Pharmacode position may change as per Supplier's m/c requirement & additional small pharma code may appear on the front / back panel

BORTEBIN P1525484

BORTEBIN P1525484

Summary of Product Characteristics

BORTEBIN

Rx Bortezomib 3.5mg Powder for Solution for Injection

1. Name of the medicinal product

BORTEBIN (Bortezomib 3.5mg Powder for Solution for Injection)

2. Qualitative and quantitative composition

Each vial contains 3.5 mg Bortezomib

After reconstitution, 1 ml of solution for subcutaneous injection contains 2.5 mg Bortezomib.

After reconstitution, 1 ml of solution for intravenous injection contains 1 mg Bortezomib.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Powder for solution for injection.

White to off-white Lyophilized cake or powder

4. Clinical particulars

4.1 Therapeutic indications

BORTEBIN (Bortezomib) for Injection is indicated as part of combination therapy for the treatment of patients with previously untreated multiple myeloma.

BORTEBIN (Bortezomib) for Injection is indicated as monotherapy for the treatment of patients with multiple myeloma who have received at least 1 prior therapy.

BORTEBIN (Bortezomib) for Injection is indicated as monotherapy for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

BORTEBIN (Bortezomib) for Injection in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.

4.2 Posology and method of administration

Bortezomib may be administered:

- Intravenously (at a concentration of 1 mg/ml) as a 3 to 5 second bolus injection or
- Subcutaneously (at a concentration of 2.5 mg/ml)

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

At least 72 hours should elapse between consecutive doses of Bortezomib.

BORTEZOMIB IS FOR INTRAVENOUS OR SUBCUTANEOUS USE ONLY.

Intrathecal administration has resulted in death.

Monotherapy

Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma

Recommended Dosage

The recommended dose of Bortezomib is 1.3 mg/m²/dose 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 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 Trials* section for a description of dose administration during the trials). At least 72 hours should elapse between consecutive doses of Bortezomib.

Dose Modification and Re-initiation of Therapy

Bortezomib therapy should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematological toxicities excluding neuropathy as discussed below (see *Special Warnings And Special Precautions For Use*). Once the symptoms of the toxicity have resolved, Bortezomib therapy may be reinitiated at a 25% reduced dose (1.3 mg/m²/dose reduced to 1.0 mg/m²/dose; 1.0 mg/m²/dose reduced to 0.7 mg/m²/dose).

Table 1 contains the recommended dose modification for the management of patients who experience Bortezomib related neuropathic pain and/or peripheral neuropathy. Severe autonomic neuropathy resulting in treatment interruption or discontinuation has been reported. Patients with pre-existing severe neuropathy should be treated with Bortezomib only after careful risk-benefit assessment.

Table 1: 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 parasthesia) 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/m² OR Change Bortezomib treatment schedule to 1.3 mg/m² once per week
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 0.7mg/m² 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.

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.

Combination Therapy

Previously Untreated Multiple Myeloma

Recommended Dosage in Combination with Melphalan and Prednisone

Bortezomib for Injection is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in Table 2. In Cycles 1- 4, Bortezomib is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, Bortezomib is administered once weekly (days 1, 8, 22 and 29). At least 72 hours should elapse between consecutive doses of Bortezomib.

Table 2: Recommended Dosage Regimen for Bortezomib when used in combination with melphalan and prednisone for Patients with Previously Untreated Multiple Myeloma

Twice Weekly Bortezomib (Cycles 1-4)

Week	1				2		3	4		5		6
Vc (1.3 mg/m²)	Day	--	--	Day	Day	Day	rest period	Day	Day	Day	Day	rest period
	1			4	8	11		22	25	29	32	
m(9 mg/m²) p(60 mg/m²)	Day	Day	Day	Day	-- --		rest period	-- --		-- --		rest period
	1	2	3	4								

Once Weekly Bortezomib (Cycles 5-9)

