FONKOZOMIB

Lyophilized powder for injection 3.5 mg

Composition:
Each vial contains:
Bortezomib 3.5 mg

List of excipients:
Mannitol

Product Description:
White to off white cake or powder contained in a clear glass vial.

Pharmacodynamics:
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. Bortezomib is cytotoxic to a variety of cancer cell types. Bortezomib causes a delay in tumor growth, including multiple myeloma.

Pharmacokinetics:
Following intravenous bolus administration of a 1.0 mg/m^2 and 1.3 mg/m^2 dose to patients with multiple myeloma, the mean first-dose maximum plasma concentrations of bortezomib were 57 and 112 ng/ml, respectively. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/ml for the 1.0 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 40−193 hours. Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses. Mean total body clearances were 102 and 112 l/hour following the first dose for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 l/hour following subsequent doses for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively. Following an IV bolus or subcutaneous (SC) injection of a 1.3 mg/m^2 dose to multiple myeloma patients, the total systemic exposure after repeat dose administration (AUC_{last}) was equivalent for SC and IV administration. The C_{max} after SC administration (20.4 ng/ml) was lower than IV (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 1,659 liters to 3,294 liters single or repeat dose IV administration of 1.0 mg/m^2 or 1.3 mg/m^2 to patients with multiple myeloma. This suggests that bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100−1,000 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 two 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 minutes and 30 minutes 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.

Special populations
Age, gender, and race
The pharmacokinetics of bortezomib were characterized following twice weekly intravenous bolus

administration of 1.3 mg/m^2 doses to pediatric patients (2−16 years old) with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML). Based on a population pharmacokinetic analysis, clearance of bortezomib increased with increasing body surface area (BSA). Geometric mean (%CV) clearance was 7.79 (25%) l/hour/m^2, volume of distribution at steady state was 834 (39%) l/m^2, and the elimination half-life was 100 (44%) hours. After correcting for the BSA effect, other demographics such as age, body weight, and sex did not have clinically significant effects on bortezomib clearance. BSA-normalized clearance of bortezomib in pediatric patients was similar to that observed in adults.
The effects of gender and race on the pharmacokinetics of bortezomib have not been evaluated.

Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of IV bortezomib was assessed in cancer patients 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 **Table 7**).

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/minute/1.73 m^2), mild (CrCL = 40–59 ml/minute/1.73 m^2), moderate (CrCL = 20–39 ml/minute/1.73 m^2), and severe (CrCL <20 ml/minute/1.73 m^2). A group of dialysis patients who were dosed after dialysis was also included in the study. 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 **Recommended Dose**).

Indications:
- For the treatment of patients with multiple myeloma.
- For the treatment of patients with mantle cell lymphoma.

Recommended Dose:
Important dosing guidelines
Bortezomib is for intravenous or subcutaneous use only. Do not administer bortezomib by any other route.

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

The recommended starting dose of bortezomib is 1.3 mg/m^2. Bortezomib may be administered intravenously at a concentration of 1 mg/ml, or subcutaneously at a concentration of 2.5 mg/ml.

Bortezomib retreatment may be considered for patients with multiple myeloma who had previously responded to treatment with bortezomib and who have relapsed at least 6 months after completing prior bortezomib treatment. Treatment may be started at the last tolerated dose.

When administered intravenously, administer bortezomib as a 3 to 5 second bolus intravenous injection.

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

Table 1: Dosage regimen for patients with previously untreated multiple myeloma

Twice weekly bortezomib (cycles 1 to 4)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
Bortezomib (1.3 mg/m^2)	day 1	--	--	day 4	day 8	day 11	rest period	day 22	day 25	day 29	day 32	rest period
Melphalan (9 mg/m^2) Prednisone (60 mg/m^2)	day 1	day 2	day 3	day 4	--	--	rest period	--	--	--	--	rest period

Once weekly bortezomib (cycles 5 to 9 when used in combination with melphalan and prednisone)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
Bortezomib (1.3 mg/m^2)	day 1	--	--		day 8		rest period	day 22		day 29		rest period
Melphalan (9 mg/m^2) Prednisone (60 mg/m^2)	day 1	day 2	day 3	day 4	--	--	rest period	--	--	--	--	rest period

Dose modification guidelines for bortezomib when given in combination with melphalan and prednisone

Prior to initiating any cycle of therapy with bortezomib in combination with melphalan and prednisone:

- platelet count should be at least 70 x 10^9/l and the absolute neutrophil count (ANC) should be at least 1.0 x 10^9/l.
- nonhematological toxicities should have resolved to grade 1 or baseline.

Table 2: Dose modifications during cycles of combination bortezomib, melphalan, and prednisone therapy

Toxicity	Dose modification or delay
Hematological toxicity during a cycle:	
− If prolonged grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25% in the next cycle
− If platelet count is not above 30 x 10^9/l or ANC is not above 0.75 x 10^9/l on a bortezomib dosing day (other than day 1)	Withhold bortezomib dose
− If several bortezomib in consecutive cycles are withheld due to toxicity	Reduce bortezomib dose by 1 dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2)
Grade 3 or higher nonhematological toxicities	Withhold bortezomib therapy until symptoms of toxicity have resolved to grade 1 or baseline. Then, bortezomib may be reinitiated with one dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). For bortezomib-related neuropathic pain and/or peripheral neuropathy, hold and/or modify bortezomib as outlined in **Table 6**

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

Dose modifications guidelines for peripheral neuropathy are provided.

Posology for previously untreated multiple myeloma patients eligible for hematopoietic stem cell transplantation (induction therapy)

Combination therapy with dexamethasone

Bortezomib 3.5 mg lyophilized powder for injection is administered via intravenous or subcutaneous 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 in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of bortezomib.

Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4, 8, 9, 10, and 11 of the bortezomib treatment cycle.

Four treatment cycles of this combination therapy are administered.

Combination therapy with dexamethasone and thalidomide

Bortezomib lyophilized powder for injection 3.5 mg is administered via intravenous or subcutaneous 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 in a 28-day treatment cycle. This 4-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of bortezomib.

Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4, 8, 9, 10 and 11 of the bortezomib treatment cycle.

Thalidomide is administered orally at 50 mg daily on days 1−14 and if tolerated the dose is increased to 100 mg on days 15−28, and thereafter may be further increased to 200 mg daily from cycle 2 (see **Table 3**).

Four treatment cycles of this combination are administered. It is recommended that patients with at least partial response receive 2 additional cycles.

Table 3: Posology for bortezomib combination therapy for patients with previously untreated multiple myeloma eligible for hematopoietic stem cell transplantation

B+Dx	**Cycles 1 to 4**				
	Week	**1**	**2**	**3**	
	B (1.3 mg/m^2)	day 1, 4	day 8, 11	rest period	
	Dx 40 mg	day 1, 2, 3, 4	day 8, 9, 10, 11	-	
B+Dx+T	**Cycle 1**				
	Week	**1**	**2**	**3**	**4**
	B (1.3 mg/m^2)	day 1, 4	day 8, 11	rest period	rest period
	T 50 mg	daily	daily	-	-
	T 100 mg[a]	-	-	daily	daily
	Dx 40 mg	day 1, 2, 3, 4	day 8, 9, 10, 11	-	-
	Cycle 2 to 4[b]				
	B (1.3 mg/m^2)	day 1, 4	day 8, 11	rest period	rest period
	T 200 mg[a]	daily	daily	daily	daily
	Dx 40 mg	day 1, 2, 3, 4	day 8, 9, 10, 11	-	-

B = bortezomib; Dx = dexamethasone; T = thalidomide

[a] Thalidomide dose is increased to 100 mg from week 3 of cycle 1 only if 50 mg is tolerated and to 200 mg from cycle 2 onwards if 100 mg is tolerated.

