BORTEZOMIB S.K. 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 S.K. is contraindicated in acute diffuse infiltrative pulmonary and pericardial disease. When BORTEZOMIB S.K. is given in combination with other medicinal products, refer to their Physician insert for additional contraindications.

BORTEZOMIB S.K. is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of BORTEZOMIB S.K.. **DO NOT ADMINISTER BORTEZOMIB S.K. INTRATHECALLY.**

5 WARNINGS AND PRECAUTIONS

BORTEZOMIB S.K. 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 S.K..

There have been fatal cases of inadvertent itrathecal administration of BORTEZOMIB S.K.. BORTEZOMIB S.K. is authorized for IV and subcutaneous use only. **DO NOT ADMINISTER BORTEZOMIB S.K. INTRATHECALLY.**

5.1 Peripheral Neuropathy

BORTEZOMIB S.K. treatment causes a peripheral neuropathy that is predominantly sensory. However, cases of severe sensory and motor peripheral neuropathy have been reported. Patients with preexisting 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 S.K.. 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 S.K. 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 S.K. 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 S.K. therapy may require a decrease in the dose and/or a less dose-intense schedule [see ***Dosage and Administration (2)***].

In the BORTEZOMIB S.K. 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 S.K. 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 S.K. vs dexamethasone, the incidence of any treatment-related cardiac disorder was 8% and 5% in the BORTEZOMIB S.K. 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 S.K. 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 S.K.. 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 (2g/m^2 per day) by continuous infusion with daunorubicin and BORTEZOMIB S.K. 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/m^2 per day) by continuous infusion over 24 hours is not recommended.

There have been reports of pulmonary hypertension associated with BORTEZOMIB S.K. administration in the absence of left heart failure or significant pulmonary disease.
In the event of new or worsening cardiopulmonary symptoms, consider interrupting BORTEZOMIB S.K. 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 S.K.. 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 S.K.. The safety of reinitiating BORTEZOMIB S.K. therapy in patients previously experiencing PRES is not known.

5.6 Gastrointestinal Toxicity

BORTEZOMIB S.K. 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 S.K. for severe symptoms.

5.7 Thrombocytopenia/Neutropenia

BORTEZOMIB S.K. 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 S.K.. Measure platelet counts prior to each dose of BORTEZOMIB S.K.. 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 S.K.. Support with transfusions and supportive care, according to published guidelines.

In the single-agent, relapsed multiple myeloma study of BORTEZOMIB S.K. 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 S.K. 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 S.K. 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 S.K. 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 S.K. 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 S.K. 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 S.K.. Bortezomib administered to rabbits during organogenesis at a dose approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area caused post-implantation loss and a decreased number of live fetuses [*see Use in Specific Populations (8.1)*].

5.12 Herpes zoster virus reactivation

Antiviral prophylaxis should be considered in patients being treated with BORTEZOMIB S.K..
In the Phase III study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in patients treated with BORTEZOMIB S.K.+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 S.K.. 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 S.K.. 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 S.K. 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 S.K., 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 S.K.. 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/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 Events (≥10% in BORTEZOMIB S.K. 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**		
	(n=340)			(n=337)		
System Organ Class	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
Preferred Term	n (%)	3	≥4	n (%)	3	≥4
Blood and Lymphatic System						
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/m^2 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 the trial, patients must have had measurable disease and 1 to 3 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 events was similar in men and women, and in patients <65 and ≥65 years of age. Most patients were Caucasian. **[*see Clinical Studies (13.1)*]**

Among the 331 BORTEZOMIB treated patients, the most commonly reported (>20%) adverse events overall were nausea (52%), diarrhea (52%), fatigue (39%), peripheral neuropathies NEC (35%), thrombocytopenia (33%), constipation (30%), vomiting (29%), and anorexia (21%). The most commonly reported (> 20%) adverse event 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 event; the most common events were thrombocytopenia (4%) and neutropenia (2%). Nine percent (9%) of dexamethasonetreated patients experienced a Grade 4 adverse event. All individual dexamethasone-related Grade 4 adverse events were less than 1%.