Week	1				2	3	4	5	6
Vc (1.3 mg/m²)	Day 1	--	--	--	Day 8	rest period	Day 22	Day 29	rest period
m (9 mg/m²) p (60 mg/m²)	Day 1	Day 2	Day 3	Day 4	--	rest period	--	--	rest period

Vc = Bortezomib m = melphalan, p=prednisone

Dose Management Guidelines for Combination Therapy with Melphalan and Prednisone

Dose modification and reinitiation of therapy when Bortezomib is administered in combination with melphalan and prednisone

Prior to initiating a new cycle of therapy:

- Platelet count should be ≥70 x 10⁹/L and the absolute neutrophil count (ANC) should be ≥ 1.0 x 10⁹/L
- Non-hematological toxicities should have resolved to Grade 1 or baseline

Table 3: Dose Modifications During Subsequent Cycles

Toxicity	Dose modification or delay
Hematological toxicity during a cycle: If prolonged Grade 4 neutropenia or thrombocytopenia or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25% in the next cycle
If platelet count ≤30 × 10⁹/L or ANC ≤0.75 x 10⁹/L on a Bortezomib dosing day (other than day 1)	Bortezomib dose should be withheld
If several Bortezomib doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	Bortezomib dose should be reduced by 1 dose level (from 1.3 mg/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²)
Grade ≥ 3 non-hematological toxicities	Bortezomib therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, Bortezomib may be reinitiated with one dose level reduction (from 1.3 mg/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²). For Bortezomib related neuropathic pain and/or peripheral neuropathy, hold and/or modify Bortezomib as outlined in Table 1.

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

Previously Untreated Mantle Cell Lymphoma Patients Not Eligible for Haematopoietic Stem Cell Transplantation

Recommended Dosage in Combination with Rituximab, Cyclophosphamide, Doxorubicin and Prednisone

For Bortezomib dosage, see Monotherapy. Six Bortezomib cycles are administered. For patients with a response first documented at Cycle 6, two additional Bortezomib cycles are recommended.

The following medicinal products are administered on Day 1 of each Bortezomib 3 week treatment cycle as intravenous infusions: rituximab at 375 mg/m², cyclophosphamide at 750 mg/m², and doxorubicin at 50 mg/m². Prednisone is administered orally at 100 mg/m² on Days 1, 2, 3, 4 and 5 of each treatment cycle.

Dose Adjustments during Treatment for Patients with Previously Untreated Mantle Cell Lymphoma

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

- Platelet count should be ≥ 100 x 10⁹/L and absolute neutrophil count (ANC) should be ≥ 1.5 x 10⁹/L
- Hemoglobin should be ≥ 8 g/dL (≥ 4.96 mmol/L)
- Non-hematologic toxicity should have recovered to Grade 1 or baseline

Bortezomib treatment must be withheld at the onset of any Grade 3 non-hematological or Grade 3 hematological toxicities, excluding neuropathy (see also section 4.4). For dose adjustments, see **Table 4** below.

Table 4: Dose Adjustments during Treatment for Patients with Previously Untreated Mantle Cell Lymphoma

Hematological toxicity	
Toxicity	**Posology modification or delay**
• ≥ Grade 3 neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, a platelet count < 10 × 10⁹/L	Bortezomib therapy should be withheld for up to 2 weeks until the patient has an ANC ≥ 0.75 × 10⁹/L and a platelet count ≥ 25 × 10⁹/L. • If, after Bortezomib has been held, the toxicity does not resolve, as defined above, then Bortezomib must be discontinued. • If toxicity resolves i.e. patient has an ANC ≥ 0.75 × 10⁹/L and a platelet count ≥ 25 × 10⁹/L, Bortezomib dose should be reduced by 1 dose level (from 1.3 mg/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²).
• If platelet counts < 25 × 10⁹/L. or ANC < 0.75 × 10⁹/L on a Bortezomib dosing day (other than Day 1)	Bortezomib dose should be withheld
Grade ≥ 3 non-hematological toxicities	Bortezomib therapy should be withheld 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/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²). For Bortezomib related neuropathic pain and/or peripheral neuropathy, hold and/or modify Bortezomib as outlined in **Table 1**.