[b] Up to 6 cycles may be given to patients who achieve at least a partial response after 4 cycles

Dosage adjustments for transplant eligible patients

For bortezomib dosage adjustments, as described under "**Dosage and dose modifications for relapsed multiple myeloma and relapsed mantle cell lymphoma**" and "**Dose modifications for peripheral neuropathy**" should be followed.

In addition, when bortezomib is given in combination with other chemotherapeutic medicinal products, appropriate dose reductions for these products should be considered in the event of toxicities according to the recommendations in the local package inserts.

Dosage in previously untreated mantle cell lymphoma

Bortezomib (1.3 mg/m^2) is administered intravenously in combination with intravenous rituximab, cyclophosphamide, doxorubicin, and oral prednisone (BR-CAP) for 6 three-week treatment cycles as shown in **Table 4**. Bortezomib is administered first followed by rituximab. Bortezomib is administered twice weekly for two weeks (days 1, 4, 8, and 11) followed by a ten-day rest period on days 12 to 21. For patients with a response first documented at cycle 6, two additional BR-CAP cycles are recommended. At least 72 hours should elapse between consecutive doses of bortezomib.

Table 4: Dosage regimen for patients with previously untreated mantle cell lymphoma

Twice weekly bortezomib (6, three-week cycles)*								
Week	**1**					**2**		**3**
Bortezomib (1.3 mg/m^2)	day 1	-	-	day 4	-	day 8	day 11	rest period
Rituximab (375 mg/m^2) Cyclophosphamide (750 mg/m^2) Doxorubicin (50 mg/m^2)	day 1	-	-	-	-	-	-	rest period
Prednisone (100 mg/m^2)	day 1	day 2	day 3	day 4	day 5	-	-	rest period

* Dosing may continue for 2 more cycles (for a total of 8 cycles) if response is first seen at cycle 6.

Dose modification guidelines for bortezomib when given in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone

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

- platelet count should be at least 100 x 10^9/l and absolute neutrophil count (ANC) should be at least 1.5 x 10^9/l.
- hemoglobin should be at least 8 g/dl (at least 4.96 mmol/l).
- nonhematologic toxicity should have recovered to grade 1 or baseline.

Interrupt bortezomib treatment at the onset of any grade 3 hematologic or nonhematological toxicities, excluding neuropathy (see **Table 6** and **Warnings and Precautions**). For dose adjustments, see **Table 5** below.

Table 5: Dose modifications on days 4, 8, and 11 during cycles of combination bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone therapy

Toxicity	Dose modification or delay
Hematological toxicity Grade 3 or higher neutropenia, or a platelet count not at or above 25 x 10^9/l	Withhold bortezomib therapy for up to 2 weeks until the patient has an ANC at or above 0.75 x 10^9/l and a platelet count at or above 25 x 10^9/l. − If, after bortezomib has been withheld, the toxicity does not resolve, discontinue bortezomib. − If toxicity resolves such that the patient has an ANC at or above 0.75 x 10^9/l and a platelet count at or above 25 x 10^9/l, bortezomib dose should be reduced by 1 dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2).
Grade 3 or higher nonhematological toxicities	Withhold bortezomib therapy until symptoms of the toxicity have resolved to grade 2 or better. Then, bortezomib may be reinitiated with one dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). For bortezomib-related neuropathic pain and/or peripheral neuropathy, hold or modify bortezomib as outlined in **Table 6**.

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

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

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

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

For dose modifications guidelines for peripheral neuropathy, see **Dose modifications for peripheral neuropathy** below.

Dose modifications for peripheral neuropathy
Starting bortezomib subcutaneously may be considered for patients with preexisting or at high risk of peripheral neuropathy. Patients with preexisting severe neuropathy should be treated with bortezomib only after careful risk-benefit assessment. Patients experiencing new or worsening peripheral neuropathy during bortezomib therapy may require a decrease in the dose and/or a less dose-intense schedule.

For dose or schedule modification guidelines for patients who experience bortezomib-related neuropathic pain and/or peripheral neuropathy see **Table 6**.

Table 6: Recommended dose modification for bortezomib related neuropathic pain and/or peripheral sensory or motor neuropathy

Severity of peripheral neuropathy signs and symptoms[a]	Modification of dose and regimen
Grade 1 (asymptomatic, loss of deep tendon reflexes or paresthesia) without pain or loss of function	No action
Grade 1 with pain or grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL)) [b]	Reduce bortezomib to 1.0 mg/m^2
Grade 2 with pain or grade 3 (severe symptoms; limiting self-care ADL[c])	Withhold bortezomib therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 once per week.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue bortezomib

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

Special populations
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, the drug should be administered after the dialysis procedure (see **Pharmacokinetics**).

Patients with hepatic impairment
Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended bortezomib dose. For patients with moderate or severe hepatic impairment, see **Table 7** below, (also, see **Pharmacokinetics**):

Table 7: Recommended starting dose modification for bortezomib in patients with hepatic impairment

	Bilirubin level	SGOT (AST) levels	Modification of starting dose in multiple myeloma and relapsed mantle cell lymphoma (1.3 mg/m^2 twice weekly)
Mild	≤1.0x ULN	>ULN	None
	>1.0x−1.5x ULN	Any	None
Moderate	>1.5x−3x ULN	Any	Reduce bortezomib 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.

Route of Administration:
Bortezomib is administered intravenously or subcutaneously.
When administered intravenously, bortezomib is administered as a 3−5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with 0.9% sodium chloride solution for injection.
For subcutaneous administration, the reconstituted solution is injected into the thighs (right or left) or abdomen (right or left). Injection sites should be rotated for successive injections.

If local injection site reactions occur following bortezomib injection subcutaneously, a less concentrated bortezomib solution (1 mg/ml instead of 2.5 mg/ml) may be administered subcutaneously, or changed to IV injection.

Instructions for Use, Handling, and Disposal:
Administration precautions
Bortezomib is an antineoplastic. Caution should be used during handling and preparation. Proper aseptic technique should be used. Use of gloves and other protective clothing to prevent skin contact is recommended. Local skin irritation was reported, but extravasation of bortezomib was not associated with tissue damage.

When administered subcutaneously, alternate sites for each injection (thigh or abdomen). New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, red, or hard.