Serious Adverse Events (SAEs) and Events Leading to Treatment Discontinuation in the Relapsed Multiple Myeloma Study of BORTEZOMIB vs. Dexamethasone

Serious adverse events are defined as any event 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 event during the study, as did 83 (25%) dexamethasone-treated patients. The most commonly reported serious adverse events 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 events 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 events. Among the 331 BORTEZOMIB treated patients, the most commonly reported adverse event leading to discontinuation was peripheral neuropathy (8%). Among the 332 patients in the dexamethasone group, the most commonly reported adverse events 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: 1 case each of cardiogenic shock, respiratory insufficiency, congestive heart failure and cardiac arrest. Four deaths were considered dexamethasone-related: 2 cases of sepsis, 1 case of bacterial meningitis, and 1 case of sudden death at home.

Most Commonly Reported Adverse Events in the Relapsed Multiple Myeloma Study of BORTEZOMIB vs. Dexamethasone

The most common adverse events from the relapsed multiple myeloma study are shown in Table 9. All adverse events with incidence ≥10% in the BORTEZOMIB arm are included.

Table 9: Most Commonly Reported Adverse Events (≥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		
Preferred Term	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Adverse events	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 NEC[a]	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

[a] Based on High Level Term

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 (13)*]**

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

The safety and efficacy of BORTEZOMIB administered subcutaneously were evaluated in one Phase 3 study at the recommended dose of 1.3 mg/m^2. This was a randomized, comparative study of BORTEZOMIB subcutaneous 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 (13.1)].

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

	Subcutaneous (N=147)			Intravenous (N=74)		
System Organ Class	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
Preferred Term	n (%)	3	≥ 4	n (%)	3	≥ 4
Blood and lymphatic system disorders						
Anemia	28 (19)	8 (5)	0	17 (23)	3 (4)	0
Leukopenia	26 (18)	8 (5)	0	15 (20)	4 (5)	1 (1)
Neutropenia	34 (23)	15 (10)	4 (3)	20 (27)	10 (14)	3 (4)
Thrombocytopenia	44 (30)	7 (5)	5 (3)	25 (34)	7 (9)	5 (7)
Gastrointestinal disorders						
Diarrhea	28 (19)	1 (1)	0	21 (28)	3 (4)	0
Nausea	24 (16)	0	0	10 (14)	0	0
Vomiting	13 (9)	3 (2)	0	8 (11)	0	0
General disorders and administration site conditions						
Asthenia	10 (7)	1 (1)	0	12 (16)	4 (5)	0
Fatigue	11 (7)	3 (2)	0	11 (15)	3 (4)	0
Pyrexia	18 (12)	0	0	6 (8)	0	0
Nervous system disorders						
Neuralgia	34 (23)	5 (3)	0	17 (23)	7 (9)	0
Peripheral neuropathies NEC[a]	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

[a] Represents MedDRA High Level Term.

In general, safety data were similar for the subcutaneous and intravenous treatment groups. Differences were observed in the rates of some Grade ≥ 3 adverse events. 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 event was reported in 6% of patients in the subcutaneous group, mostly redness. Only 2 (1%) patients were reported as having severe events, 1 case of pruritus and 1 case of redness. Local events led to reduction in injection concentration in one patient and drug discontinuation in one patient.
Local events resolved in a median of 6 days.
Dose reductions occurred due to adverse events in 31% of patients in the subcutaneous treatment group compared with 43% of the intravenously-treated patients. The most common adverse events 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 Events and Adverse Events Leading to Treatment Discontinuation in the Relapsed Multiple Myeloma Study of BORTEZOMIB Subcutaneous versus Intravenous

The incidence of serious adverse events was similar for the subcutaneous treatment group (20%) and the intravenous treatment group (19%). The most commonly reported serious adverse events in the subcutaneous treatment arm were pneumonia and pyrexia (2% each). In the intravenous treatment group, the most commonly reported serious adverse events were pneumonia, diarrhea, and peripheral sensory neuropathy (3% each).

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

Two patients (1%) in the subcutaneous treatment group and 1 (1%) patient in the intravenous treatment group died due to an adverse event 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/m^2) administered intravenously in combination with rituximab (375 mg/m^2), cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2), and prednisone (100 mg/m^2) (VcR-CAP) in a prospective randomized study.
Infections were reported for 31% of patients in the VcR-CAP arm and 23% of the patients in the comparator (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) arm, including the predominant preferred term of pneumonia (VcR-CAP 8% 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		
System Organ Class Preferred Term	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[a]	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.