For dosing instructions for rituximab, cyclophosphamide, doxorubicin, or prednisone, see manufacturer's prescribing information.

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 Pharmacokinetic Properties).*

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. Patients with moderate or severe hepatic impairment should be started on Bortezomib at a reduced dose of 0.7 mg/m² per injection during the first cycle, and a subsequent dose escalation to 1.0mg/m² or further dose reduction to 0.5mg/m² may be considered based on patient tolerance **(see Table 5).**

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

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

Abbreviations: SGOT = serum glutamic oxaloacetic transaminase;

AST = aspartate aminotransferase; ULN = upper limit of the normal range.

4.3 Contraindications

Hypersensitivity to the active substance, to boron or to any of the excipients listed in section 6.1.

Acute diffuse infiltrative pulmonary and pericardial disease.

When Bortezomib is given in combination with other medicinal products, refer to their Product information for additional contraindications.

4.4 Special warnings and precautions for use

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 pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral neuropathy (including ≥Grade 3) during treatment with Bortezomib Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness. In the Phase 3 study comparing Bortezomib IV vs SC the incidence of Grade ≥ 2 peripheral neuropathy events was 24% for SC and 41% for IV (p = 0.0124). Grade ≥ 3 peripheral neuropathy occurred in 6% of subjects in the SC treatment group, compared with 16% in the IV treatment group (p = 0.0264) (**Table 9**). Therefore, patients with pre-existing 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 *Posology and Method of Administration*). Following dose adjustments, improvement in or resolution of peripheral neuropathy was reported in 51% of patients with ≥Grade 2 peripheral neuropathy in the single agent phase 3 multiple myeloma study of Bortezomib vs dexamethasone. Improvement in or resolution of peripheral neuropathy was reported in 73% of patients who discontinued due to Grade 2 neuropathy or who had ≥Grade 3 peripheral neuropathy in the phase 2 multiple myeloma studies.

The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

Hypotension

In phase 2 and 3 single agent multiple myeloma studies, the incidence of hypotension (postural, orthostatic, and hypotension Not Otherwise Specified) was 11% to 12%. 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 *Undesirable 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 the single agent phase 3 multiple myeloma study of Bortezomib vs dexamethasone, the incidence of any treatment-emergent cardiac disorder was 15% and 13% respectively. The incidence of heart failure events (acute pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock, pulmonary edema) was similar in the Bortezomib and dexamethasone groups, 5% and 4%, respectively.

There have been isolated cases of QT-interval prolongation in clinical studies; 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 re-challenge 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. A higher proportion of these events have been reported in Japan. In the event of new or worsening pulmonary symptoms, a prompt comprehensive diagnostic evaluation should be performed and patients treated appropriately.

In a clinical trial, two patients given high-dose cytarabine (2g/m² per day) by continuous infusion with daunorubicin and Bortezomib for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy. Therefore, this specific regimen with concomitant administration with high-dose cytarabine (2g/m² per day) by continuous infusion over 24 hours is not recommended.

There have been rare reports of pulmonary hypertension associated with Bortezomib administration in the absence of left heart failure or significant pulmonary disease.

Laboratory Tests

Complete blood counts (CBC) should be frequently monitored during treatment with Bortezomib.

Thrombocytopenia/Neutropenia

Bortezomib is associated with thrombocytopenia and neutropenia (see *Undesirable 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 the 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/µL (see *Posology and Method of Administration* and *Undesirable Effects*). There have been reports of gastrointestinal and intracerebral hemorrhage in association with Bortezomib. Transfusions 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 6**. The incidence of significant bleeding events (≥ Grade 3) was similar on both the Bortezomib (4%) and dexamethasone (5%) arms.