There have been fatal cases of inadvertent intrathecal administration of bortezomib. Bortezomib is for IV and subcutaneous use only**. DO NOT ADMINISTER BORTEZOMIB INTRATHECALLY.**

Reconstitution/preparation for intravenous administration
The contents of each vial should be reconstituted only with normal (0.9%) saline according to the following instruction:

	IV	**SC**
	3.5 mg bortezomib	3.5 mg bortezomib
Volume of diluent (0.9% sodium chloride) added to reconstitute one vial	3.5 ml	1.4 ml
Final concentration after reconstitution (mg/ml)	1.0 mg/ml	2.5 mg/ml

The reconstituted product should be a clear and colorless solution. 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.

Procedure for proper disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

Contraindication:
Bortezomib is contraindicated in patients with hypersensitivity to bortezomib, boron, or mannitol.

Warnings and Precautions:
Bortezomib should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

There have been fatal cases of inadvertent intrathecal administration of bortezomib. Bortezomib is for IV and subcutaneous use only**. DO NOT ADMINISTER BORTEZOMIB INTRATHECALLY.**

Overall, the safety profile of patients treated with bortezomib in monotherapy was similar to that observed in patients treated with bortezomib in combination with melphalan and prednisone.

Peripheral neuropathy
Bortezomib treatment causes a peripheral neuropathy (PN) that is predominantly sensory. However, cases of severe motor neuropathy with or without sensory 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. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain, or weakness. Patients with preexisting PN or at high risk of peripheral neuropathy may benefit from starting bortezomib subcutaneously.
Patients experiencing new or worsening peripheral neuropathy may require a change in dose schedule or route of administration to SC (see **Recommended Dose**). Following dose adjustments, improvement in or resolution of peripheral neuropathy was reported. Improvement in or resolution of peripheral neuropathy was reported in patients with multiple myeloma who discontinued due to grade 2 neuropathy or who had ≥ grade 3 peripheral neuropathy. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

Hypotension
The incidence of hypotension (postural, orthostatic, and hypotension not otherwise specified) was reported in patients with multiple myeloma. 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, or administration of mineralocorticoids and/or sympathomimetics (see **Adverse Effects**).

Cardiac disorders
Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported, including reports in patients with few or no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or existing heart disease should be closely monitored. In patients with multiple myeloma, the incidence of any treatment-emergent cardiac disorder was reported. The incidence of heart failure events including acute pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock, pulmonary edema were also reported. There have been isolated cases of QT-interval prolongation; causality has not been established.

Hepatic events
Rare 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. Such changes may be reversible upon discontinuation of bortezomib. There is limited rechallenge information in these patients.

Pulmonary disorders
There have been rare reports of acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration, and acute respiratory distress syndrome (ARDS) in patients receiving bortezomib. Some of these events have been fatal. In the event of new or worsening pulmonary symptoms, a prompt diagnostic evaluation should be performed and patients treated appropriately. There have been two patients given high dose cytarabine (2 g/m^2 per day) by continuous infusion with daunorubicin and bortezomib for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy.

Laboratory tests
Complete blood counts (CBC) should be frequently monitored throughout treatment with bortezomib.

Thrombocytopenia/neutropenia
Bortezomib is associated with thrombocytopenia and neutropenia (see **Adverse Effects**). Platelets were lowest at day 11 of each cycle of bortezomib treatment and typically recovered to baseline by the next cycle. The cyclical pattern of platelet count decrease and recovery remain consistent in studies of multiple myeloma and mantle cell lymphoma, with no evidence of cumulative thrombocytopenia or neutropenia in any of the regimens studied.

Platelet counts should be monitored prior to each dose of bortezomib. Bortezomib therapy should be held when the platelet count is <25,000/mcl (see **Recommended Dose** and **Adverse Effects**). There have been reports of gastrointestinal and intracerebral hemorrhage in association with bortezomib. Transfusion and supportive care may be considered.

In the single-agent multiple myeloma study of bortezomib vs dexamethasone, the mean platelet count nadir measured was approximately 40% of baseline. The severity of thrombocytopenia related to pretreatment platelet count is shown in **Table 8**. The incidence of significant bleeding events (≥ grade 3) was similar on both the bortezomib (4%) and dexamethasone (5%) arms**.**

Table 8: Severity of thrombocytopenia related to pretreatment platelet count in the single agent phase 3 multiple myeloma study of bortezomib vs dexamethasone

Pretreatment platelet count[a]	Number of patients (N = 331)[b]	Number (%) of patients with platelet count (<10,000/mcl)	Number (%) of patients with platelet count 10,000–25,000/mcl
≥75,000/mcl	309	8 (3%)	36 (12%)
≥50,000/mcl–<75,000/mcl	14	2 (14%)	11 (79%)
≥10,000/mcl–<50,000/mcl	7	1 (14%)	5 (71%)

[a] A baseline platelet count of 50,000/mcl was required for study eligibility.
[b] Data were missing at baseline for 1 patient.

In the combination study of bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone (BR-CAP) in previously untreated mantle cell lymphoma patients, the incidence of thrombocytopenia adverse

events (≥ grade 4) was 32% versus 2% for the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) arm. The incidence of bleeding adverse events (≥ grade 3) was 1.7% (4 patients) in the BR-CAP arm and was 1.2% (3 patients) in the R-CHOP arm.

There were no deaths due to bleeding events in either arm. There were no CNS bleeding events in the BR-CAP arm; there was 1 bleeding event in the R-CHOP arm. Platelet transfusions were given to 23% of the patients in the BR-CAP arm and 3% of the patients in the R-CHOP arm.

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

Gastrointestinal adverse events
Bortezomib treatment can cause nausea, diarrhea, constipation, and vomiting (see **Adverse Effects**) sometimes requiring use of antiemetics and antidiarrheal medications. Fluid and electrolyte replacement should be administered to prevent dehydration. Since patients receiving bortezomib therapy may experience vomiting and/or diarrhea, patients should be advised regarding appropriate measures to avoid dehydration. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light headedness, or fainting spells.

Tumor lysis syndrome
Because bortezomib is a cytotoxic agent and can rapidly kill malignant cells the complications of tumor lysis syndrome may occur. The patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Patients with 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 at reduced starting doses and closely monitored for toxicities (see **Recommended Dose** and **Pharmacokinetics**).

***Posterior reversible encephalopathy syndrome* (PRES)**
There have been reports of PRES in patients receiving bortezomib. PRES is a rare, reversible, neurological disorder which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably MRI (magnetic resonance imaging), is used to confirm the diagnosis. In patients developing PRES, discontinue bortezomib. The safety of reinitiating bortezomib therapy in patients previously experiencing PRES is not known.

Effects on ability to drive and use machines
Bortezomib may cause tiredness, dizziness, fainting, or blurred vision. Patients should be advised not to drive or operate machinery if they experience these symptoms.

Interactions with Other Medicaments:
In vitro and animal *ex vivo* studies indicate that bortezomib is a weak inhibitor of cytochrome P450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6, and 3A4. Based on the limited contribution (7%) of CYP2D6 to the metabolism of bortezomib, the CYP2D6 poor metabolizer phenotype is not expected to affect the overall disposition of bortezomib.

A drug-drug interaction study assessing the effect of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of bortezomib, showed a bortezomib AUC mean increase of 35%, based on data from 12 patients. Therefore, patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g., ketoconazole, ritonavir).