[a] 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 2 arms (3 patients in the VcR-CAP arm and 1 patient 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%; 3 patients). The most commonly reported adverse reaction leading to discontinuation in the R-CHOP group was febrile neutropenia (< 1%; 2 patients).

Integrated Summary of Safety (Multiple Myeloma and Mantle Cell Lymphoma)
Safety data from phase 2 and 3 studies of single agent BORTEZOMIB 1.3 mg/m^2/dose twice weekly for 2 weeks followed by a 10-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 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 (13)*]**

In the integrated analysis, the most commonly reported (> 20%) adverse events were nausea (49%), diarrhea (46%), asthenic conditions including fatigue (41%) and weakness (11%), peripheral neuropathies NEC (38%), thrombocytopenia (32%), vomiting (28%), constipation (25%), and pyrexia (21%). Eleven percent (11%) of patients experienced at least 1 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 Events (SAEs) and Events Leading to Treatment Discontinuation in the Integrated Summary of Safety
A total of 26% of patients experienced a serious adverse event during the studies. The most commonly reported serious adverse events included diarrhea, vomiting and pyrexia (3% each), nausea, dehydration, and thrombocytopenia (2% each) and pneumonia, dyspnea, peripheral neuropathies NEC, and herpes zoster (1% each).

Adverse events 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 Events in the Integrated Summary of Safety

The most common adverse events are shown in Table 12. All adverse events occurring at ≥10% are included. In the absence of a randomized comparator arm, it is often not possible to distinguish between adverse events that are drug-caused and those that reflect the patient's underlying disease. Please see the discussion of specific adverse events that follows.

Table 12: Most Commonly Reported (≥10% Overall) Adverse Events in Integrated Analyses of Relapsed Multiple Myeloma and Mantle Cell Lymphoma Studies using the 1.3 mg/m^2 Dose (N=1163)

	All Patients N=1163		Multiple Myeloma N=1008		Mantle Cell Lymphoma N=155	
	All	≥Grade 3	All	≥Grade 3	All	≥Grade 3
Preferred Term						
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 NEC[a]	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)

[a] Based on High Level Term

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

Gastrointestinal Events

A total of 75% of patients experienced at least one GI disorder. The most common GI disorders included nausea, diarrhea, constipation, vomiting, and appetite decreased. Other GI disorders included dyspepsia and dysgeusia. Grade 3 GI events occurred in 14% of patients; ≥Grade 4 events were rare (≤1%). GI events were considered serious in 7% of patients. Four percent (4%) of patients discontinued due to a GI event. 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 10-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 event resulted in BORTEZOMIB S.K. discontinuation in 2% of patients [*see Warnings and Precautions (5. 7)]*. Thrombocytopenia was reported more often in patients with multiple myeloma (34%) compared to patients with mantle cell lymphoma (16%). The incidence of ≥Grade 3 thrombocytopenia also was higher in patients with multiple myeloma (28%) compared to patients with mantle cell lymphoma (8%)

Peripheral Neuropathy

Overall, peripheral neuropathy NEC 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 S.K..

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 (>38ºC) 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. 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 Postmarketing 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 authorisation 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/

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 S.K. is used in combination with strong CYP3A4 inducers;

therefore, concomitant use of strong CYP3A4 inducers is not recommended in patients receiving BORTEZOMIB S.K.. (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 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 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 S.K. may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If BORTEZOMIB S.K. 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 0.05mg/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. 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 S.K., 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 S.K. 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 reinduction 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 reinduction 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 $\leq$ 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 are not necessary for patients with renal insufficiency. Since dialysis may reduce BORTEZOMIB concentrations, BORTEZOMIB 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 S.K. 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.

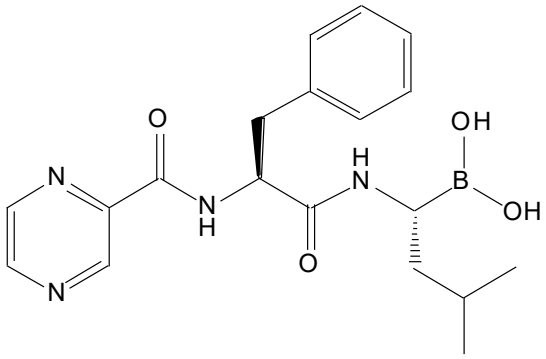
10. DESCRIPTION

BORTEZOMIB S.K. 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 S.K. 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, USP. The product is provided as a mannitol boronic ester which, in reconstituted form, consists of the mannitol ester in equilibrium with its hydrolysis product, the monomeric boronic acid. The drug substance exists in its cyclic anhydride form as a trimeric boroxine.