Table 6: 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/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] A baseline platelet count of 50,000/µL 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 (VcR-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 VcR-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 VcR-CAP arm; there was 1 bleeding event in the R-CHOP arm. 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. Colony-stimulating factor support was provided at a rate of 78% in the VcR-CAP arm and 61% in the R-CHOP arm.

Gastrointestinal Adverse Events

Bortezomib treatment can cause nausea, diarrhea, constipation, and vomiting (see *Undesirable 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. 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 *Posology and Method of Administration* and *Pharmacokinetic Properties*).

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.

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.

Renal Impairment

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

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 hypoglycemic.

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.

Thrombotic Microangiopathy

Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/haemolytic uremic syndrome (TTP/HUS), have been reported in the postmarketing setting in patients who received Bortezomib. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop Bortezomib and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting Bortezomib. The safety of reinitiating Bortezomib therapy in patients previously experiencing TTP/HUS is not known.

4.5 Interaction with other medicinal products and other forms of interaction

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 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 assessed. There was no significant effect on Bortezomib b 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, anti-virals, isoniazid, nitrofurantoin, or statins), or with a decrease in blood pressure.

Drug Laboratory Test Interactions

None known.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Male and female patients of childbearing potential must use effective contraceptive measures during and for 3 months following treatment.

Pregnancy

No clinical data are available for Bortezomib with regard to exposure during pregnancy. The teratogenic potential of Bortezomib has not been fully investigated.

In non-clinical studies, Bortezomib had no effects on embryonal/foetal development in rats and rabbits at the highest maternally tolerated doses. Animal studies to determine the effects of Bortezomib on parturition and post-natal development were not conducted (see section 5.3). Bortezomib should not be used during pregnancy unless the clinical condition of the woman requires treatment with Bortezomib.

If Bortezomib is used during pregnancy, or if the patient becomes pregnant while receiving this medicinal product, the patient should be informed of potential for hazard to the foetus.

Breast-feeding

It is not known whether Bortezomib is excreted in human milk. Because of the potential for serious adverse reactions in breast-fed infants, breast-feeding should be discontinued during treatment with Bortezomib.

Fertility

Fertility studies were not conducted with Bortezomib (see section 5.3).

4.7 Effects on ability to drive and use machines

Bortezomib may have a moderate influence on the ability to drive and use machines. Bortezomib may be associated with fatigue very commonly, dizziness commonly, syncope uncommonly and orthostatic/postural hypotension or blurred vision commonly. Therefore, patients must be cautious when driving or using machines and should be advised not to drive or operate machinery if they experience these symptoms (see section 4.8).

4.8 Undesirable 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/m². 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/m² or 1.3 mg/m² (M34100-024).

Table 7: Bortezomib Adverse Drug Reactions in Phase 2 and Phase 3 Relapsed/Refractory Multiple Myeloma Studies

	Study No.	
MedDRA System Organ Class Preferred Term	039 (N=331)	024/025 (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%)
	Study No.	
MedDRA System Organ Class Preferred Term	039 (N=331)	024/025 (N=228[a])
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	35 (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	8 (2%)	2 (<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%)
Rhinorrhoea	4 (1%)	14 (6%)
Hemoptysis	3 (<1%)	1 (<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%)
	Study No.	
MedDRA System Organ Class Preferred Term	039 (N=331)	024/025 (N=228[a])
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/m²
[b] *includes fatal outcome*
[c] *A study of* Bortezomib *at the recommended dose of* 1.3 mg/m² *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"*

Serious Adverse Events (SAEs) and Events Leading to Treatment Discontinuation in the Phase 3 Multiple Myeloma Study

Serious adverse events are defined as any event, regardless of causality, 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 144 (44%) patients from the Bortezomib treatment arm experienced an SAE during the study. The most commonly reported SAEs in the Bortezomib treatment arm were pyrexia (6%), diarrhea (5%), dyspnea and pneumonia (4%), and vomiting (3%). 84 (25%) of 331 patients in the Bortezomib treatment group were discontinued from treatment due to adverse events assessed as drug-related by the investigators. Among the 331 Bortezomib treated patients, the most commonly reported drug-related event leading to discontinuation was peripheral neuropathy (8%). Four deaths were considered to be Bortezomib related in the phase 3 multiple myeloma study: 1 case each of cardiogenic shock, respiratory insufficiency, congestive heart failure and cardiac arrest.