In a drug-drug interaction study assessing the effect of omeprazole, a potent inhibitor of CYP2C19, on the pharmacokinetics of bortezomib there was no significant effect on the pharmacokinetics of bortezomib, based on data from 17 patients.

A drug-drug interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of bortezomib showed a mean bortezomib AUC reduction of 45% based on data from 6 patients. The concomitant use of bortezomib with strong CYP3A4 inducers is therefore not recommended, as

efficacy may be reduced. Examples of CYP3A4 inducers are rifampicin, carbamazepine, phenytoin, phenobarbital, and St. John's Wort. In the same drug-drug interaction study, the effect of dexamethasone, a weaker CYP3A4 inducer was also assessed. There was no significant effect on bortezomib pharmacokinetics based on data from 7 patients.

A drug-drug interaction study assessing the effect of melphalan-prednisone on bortezomib showed a 17% increase in mean bortezomib AUC based on data from 21 patients. This is not considered clinically relevant.

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.

Patients should be cautioned about the use of concomitant medications that may be associated with peripheral neuropathy (such as amiodarone, antivirals, isoniazid, nitrofurantoin, or statins), or with a decrease in blood pressure.

Drug laboratory test interactions
None known.

Pregnancy and Lactation:
Women of childbearing potential should avoid becoming pregnant while being treated with bortezomib.

No placental transfer studies have been conducted with bortezomib. There are no adequate and well-controlled studies in pregnant women. If bortezomib 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.

Patients should be advised to use effective contraceptive measures to prevent pregnancy and to avoid breastfeeding during treatment with bortezomib.

Lactation
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 reactions in nursing infants from bortezomib, women should be advised against breastfeeding while being treated with bortezomib.

Adverse Effects:
Summary of clinical trials of bortezomib IV in patients with relapsed/refractory multiple myeloma
The safety and efficacy of bortezomib were evaluated in 3 studies at the recommended dose of 1.3 mg/m^2. These included a phase 3 randomized, comparative study, versus dexamethasone of 669 patients with relapsed or refractory multiple myeloma who had received 1–3 prior lines of therapy (M34101-039); a phase 2 single arm, open-label, multicenter study of 202 patients who had received at least 2 prior therapies and demonstrated disease progression on their most recent therapy (M34100-025); and a phase 2 dose-response clinical study in relapsed multiple myeloma for patients who had progressed or relapsed on or after first line therapy with bortezomib 1.0 mg/m^2 or 1.3 mg/m^2 (M34100-024).

Table 9: Bortezomib adverse drug reactions in phase 2 and phase 3 relapsed/refractory multiple myeloma studies

	Study No.	
MedDRA system organ class Preferred term	M34101-039 (N = 331)	M34100-024/M34100-025 (N = 228[a])
Blood and lymphatic system disorders		
Thrombocytopenia	115 (35%)	97 (43%)
Anemia	87 (26%)	74 (32%)
Neutropenia	62 (19%)	55 (24%)
Leucopenia	24 (7%)	15 (7%)
Lymphopenia	15 (5%)	11 (5%)
Pancytopenia	2 (<1%)	6 (3%)
Febrile neutropenia	1 (<1%)	1 (<1%)
Cardiac disorders		
Arrhythmias	4 (1%)	2 (<1%)
Tachycardia	9 (3%)	17 (7%)
Atrial fibrillation	6 (2%)	2 (<1%)

Palpitations	5 (2%)	4 (2%)
Acute development or exacerbation of cardiac failure, including CHF	7 (2%)	8 (4%)
Pulmonary edema	6 (2%)	3 (1%)
Cardiogenic shock[b]	1 (<1%)	-
New onset of decreased left ventricular ejection fraction	1 (<1%)	-
Atrial flutter	1 (<1%)	-
Bradycardia	3 (<1%)	1 (<1%)
Ear & labyrinth disorders		
Hearing impairment	1 (<1%)	1 (<1%)
Eye disorders		
Blurred vision	9 (3%)	25 (11%)
Conjunctival infection and irritation	14 (4%)	7 (3%)
Gastrointestinal (GI) disorders		
Constipation	140 (42%)	97 (43%)
Diarrhea	190 (57%)	116 (51%)
Nausea	190 (57%)	145 (64%)
Vomiting	117 (35%)	82 (36%)
Gastrointestinal and abdominal pain, excluding oral and throat	80 (24%)	48 (21%)
Dyspepsia	32 (10%)	30 (13%)
Pharyngolaryngeal pain	25 (8%)	19 (8%)
Gastroesophageal reflux	10 (3%)	1 (<1%)
Eructation	2 (<1%)	4 (2%)
Abdominal distension	14 (4%)	13 (6%)
Stomatitis and mouth ulceration	24 (7%)	10 (4%)
Dysphagia	4 (1%)	5 (2%)
GI hemorrhage (upper and lower GI tract)[b]	7 (2%)	3 (1%)
Rectal hemorrhage (includes hemorrhagic diarrhea)	7 (2%)	3 (1%)
Tongue ulceration	2 (<1%)	1 (<1%)
Retching	3 (<1%)	2 (<1%)
Upper GI hemorrhage	1 (<1%)	-
Hematemesis	1 (<1%)	-
Oral mucosal petechiae	3 (<1%)	-
Ileus paralytic	1 (<1%)	2 (<1%)
General disorders and administration site conditions		
Asthenic conditions	201 (61%)	149 (65%)
weakness	40 (12%)	44 (19%)
fatigue	140 (42%)	118 (52%)
lethargy	12 (4%)	9 (4%)
malaise	13 (4%)	22 (10%)
Pyrexia	116 (35%)	82 (36%)
Rigors	37 (11%)	27 (12%)
Edema of the lower limbs	37 (11%)	27 (12%)
Neuralgia	21 (6%)	5 (2%)
Chest pain	26 (8%)	16 (7%)
Injection site pain and irritation	1 (<1%)	1 (<1%)
Injection site phlebitis	1 (<1%)	1 (<1%)
Hepatobiliary disorders		
Hyperbilirubinemia	1 (<1%)	-
Abnormal liver function tests	3 (<1%)	2 (<1%)
Hepatitis	2 (<1%) in study M34101-040[c]	-
Immune system disorders		
Drug hypersensitivity	1 (<1%)	1 (<1%)
Infections and infestations		
Upper respiratory tract infection	26 (8%)	41 (18%)
Nasopharyngitis	45 (14%)	17 (7%)
Lower respiratory tract and lung infections	48 (15%)	29 (13%)
Pneumonia[b]	21 (6%)	23 (10%)