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 1.3mg/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 1.3mg/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 IC_{50} values of >30μM (>11.5μg/mL). Bortezomib may inhibit 2C19 activity (IC_{50} = 18 μM, 6.9 μg/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: beta2- 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: beta2-microglobulin, albumin, and region*

[d] EBMT criteria

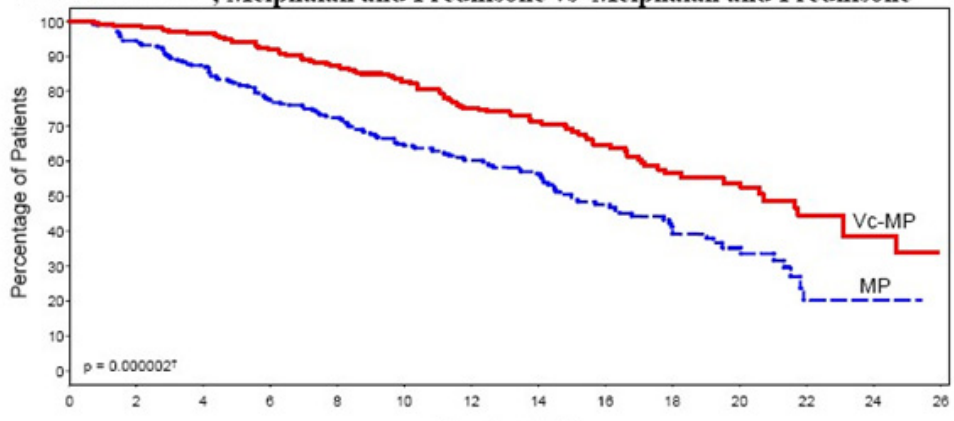
[e] p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors

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 S.K., **Melphalan and Prednisone vs Melphalan and Prednisone**



Number of patients at risk:

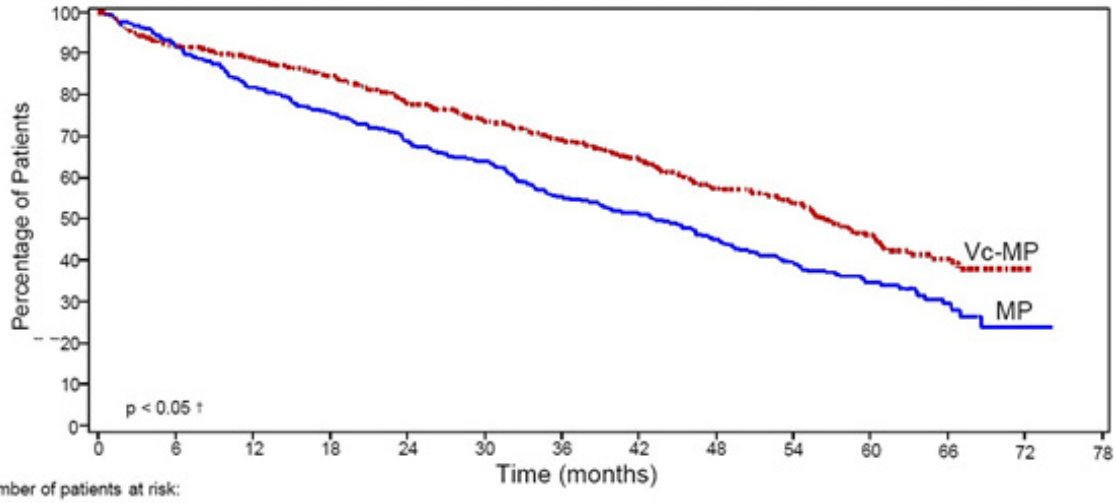
Vc-MP (n*)	344	309	280	258	240	200	159	114	81	53	35	20	13
MP (n*)	338	298	264	218	200	160	128	90	61	41	20	6	3

* 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 60.1months)

Figure 2: Overall Survival

BORTEZOMIB S.K, **Melphalan and Prednisone versus Melphalan and Prednisone**



Number of patients at risk:

Vc-MP (n*):	344	300	288	270	246	232	216	199	176	158	78	34	1	0
MP (n*):	338	301	262	240	216	196	168	153	133	112	61	24	3	0

* 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^+).