Non-randomized Phase 2 Clinical Studies

Serious Adverse Events (SAEs)

A total of 113 (50%) of 228 patients in the phase 2 studies experienced SAEs during the studies. The most commonly reported SAEs included pyrexia and pneumonia (each 7%), diarrhea (6%), vomiting and dehydration (each 5%) and nausea (4%).

In phase 2 clinical studies, adverse events thought by the investigator to be drug-related and leading to discontinuation occurred in 22% of patients. The reasons for discontinuation included peripheral neuropathy (5%), thrombocytopenia (4%), and diarrhea and fatigue (each 2%).

Two deaths were reported and considered by the investigator to be possibly related to study drug:

1 case pulmonary arrest and 1 case of respiratory failure.

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/m². This was a randomized, comparative study of Bortezomib IV vs SC in 222 patients with relapsed multiple myeloma.

Table 8: Incidence of Bortezomib Adverse Drug Reactions reported in ≥ 10% of patients in the Phase 3 Relapsed Multiple Myeloma Study comparing Bortezomib IV and SC

	--------------- IV --------------- (N = 74)			--------------- SC -------------- (N = 147)		
	Toxicity Grade, n (%)			Toxicity Grade, n (%)		
MedDRA System Organ Preferred Term	Total n (%)	3	≥ 4	Total n (%)	3	≥ 4
Blood and lymphatic system disorders						
Anaemia	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
Diarrhoea	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 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						
Dyspnoea	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 9: 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 --------------- (N = 74)			--------------- SC -------------- (N = 147)		
	------- Category, n (%) -------			------- Category, n (%) -------		
MedDRA System Organ Class 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						
Diarrhoea (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 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.

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 IV (1.3 mg/m²) in combination with melphalan (9 mg/m²) and prednisone (60 mg/m²) in a prospective phase 3 study.

Table 10: Treatment-Emergent Drug-Related Adverse Events reported in ≥ 10% of patients treated with Bortezomib IV in combination with melphalan and prednisone

	-------------- Vc-MP -------------- (n=340)			---------------- MP --------------- (n=337)		
	Toxicity Grade, n (%)			Toxicity Grade, n (%)		
MedDRA System Organ Class MedDRA High Level Term	Total n (%)	3	≥4	Total 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

Physicians 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 VcMP compared with MP (14% vs 4% respectively). Antiviral prophylaxis was administered to 26% of the patients in the VcMP arm. The incidence of herpes zoster among patients in the VcMP treatment group was 17% for patients not administered antiviral prophylaxis compared to 3% for patients administered antiviral prophylaxis.

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/m². 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 11 describes safety data from 240 patients with previously untreated mantle cell lymphoma who received Bortezomib 1.3 mg/m²) administered IV in combination with rituximab (375 mg/m²), cyclophosphamide (750 mg/m²), doxorubicin (50 mg/m²), and prednisone (100 mg/m²) (VcR-CAP) in a prospective randomized study.

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

Infections were reported for 31% of patients in the VcR-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 (VcR-CAP 8% versus R-CHOP 5%).

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

Table 11: Most Commonly Reported Adverse Reactions (≥ 5%) with Grades 3 and ≥ 4 Intensity in the Mantle Cell Lymphoma Study of VcR-CAP versus R-CHOP (N=482) (Study LYM-3002)

	VcR-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)
Anaemia	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
Hypoaesthesia	14 (6)	3 (1)	0	13 (5)	0	0
Paraesthesia	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
Oedema 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)
Diarrhoea	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						
Hyperglycaemia	10 (4)	1 (< 1)	0	17 (7)	10 (4)	0
Decreased appetite	36 (15)	2 (1)	0	15 (6)	1 (< 1)	0
Hypokalaemia	11 (5)	3 (1)	1 (< 1)	6 (2)	1 (< 1)	0
Vascular disorders						
Hypertension	15 (6)	1 (< 1)	0	6 (2)	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.