Herpes zoster (including multidermatomal or disseminated)	42 (13%)	26 (11%)
Herpes simplex	25 (8%)	13 (6%)
Bronchitis	26 (8%)	6 (3%)
Postherpetic neuralgia	4 (1%)	1 (<1%)
Sinusitis	14 (4%)	15 (7%)
Pharyngitis	6 (2%)	2 (<1%)
Oral candidiasis	6 (2%)	3 (1%)
Urinary tract infection	13 (4%)	14 (6%)
Catheter related infection	10 (3%)	6 (3%)
Sepsis and bacteremia[b]	9 (3%)	9 (4%)
Gastroenteritis	7 (2%)	-
Injury, poisoning, and procedural complications		
Catheter related complication	7 (2%)	8 (4%)
Investigations		
Increased ALT	3 (<1%)	10 (4%)
Increased AST	5 (2%)	12 (5%)
Increased alkaline phosphatase	6 (2%)	8 (4%)
Increased GGT	1 (<1%)	4 (2%)
Metabolism and nutritional disorders		
Decreased appetite and anorexia	112 (34%)	99 (43%)
Dehydration	24 (7%)	42 (18%)
Hyperglycemia	5 (2%)	16 (7%)
Hypoglycemia	7 (2%)	4 (2%)
Hyponatremia	8 (2%)	18 (8%)
Tumor lysis syndrome	2 (<1%) in study M34101-040[c]	-
Musculoskeletal and connective tissue disorders		
Pain in limb	50 (15%)	59 (26%)
Myalgia	39 (12%)	32 (14%)
Arthralgia	45 (14%)	60 (26%)
Nervous system disorders		
Peripheral neuropathy[d]	120 (36%)	84 (37%)
Paresthesia and dysesthesia	91 (27%)	53 (23%)
Dizziness, excluding vertigo	45 (14%)	48 (21%)
Headache	85 (26%)	63 (28%)
Dysgeusia	17 (5%)	29 (13%)
Polyneuropathy	9 (3%)	1 (<1%)
Syncope	8 (2%)	17 (7%)
Convulsions	4 (1%)	-
Loss of consciousness	2 (<1%)	-
Ageusia	2 (<1%)	-
Psychiatric disorders		
Anxiety	31 (9%)	32 (14%)
Renal and urinary disorders		
Renal impairment and failure	21 (6%)	21 (9%)
Difficulty in micturition	2 (1%)	3 (1%)
Hematuria	5 (2%)	4 (2%)
Respiratory, thoracic, and mediastinal disorders		
Epistaxis	21 (6%)	23 (10%)
Cough	70 (21%)	39 (17%)
Dyspnea	65 (20%)	50 (22%)
Exertional dyspnea	21 (6%)	18 (8%)
Pleural effusion	4 (1%)	9 (4%)
Rhinorrhea	4 (1%)	14 (6%)
Hemoptysis	3 (<1%)	2 (<1%)
Skin and subcutaneous tissue disorders		
Skin rash, which can be pruritic, erythematous, and can include evidence of leukocytoclastic vasculitis	61 (18%)	47 (21%)
Urticaria	7 (2%)	5 (2%)
Vascular disorders		
Hypotension	20 (6%)	27 (12%)
Orthostatic/postural hypotension	14 (4%)	8 (4%)

Petechiae	6 (2%)	7 (3%)
Cerebral hemorrhage[b]	1 (<1%)	-

[a]All 228 patients received bortezomib at a dose of 1.3 mg/m^2
[b]includes fatal outcome
[c]A study of bortezomib at the recommended dose of 1.3 mg/m^2 in multiple myeloma patients who experienced progressive disease after receiving at least four previous therapies or after receiving high-dose dexamethasone in Protocol M34101-039
[d]including all preferred terms under the MedDRA HLT "peripheral neuropathy NEC"

Summary of clinical trials of bortezomib IV vs SC in patients with relapsed multiple myeloma
The safety and efficacy of bortezomib SC 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 IV vs SC in 222 patients with relapsed multiple myeloma.

Table 10: Incidence of bortezomib adverse drug reactions reported in ≥10% of patients in the phase 3 relapsed multiple myeloma study comparing bortezomib IV and SC

MedDRA system organ class	IV (N=74)			SC (N=147)		
	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
Preferred term	n (%)	3	≥4	n (%)	3	≥4
Blood and lymphatic system disorders						
Anemia	26 (35)	6 (8)	0	53 (36)	14 (10)	4 (3)
Leukopenia	16 (22)	4 (5)	1 (1)	29 (20)	9 (6)	0
Neutropenia	20 (27)	10 (14)	3 (4)	42 (29)	22 (15)	4 (3)
Thrombocytopenia	27 (36)	8 (11)	6 (8)	52 (35)	12 (8)	7 (5)
Gastrointestinal disorders						
Abdominal pain	8 (11)	0	0	5 (3)	1 (1)	0
Abdominal pain upper	8 (11)	0	0	3 (2)	0	0
Constipation	11 (15)	1 (1)	0	21 (14)	1 (1)	0
Diarrhea	27 (36)	3 (4)	1 (1)	35 (24)	2 (1)	1 (1)
Nausea	14 (19)	0	0	27 (18)	0	0
Vomiting	12 (16)	0	1 (1)	17 (12)	3 (2)	0
General disorders and administration site conditions						
Asthenia	14 (19)	4 (5)	0	23 (16)	3 (2)	0
Fatigue	15 (20)	3 (4)	0	17 (12)	3 (2)	0
Pyrexia	12 (16)	0	0	28 (19)	0	0
Infections and infestations						
Herpes zoster	7 (9)	1 (1)	0	16 (11)	2 (1)	0
Metabolism and nutrition disorders						
Decreased appetite	7 (9)	0	0	14 (10)	0	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	8 (11)	2 (3)	0	8 (5)	1 (1)	0
Nervous system disorders						
Headache	8 (11)	0	0	5 (3)	0	0
Neuralgia	17 (23)	7 (9)	0	35 (24)	5 (3)	0
Peripheral sensory neuropathy	36 (49)	10 (14)	1 (1)	51 (35)	7 (5)	0
Psychiatric disorders						
Insomnia	8 (11)	0	0	18 (12)	0	0

Respiratory, thoracic, and mediastinal disorders						
Dyspnea	9 (12)	2 (3)	0	11 (7)	2 (1)	0

Note: Percentages in 'Total' column for each group calculated with the number of subjects in each group as denominator.
Percentages of toxicity grade sub-groups calculated with the number of subjects in each group as denominator.

Although, in general safety data were similar for the IV and SC treatment groups, the following table highlights differences larger than 10% in the overall incidence of adverse drug reactions between the two treatment arms.