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

[a] Kaplan-Meier estimate. [b] Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable. A hazard ratio less than 1 indicates an advantage for BORTEZOMIB.

	All Patients		**1 Prior Line of Therapy**		**> 1 Prior Line of Therapy**	
	BORT	**Dex**	**BORT**	**Dex**	**BORT**	**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, 6.3)	2.9 mo (2.8, 3.5)
Hazard ratio [b] (95% CI)	0.55 (0.44, 0.69)		0.55 (0.38, 0.81)		0.54 (0.41, 0.72)	
p-value [c]	< 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 [b] (95% CI)	0.57 (0.40, 0.81)		0.39 (0.19, 0.81)		0.65 (0.43, 0.97)	
p-value [c,d]	<0.05		<0.05		<0.05	
Response Rate population[e] n = 627	n=315	n=312	n=128	n=110	n=187	n=202
CR[f] n (%)	20(6)	2(<1)	8(6)	2(2)	12(6)	0(0)
PR[f] n(%)	101(32)	54(17)	49(38)	27(25)	52(28)	27(13)
nCR[f,g] n(%)	21(7)	3(<1)	8(6)	2(2)	13(7)	1(<1)
CR + PR[f] n (%)	121 (38)	56 (18)	57(45)	29(26)	64(34)	27(13)
p-value [h]	<0.0001		0.0035		<0.0001	

[a] Kaplan-Meier estimate

[b] Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable. A hazard ratio less than 1 indicates an advantage for BORTEZOMIB

[c] p-value based on the stratified log-rank test including randomization stratification factors.

[d] Precise p-value cannot be rendered

[e] Response population includes patients who had measurable disease at baseline and received at least 1 dose of study drug.

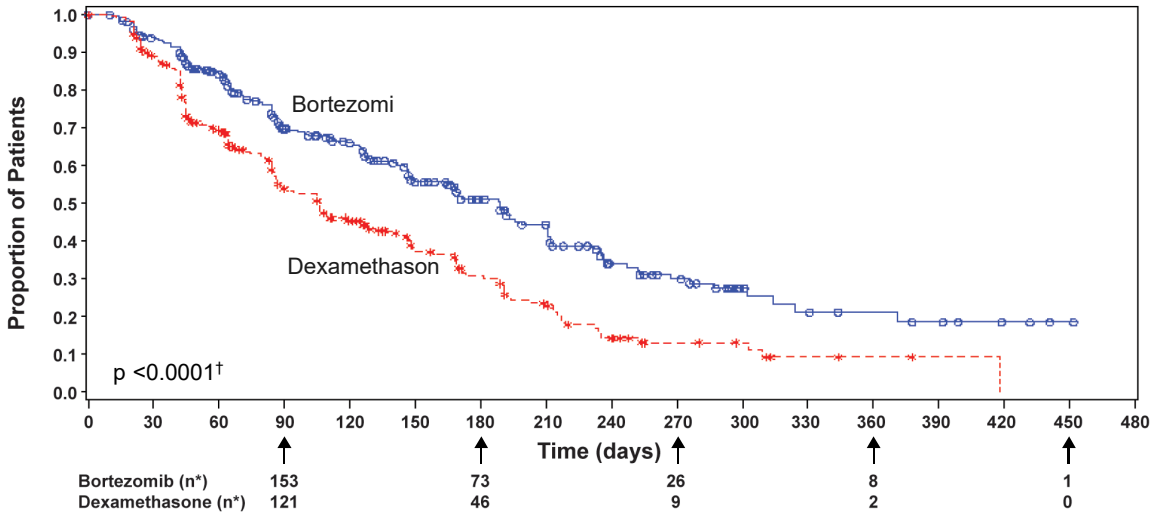
[f] EBMT criteria[1]; nCR meets all EBMT criteria for CR but has positive IF. Under EBMT criteria nCR is in the PR category.