Post-Marketing Experience

[illegible]

Table 12: Post-marketing 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

Black A/s: 420 x 900 mm

AUROBINDO Packaging Development	Product Name: BORTEBIN Injection	Component: Leaflet	Item Code: P1525484	Date & Time: 19.10.2021 & 4:00 PM
	Customer / Country: Eugia_Pharma_Singapore	Version No.: 08	Reason Of Issue: NEW	Reviewed / Approved by
Team Leader: Sravan	Dimensions: 420 x 900 mm	No. of Colours : 01		
Initiator: Ramesh				
Artist: Vision Graphic Designers	Pharmacode: 25484	25484		
Additional Information :				Sign / Date

Gastrointestinal disorders	
Ischemic colitis, acute pancreatitis	Rare
Intestinal obstruction	Uncommon
Infections and infestations	
Herpes meningoencephalitis, septic shock	Rare
Progressive multifocal leukoencephalopathy [a]	Very rare
Immune system disorders	
Angioedema	Rare
Anaphylactic reaction	Very rare
Nervous system disorders	
Encephalopathy, autonomic neuropathy, posterior reversible encephalopathy syndrome	Rare
Respiratory, thoracic and mediastinal disorders	
Acute diffuse infiltrative pulmonary disease (see Special Warnings and Special Precautions for Use)	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.

Hepatitis B Virus (HBV) reactivation and infection

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

4.9 Overdose

Cardiovascular safety pharmacology studies in monkeys and dogs showed that IV doses approximately two to three times the recommended clinical dose on a mg/m² 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. In dog studies, a slight increase in the corrected QT interval was observed at a lethal dose. In monkeys, doses of 3.0 mg/m² 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.

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 Special Warnings and Special Precautions for Use and Posology and Method of Administration).

5.0 Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XG01.

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.

Data from in vitro, ex vivo, and animal models with bortezomib suggest that it increases osteoblast differentiation and activity and inhibits osteoclast function. These effects have been observed in patients with multiple myeloma affected by an advanced osteolytic disease and treated with bortezomib.

Clinical Studies

Phase 2 Clinical Studies in Relapsed Multiple Myeloma

The safety and efficacy of bortezomib IV in relapsed multiple myeloma were evaluated in an open-label, single-arm, multicenter study of 202 patients who had received at least 2 prior therapies and demonstrated disease progression on their most recent therapy. The median number of prior therapies was 6. Baseline patient and disease characteristics are summarized in **Table 13.**

An IV bolus injection of bortezomib 1.3 mg/m²/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 8 treatment cycles. The study employed dose modifications for toxicity (see Posology and Method of Administration). Patients who experienced a response to bortezomib were allowed to continue bortezomib treatment in an extension study.

Table 13: Summary of Patient Population and Disease Characteristicsin a Phase 2 Multiple Myeloma Study[a]

	N = 202
Patient Characteristics	
Median age in years (range)	59 (34, 84)
Gender: Male/female	60% / 40%
Race: Caucasian/black/other	81% / 10% /8%
Karnofsky Performance Status score ≤70	20%
Hemoglobin <100 g/L	44%
Platelet count <75 x 10⁹/L	21%
Disease Characteristics	
Type of myeloma (%): IgG/IgA/Light chain	60% / 24% / 14%
Median β2-microglobulin (mg/L)	3.5
Median creatinine clearance (mL/min)	73.9
Abnormal cytogenetics Chromosome 13 deletion	35% 15%
Median Duration of Multiple Myeloma Since Diagnosis in Years	4.0
Previous Therapy	
Any prior steroids, e.g., dexamethasone, VAD	99%
Any prior alkylating agents, e.g., MP, VBMCP	92%
Any prior anthracyclines, e.g., VAD, mitoxantrone	81%
Any prior thalidomide therapy	83%
Received at least 2 of the above	98%
Received at least 3 of the above	92%
Received all 4 of the above	66%
Any prior stem cell transplant/other high-dose therapy	64%
Prior experimental or other types of therapy	44%