Table 11: Incidence of adverse drug reactions with >10% difference in overall incidence between treatment arms in the phase 3 relapsed multiple myeloma study comparing bortezomib IV and SC, by toxicity grade and discontinuation

	IV			**SC**		
	(N=74)			**(N=147)**		
MedDRA system organ class	**Category, n (%)**			**Category, n (%)**		
MedDRA high level term	**TEAE**	**G ≥3**	**Disc**	**TEAE**	**G ≥3**	**Disc**
All subjects with TEAE	73 (99)	52 (70)	20 (27)	140 (95)	84 (57)	33 (22)
Gastrointestinal disorders						
Diarrhea (excl infective)	27 (36)	4 (5)	1 (1)	35 (24)	3 (2)	1 (1)
Gastrointestinal and abdominal pains (excl oral and throat)	14 (19)	0	0	9 (6)	1 (1)	0
General disorders and administration site conditions						
Asthenic conditions	29 (39)	7 (9)	1 (1)	40 (27)	6 (4)	2 (1)
Infections and infestations						
Upper respiratory tract infections	19 (26)	2 (3)	0	20 (14)	0	0
Nervous system disorders						
Peripheral neuropathies[a]	39 (53)	12 (16)	10 (14)	56 (38)	9 (6)	9 (6)

[a] Represents the high level term
TEAE = Treatment-Emergent Adverse Event; G ≥3 = Toxicity grade greater than or equal to 3
Disc = Discontinuation of any study drug

Patients who received bortezomib subcutaneously compared to intravenous administration had 13% lower overall incidence of treatment-emergent adverse drug reactions that were grade 3 or higher in toxicity (57% vs 70% respectively), and a 5% lower incidence of discontinuation of bortezomib (22% vs 27%). The overall incidence of diarrhea (24% for the SC arm vs 36% for the IV arm), gastrointestinal and abdominal pain (6% for the SC arm vs 19% for the IV arm), asthenic conditions (27% for SC arm vs 39% for IV arm), upper respiratory tract infections (14% SC arm vs 26% IV arm), and peripheral neuropathy NEC (38% SC arm vs 53% IV arm) were 12%–15% lower in the subcutaneous group than the intravenous group. In addition, the incidence of peripheral neuropathies that were grade 3 or higher in toxicity was 10% lower (6% for SC vs 16% for IV), and the discontinuation rate due to peripheral neuropathies was 8% lower for the subcutaneous group (5%) as compared to the intravenous group (12%).
Six percent of patients were reported to have had an adverse local reaction to SC administration, mostly redness. Only 2 (1%) subjects were reported as having severe reactions. These severe local reactions were 1 case of pruritus and 1 case of redness. These reactions seldom led to dose modifications and all resolved in a median of 6 days.

Bortezomib retreatment in relapsed multiple myeloma

The following table describes adverse drug reactions reported for at least 10% of patients with relapsed multiple myeloma who received retreatment with bortezomib IV (study MMY-2036).

Table 12: Incidence of bortezomib adverse drug reactions reported in ≥10% of patients (study MMY-2036)

	Bortezomib retreatment (MMY-2036)		
		Toxicity grade	
	Total	**3**	**≥4**
Analysis set: safety, N	130		
Total no. subjects with adverse drug reactions, n (%)	126 (97)		
MedDRA system organ class			
Preferred term			
Blood and lymphatic system disorders			
Thrombocytopenia	71 (55)	19 (15)	14 (11)
Anemia	48 (37)	5 (4)	1 (1)
Neutropenia	23 (18)	9 (7)	0
Leukopenia	20 (15)	5 (4)	0
Gastrointestinal disorders			
Diarrhea	45 (35)	9 (7)	0
Constipation	36 (28)	0	0
Nausea	14 (11)	0	0
General disorders and administration site conditions			
Pyrexia	31 (24)	2 (2)	0
Asthenia	29 (22)	6 (5)	0
Fatigue	21 (16)	0	0
Edema peripheral	15 (12)	0	0
Infections and infestations			
Respiratory tract infection	17 (13)	3 (2)	1 (1)
Bronchitis	13 (10)	1 (1)	0
Nervous system disorders			
Peripheral sensory neuropathy	22 (17)	4 (3)	0
Neuropathy peripheral	13 (10)	3 (2)	0
Respiratory, thoracic, and mediastinal disorders			
Cough	15 (12)	1 (1)	0
Dyspnea	14 (11)	1 (1)	0

Key: AE = Adverse event; NCI = National Cancer Institute; CTCAE = Common Toxicity Criteria for Adverse Events

Note: Percentages are calculated with the number of subjects in each group as denominator.

Adverse events are reported using MedDRA version 14.1.

In Study MMY-2036, for AEs where only a severity grade is reported, the severity grade is remapped to an NCI CTCAE toxicity grade.

AEs with missing toxicity grade are assigned grade 3.

Summary of clinical trials of bortezomib combination therapy in patients with relapsed multiple myeloma

The following table describe adverse drug reactions reported for at least 10% of patients with relapsed multiple myeloma who received bortezomib in combination with dexamethasone (study MMY-2045) or bortezomib in combination with pegylated liposomal doxorubicin (study DOXIL-MMY-3001).

Table 13: Most frequent (at least 10 percent in any treatment group) treatment emergent adverse drug reactions by toxicity grade, system organ class and preferred term; safety analysis set (studies DOXIL-MMY-3001 and MMY-2045)

	Bortezomib combination therapy					
	Bortezomib monotherapy		Bortezomib + DOXIL		Bortezomib + Dex	
	Total n (%)	Grade ≥3 n (%)	Total n (%)	Grade ≥3 n (%)	Total n (%)	Grade ≥3 n (%)
Analysis set: safety	318		318		163	
Total no. subjects with adverse drug reactions	301 (95)		314 (99)		154 (94)	
MedDRA system organ class						
Preferred term						
Gastrointestinal disorders						
Diarrhea	124 (39)	16 (5)	145 (46)	23 (7)	51 (31)	7 (4)
Nausea	126 (40)	3 (1)	154 (48)	8 (3)	20 (12)	1 (1)
Constipation	98 (31)	2 (1)	99 (31)	3 (1)	50 (31)	9 (6)
Vomiting	69 (22)	3 (1)	101 (32)	13 (4)	11 (7)	2 (1)
Stomatitis	11 (3)	1 (<1)	56 (18)	7 (2)	1 (1)	0
Abdominal pain	24 (8)	4 (1)	34 (11)	2 (1)	11 (7)	1 (1)
Nervous system disorders						
Peripheral neuropathy[a]	143 (45)	35 (11)	133 (42)	22 (7)	79 (48)	23 (14)
Neuralgia	63 (20)	14 (4)	54 (17)	9 (3)	26 (16)	4 (2)
Headache	56 (18)	0	59 (19)	3 (1)	9 (6)	0
Paresthesia	31 (10)	0	41 (13)	1 (<1)	22 (13)	2 (1)
Dizziness	26 (8)	4 (1)	32 (10)	4 (1)	14 (9)	0
General disorders and administration site conditions						
Fatigue	88 (28)	8 (3)	115 (36)	22 (7)	37 (23)	2 (1)
Pyrexia	71 (22)	4 (1)	100 (31)	4 (1)	21 (13)	4 (2)
Asthenia	56 (18)	12 (4)	71 (22)	19 (6)	33 (20)	2 (1)
Edema peripheral	27 (8)	1 (<1)	32 (10)	1 (<1)	43 (26)	3 (2)
Blood and lymphatic system disorders						
Thrombocytopenia	89 (28)	53 (17)	106 (33)	76 (24)	61 (37)	28 (17)
Neutropenia	71 (22)	51 (16)	114 (36)	102 (32)	12 (7)	6 (4)
Anemia	68 (21)	30 (9)	80 (25)	29 (9)	35 (21)	16 (10)
Infections and infestations						
Herpes zoster	29 (9)	6 (2)	34 (11)	6 (2)	16 (10)	1 (1)
Bronchitis	21 (7)	3 (1)	31 (10)	1 (<1)	18 (11)	1 (1)
Upper respiratory tract infection	33 (10)	3 (1)	33 (10)	2 (1)	15 (9)	3 (2)
Musculoskeletal and connective tissue disorders						
Back pain	39 (12)	6 (2)	39 (12)	4 (1)	25 (15)	2 (1)
Pain in extremity	48 (15)	8 (3)	34 (11)	1 (<1)	16 (10)	2 (1)
Arthralgia	27 (8)	5 (2)	34 (11)	1 (<1)	14 (9)	1 (1)
Respiratory, thoracic, and mediastinal disorders						
Cough	38 (12)	0	58 (18)	0	26 (16)	1 (1)