[g] In 2 patients, the IF was unknown.

[h] 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 Fig. **3**).

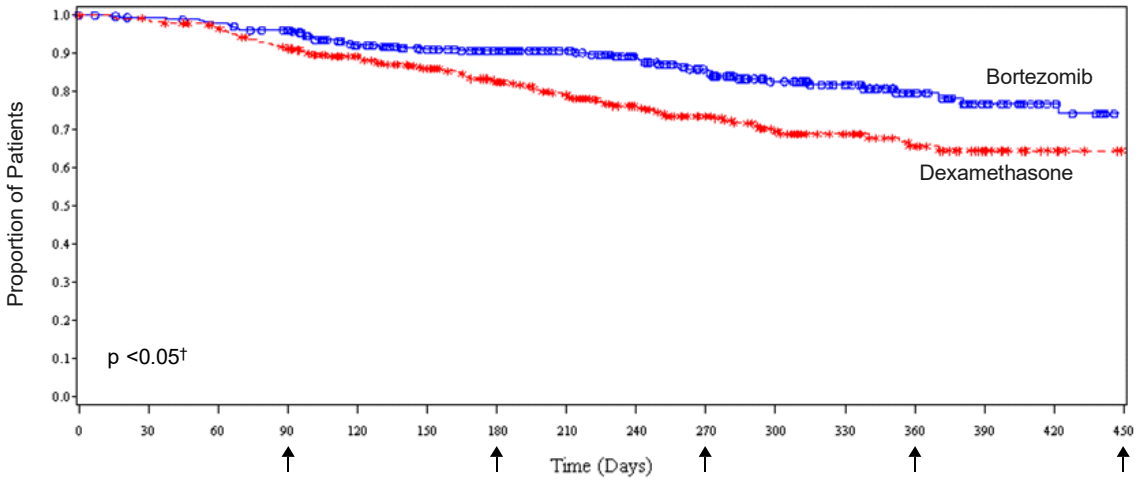
Fig. 3: Time to Progression
Bortezomib vs. Dexamethasone (relapsed multiple meyeloma study)



* 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.

Fig. 4: Overall Survival
Bortezomib vs. Dexamethasone (relapsed multiple myeloma 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 compared the efficacy and safety of the subcutaneous administration of BORTEZOMIB versus the intravenous administration. This study included 222 bortezomib naïve 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 8 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 (1 previous line versus more than 1 line of therapy), and international staging system (ISS) stage (incorporating beta$_2$-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 38-88 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 4 cycles relative to single agent intravenous BORTEZOMIB. The results are provided in Table 16.

Table 16: 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 (%)[a]	72.6	76.7

[a]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 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). The median duration of time between diagnosis of multiple myeloma and first dose of BORTEZOMIB on this trial was 2.0 years, and patients had received a median of 1 prior line of treatment (median of 3 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 (6.1)*]**

13.2 Mantle Cell Lymphoma

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

A randomized, open-label, Phase 3 study 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 12-21); 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 3 (high-intermediate) or higher and 76% had Stage IV disease.

The majority of the patients in both groups received 6 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 2 additional cycles.

The efficacy results of the study with a median follow-up of 40 months are presented in Table 18. The response criteria used to assess efficacy were based on the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma (IWRC). The combination of VcR-CAP resulted in statistically significant prolongation of PFS compared with R-CHOP (see Table 17 and Figure 5).

Table 17: Summary of Efficacy Analyses in the Previously Untreated Mantle Cell Lymphoma Study