Dyspnea	28 (9)	10 (3)	34 (11)	3 (1)	13 (8)	3 (2)
Metabolism and nutritional disorders						
Decreased appetite	50 (16)	1 (<1)	83 (26)	8 (3)	9 (6)	0
Skin and subcutaneous tissue disorders						
Rash	29 (9)	3 (1)	48 (15)	2 (1)	8 (5)	0
Investigations						
Weight decreased	12 (4)	0	37 (12)	0	3 (2)	0
Psychiatric disorders						
Insomnia	43 (14)	2 (1)	35 (11)	0	18 (11)	1 (1)

Key: Dex = dexamethasone; NCI = National Cancer Institute; CTCAE = Common Toxicity Criteria for Adverse Events

[a] Includes the preferred terms of neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, and polyneuropathy.

Note: Percentages are calculated with the number of subjects in each group as denominator.

Adverse events are reported using MedDRA version 14.1.

In Study MMY-2045, for AEs where only a severity grade is reported, the severity grade is remapped to an NCI CTCAE toxicity grade.

Summary of clinical trials in patients with previously untreated multiple myeloma

The following table describes safety data from 340 patients with previously untreated multiple myeloma who received bortezomib (1.3 mg/m^2) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in a prospective phase 3 study.

Table 14: Treatment-emergent drug-related adverse events reported in ≥10% of patients treated with bortezomib IV in combination with melphalan and prednisone

	Bortezomib-MP (n=340)			**MP (n=337)**		
MedDRA system organ class	**Total**	**Toxicity Grade, n (%)**		**Total**	**Toxicity Grade, n (%)**	
Preferred Term	**n (%)**	**3**	**≥4**	**n (%)**	**3**	**≥4**
Blood and lymphatic system disorders						
Thrombocytopenia	164 (48)	60 (18)	57 (17)	140 (42)	48 (14)	39 (12)
Neutropenia	160 (47)	101 (30)	33 (10)	143 (42)	77 (23)	42 (12)
Anemia	109 (32)	41 (12)	4 (1)	156 (46)	61 (18)	18 (5)
Leukopenia	108 (32)	64 (19)	8 (2)	93 (28)	53 (16)	11 (3)
Lymphopenia	78 (23)	46 (14)	17 (5)	51 (15)	26 (8)	7 (2)
Gastrointestinal disorders						
Nausea	134 (39)	10 (3)	0	70 (21)	1 (<1)	0
Diarrhea	119 (35)	19 (6)	2 (1)	20 (6)	1 (<1)	0
Vomiting	87 (26)	13 (4)	0	41 (12)	2 (1)	0
Constipation	77 (23)	2 (1)	0	14 (4)	0	0
Abdominal pain upper	34 (10)	1 (<1)	0	20 (6)	0	0
Nervous system disorders						
Peripheral neuropathy	156 (46)	42 (12)	2 (1)	4 (1)	0	0
Neuralgia	117 (34)	27 (8)	2 (1)	1 (<1)	0	0
Paresthesia	42 (12)	6 (2)	0	4 (1)	0	0
General disorders and administration site conditions						
Fatigue	85 (25)	19 (6)	2 (1)	48 (14)	4 (1)	0

Asthenia	54 (16)	18 (5)	0	23 (7)	3 (1)	0
Pyrexia	53 (16)	4 (1)	0	19 (6)	1 (<1)	1 (<1)
Infections and infestations						
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

Herpes zoster virus reactivation:
Physician should consider using antiviral prophylaxis in patients being treated with bortezomib. In the phase 3 study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in patients treated with bortezomib-MP compared with MP (14% vs 4% respectively). Antiviral prophylaxis was administered to 26% of the patients in the bortezomib-MP arm. The incidence of herpes zoster among patients in the bortezomib-MP treatment group was 17% for patients not administered antiviral prophylaxis compared to 3% for patients administered antiviral prophylaxis.

The following table describes adverse drug reactions to have at least a possible causal relationship to bortezomib from patients with previously untreated multiple myeloma eligible for stem cell transplantation who received bortezomib IV (1.3 mg/m^2). 410 patients were treated with bortezomib in combination with doxorubicin and dexamethasone compared with 411 patients treated with vincristine, doxorubicin and dexamethasone in study MMY-3003, 239 were treated with bortezomib in combination with dexamethasone alone compared with 239 patients treated with vincristine, doxorubicin, and dexamethasone in study IFM 2005-01, and 130 were treated with bortezomib in combination with thalidomide and dexamethasone compared with 126 patients treated with thalidomide and dexamethasone in study MMY-3010. For these 3 studies conducted in the transplant setting (MMY3003, IFM2005-01, MMY3010), only the adverse reactions during the induction phase of treatment are considered for the table.

Table 15: Incidence of most frequent (≥10% in either treatment group) treatment emergent adverse drug reactions during induction stage
(Bortezomib transplant integrated analysis of safety: safety analysis set)

	Bortezomib-based (N=779)			**Non bortezomib-based (N=776)**		
MedDRA system organ class	**Total**	**Toxicity grade, n (%)**		**Total**	**Toxicity grade, n (%)**	
Preferred term	**n (%)**	**2**	**≥3**	**n (%)**	**2**	**≥3**
Total no. subjects with adverse drug reactions	715 (92)			679 (88)		
Gastrointestinal disorders						
Constipation	242 (31)	89 (11)	10 (1)	214 (28)	67 (9)	8 (1)
Nausea	215 (28)	71 (9)	22 (3)	206 (27)	77 (10)	9 (1)
Diarrhea	133 (17)	29 (4)	23 (3)	110 (14)	26 (3)	6 (1)
Vomiting	95 (12)	30 (4)	18 (2)	87 (11)	35 (5)	6 (1)
Nervous system disorders						
Neuropathy peripheral	147 (19)	53 (7)	20 (3)	54 (7)	11 (1)	4 (1)
Paresthesia	101 (13)	24 (3)	11 (1)	80 (10)	15 (2)	2 (<1)
Peripheral sensory neuropathy	101 (13)	41 (5)	19 (2)	55 (7)	13 (2)	1 (<1)
Headache	64 (8)	23 (3)	4 (1)	76 (10)	23 (3)	1 (<1)

General disorders and administration site conditions						
Fatigue	158 (20)	50 (6)	21 (3)	161 (21)	68 (9)	21 (3)
Pyrexia	153 (20)	56 (7)	25 (3)	159 (20)	40 (5)	36 (5)
Asthenia	110 (14)	33 (4)	16 (2)	91 (12)	33 (4)	10 (1)
Blood and lymphatic system disorders						
Thrombocytopenia	239 (31)	54 (7)	63 (8)	171 (22)	27 (3)	27 (3)
Anemia	211 (27)	95 (12)	55 (7)	222 (29)	108 (14)	77 (10)
Leukopenia	196 (25)	51 (7)	109 (14)	206 (27)	53 (7)	120 (15)
Infections and infestations						
Herpes zoster	86 (11)	50 (6)	24 (3)	18 (2)	9 (1)	5 (1)
Metabolism and nutrition disorders						
Hyperglycemia	122 (16)	46 (6)	26 (3)	138 (18)	46 (6)	31 (4)
Hyponatremia	100 (13)	2 (<1)	29 (4)	82 (11)	6 (1)	12 (2)
Psychiatric disorders						
Insomnia	96 (12)	32 (4)	6 (1)	82 (11)	30 (4)	6 (1)

Note: Percentages for each group calculated with the number of subjects in each group as denominator.
Incidence is based on the number of subjects experiencing at least 1 adverse reaction, not the number of events.
Adverse Events are coded using MedDRA 13.1

Summary of the clinical trial in patients with relapsed mantle cell lymphoma

Safety data for patients with relapsed mantle cell lymphoma were evaluated in a phase 2 study [M34103-053 (PINNACLE)], which included 155 patients treated with bortezomib at the recommended dose of 1.3 mg/m^2. The safety profile of bortezomib in these patients was similar to that observed in patients with multiple myeloma. Notable differences between the two patient populations were that thrombocytopenia, neutropenia, anemia, nausea, vomiting, and pyrexia were reported more often in the patients with multiple myeloma than in those with mantle cell lymphoma; whereas peripheral neuropathy, rash and pruritus were higher among patients with mantle cell lymphoma compared to patients with multiple myeloma.

Summary of clinical trial in patients with previously untreated mantle cell lymphoma

Table 16 describes safety data from 240 patients with previously untreated mantle cell lymphoma who received bortezomib (1.3 mg/m^2) administered IV in combination with rituximab (375 mg/m^2), cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2), and prednisone (100 mg/m^2) (BR-CAP) in a prospective randomized study.

The incidences of grade ≥3 bleeding events were similar between the 2 arms (4 patients in the BR-CAP arm and 3 patients in the R-CHOP arm). All of the grade ≥3 bleeding events resolved without sequelae in the BR-CAP arm.

Infections were reported for 31% of patients in the BR-CAP arm and 23% of the patients in the R-CHOP arm. Respiratory tract and lung infections were reported, with the predominant preferred term of pneumonia (BR-CAP 8% versus R-CHOP 5%).

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

Table 16: Most commonly reported adverse reactions (≥5%) with grades 3 and ≥4 intensity in the mantle cell lymphoma study of BR-CAP versus R-CHOP (n=482) (study LYM-3002)

	BR-CAP n=240			R-CHOP n=242		
System Organ Class Preferred Term	**Total n (%)**	**Toxicity grade 3 n (%)**	**Toxicity grade ≥4 n (%)**	**Total 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 sensory neuropathy	53 (22)	11 (5)	1 (<1)	45 (19)	6 (3)	0
Neuropathy peripheral	18 (8)	4 (2)	0	18 (7)	2 (1)	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
Hypokalemia	11 (5)	3 (1)	1 (<1)	6 (2)	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;
BR-CAP=bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Postmarketing experience

Clinically significant adverse drug reactions are listed here if they have not been reported above.

The frequencies provided below reflect reporting rates of adverse drug reactions from the worldwide postmarketing experience with bortezomib. The frequencies provided below reflect reporting rates and precise estimates of incidence cannot be made. These adverse drug reactions are ranked by frequency, using the following convention: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000), very rare (<1/10,000, including isolated reports)

Table 17: Postmarketing reports of adverse reactions

Blood and lymphatic system disorders	
Disseminated intravascular coagulation	Rare
Thrombotic microangiopathy	Very rare
Cardiac disorders	
Atrioventricular block complete, cardiac tamponade	Rare
Ear and labyrinth disorders	
Deafness bilateral	Rare
Eye disorders	
Ophthalmic herpes, optic neuropathy, blindness	Rare
Chalazion/blepharitis	Rare
Gastrointestinal disorders	
Ischemic colitis, acute pancreatitis	Rare
Intestinal obstruction	Uncommon
Infections and infestations	
Herpes meningoencephalitis, septic shock	Rare
Progressive multifocal leukoencephalopathy	Very rare
Immune system disorders	
Angioedema	Rare
Anaphylactic reaction	Very rare
Nervous system disorders	
Encephalopathy, autonomic neuropathy, posterior reversible encephalopathy syndrome	Rare
Guillain-Barré syndrome, demyelinating polyneuropathy	Rare
Respiratory, thoracic and mediastinal disorders	
Acute diffuse infiltrative pulmonary disease	Rare
Pulmonary hypertension	Rare
Skin and subcutaneous tissue disorders	
Stevens-Johnson syndrome and toxic epidermal necrolysis	Very rare
Acute febrile neutrophilic dermatosis (Sweet's syndrome)	Rare

[a]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.

Overdose and Treatment:

IV doses approximately two to three times the recommended clinical dose on a mg/m^2 basis are associated with increases in heart rate, decreases in contractility, hypotension, and death. The decreased cardiac contractility and hypotension responded to acute intervention with positive inotropic or pressor agents. A slight increase in the corrected QT interval was observed at a lethal dose.

Overdosage more than twice the recommended dose in patients has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes.

There is no known specific antidote for bortezomib overdosage. 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 (see **Warnings and Precautions** and **Recommended Dose**).

Incompatibilities:
This product must not be mixed with other medicinal products except those mentioned in **Instructions for Use, Handling, and Disposal**.

STORE AT TEMPERATURE BELOW 30°C, PROTECT FROM LIGHT.

RETAIN IN THE ORIGINAL PACKAGE.

RECONSTITUTED BORTEZOMIB IN SODIUM CHLORIDE 0.9% SOLUTION FOR INJECTION STABLE FOR 8 HOURS AT TEMPERATURE 25°C.

KEEP MEDICINES OUT OF REACH OF CHILDREN.

ON MEDICAL PRESCRIPTION ONLY.

Presentation
Box, 1 vial x 3.5 mg

Nature and Contents of Container
10 mL clear tubular glass vial, type I, 20 mm neck diameter with 20mm Bromo butyl grey rubber stopper and 20mm white flip off seal. Packed in a folding box with leaflet enclosed

Registration Number: MAL xxxxx

CAUTION: CYTOTOXIC AGENT

Manufactured by:
PT FONKO INTERNATIONAL PHARMACEUTICALS
Kawasan Industri Jababeka II
Jl. Industri Selatan V Blok PP No. 7
Cikarang Selatan
Bekasi-Indonesia

Product Registration Holder:
IMEKS PHARMA SDN. BHD.
5 & 9 Jalan Udang Harimau 2,
Medan Niaga Kepong, 51200
Kuala Lumpur, Malaysia

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