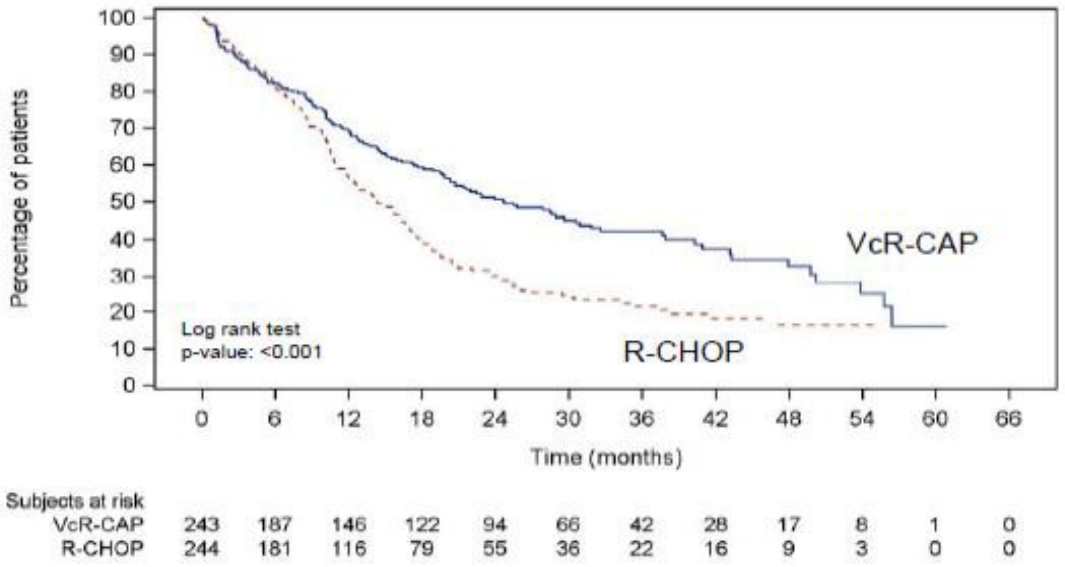
Efficacy endpoint **n: Intent to Treat patients**	**VcR-CAP** **n=243**	**R-CHOP** **n=244**
Progression-free Survival (by independent radiographic assessment)		
Events n (%)	133 (55)	165 (68)

Median[a] (months)	25		14
(95% CI)	(20, 32)		(12, 17)
Hazard ratio[b]		0.63	
(95% CI)		(0.50, 0.79)	
p-value[c]		<0.001	
Complete Response Rate (CR)[d]			
n (%)	108 (44)		82 (34)
(95% CI)	(38, 51)		(28, 40)
Efficacy endpoint **n: Intent to Treat patients**	**VcR-CAP** **n=243**		**R-CHOP** **n=244**
Overall Response Rate (CR+CRu+PR)[e]			
n (%)	214 (88)		208 (85)
(95% CI)	(83, 92)		(80, 89)

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

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.

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 1 prior therapy. The median age of the patients was 65 years (42, 89), 81% were male, and 92% were caucasian. Of the total, 75% had one or more extra-nodal sites of disease, and 77% were stage 4. 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 IV 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 10-day rest period (Days 12 to 21) for a maximum of 17 treatment cycles.
Patients achieving a CR or Cru were treated for 4 cycles beyond first evidence of CR or CRu. The study employed dose modifications for toxicity **[*see Dosage and Administration (2)*]**

Responses to BORTEZOMIB are shown in Table 18. Response rates to BORTEZOMIB were determined according to the International Workshop Criteria (IWRC) based on independent radiologic review of CT scans. The median number of cycles administered across all patients was 4; in responding patients the median number of cycles was 8. 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 18: Response Outcomes in a Phase 2 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)

14 HOW SUPPLIED/STORAGE AND HANDLING

BORTEZOMIB S.K. for Injection is supplied as individually cartoned 8 ml type I glass vials containing 3.5 mg of bortezomib as a white to off-white cake or powder.

BORTEZOMIB S.K. 3.5 mg is available in cartons containing 1 single-use vial.
There have been fatal cases of inadvertent intrathecal administration of BORTEZOMIB S.K..
BORTEZOMIB S.K. is authorized for IV or subcutaneous use only.
DO NOT ADMINISTER BORTEZOMIB S.K. INTRATHECALLY

Unopened vials: Do not store above 25°C. Store in original package in order to protect from light.

Consider handling and disposal of BORTEZOMIB S.K. according to guidelines issued for cytotoxic drugs, including the use of gloves and other protective clothing to prevent skin contact.

Shelf-life of unopened vial: The expiry date of the product is indicated on the packaging materials

Reconstituted solution:
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.

List of excipients

Mannitol

Nitrogen

MANUFACTURER
Pharmidea, 4 Rupnicu St., Olaine, Olaine district, LV-2114, Latvia.

LICENSE HOLDER
K.S. Kim International Ltd. 94 Yigal Alon Str., Tel-Aviv-Yafo, 6789139.

Registration Number: 157-36-34619-00

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