[a] Based on number of patients with baseline data available

Responses to Bortezomib alone are shown in **Table 14**. Response rates to Bortezomib alone were determined by an independent review committee (IRC) based on criteria published by Bladé and others. Complete response required <5% plasma cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test (IF⁻). Response rates using the Southwest Oncology Group (SWOG) criteria are also shown. SWOG response required a ≥75% reduction in serum myeloma protein and/or ≥90% urine protein. A total of 188 patients were evaluable for response; 9 patients with nonmeasurable disease could not be evaluated for response by the IRC, and 5 patients were excluded from the efficacy analyses because they had had minimal prior therapy.

Ninety-eight percent of study patients received a starting dose of 1.3 mg/m² administered IV. Twenty-eight percent of these patients received a dose of 1.3 mg/m² throughout the study, while 33% of patients who started at a dose of 1.3 mg/m² had to have their dose reduced during the study. Sixty-three percent of patients had at least one dose held during the study. In general, patients who had a confirmed CR received 2 additional cycles of Bortezomib treatment beyond confirmation. It was recommended that responding patients receive up to 8 cycles of Bortezomib therapy. The mean number of cycles administered was 6.

The median time to response was 38 days (range 30 to 127 days).

The median survival of all patients enrolled was 16 months (range <1 to 18+ months).

Table 14: Summary of Disease Outcomes in a Phase 2 Multiple Myeloma Study

Response Analyses (Bortezomib.monotherapy) N = 188	N (%)	(95% CI)
Overall Response Rate (Bladé) (CR + PR)	52 (27.7%)	(21, 35)
Complete Response (CR)[a]	5 (2.7%)	(1, 6)
Partial Response (PR)[b]	47 (25%)	(19, 32)
Clinical Remission (SWOG)[c]	33 (17.6%)	(12, 24)
Kaplan-Meier Estimated Median Duration of Response (95% CI)	365 Days	(224, NE)

[a] Complete Response required < 5% plasma cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test (IF⁻).
[b] Partial Response 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, stable bone disease and calcium.
[c] Clinical Remission (SWOG) required ≥75% reduction in serum myeloma protein and/or ≥90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.

Of the 202 patients enrolled, 35% were 65 years of age or older. Nineteen percent (19%) of patients aged 65 years or older experienced CR or PR.

In this study, the response rate to Bortezomib, based on a univariate analysis, was independent of the number and types of prior therapies. There was a decreased likelihood of response in patients with either >50% plasma cells or abnormal cytogenetics in the bone marrow. Responses were seen in patients with chromosome 13 abnormalities.

A small dose-response study was performed in 54 patients with multiple myeloma who received a 1.0 mg/m²/dose or a 1.3 mg/m²/dose twice weekly for two out of three weeks. A single complete response was seen at each dose, and there were overall (CR + PR) response rates of 30% (8/27) at 1.0 mg/m² and 38% (10/26) at 1.3 mg/m².

Patients who did not obtain an optimal response to therapy with Bortezomib alone (progressive or stable disease after 2 or 4 cycles, respectively) were able to receive high-dose dexamethasone in conjunction with Bortezomib i.e., 40 mg dexamethasone with each dose of Bortezomib administered orally as 20 mg on the day of and 20 mg the day after Bortezomib administration, (i.e., Days 1, 2, 4, 5, 8, 9, 11, and 12), thus 160 mg over 3 weeks. A total of 74 patients were administered dexamethasone in combination with Bortezomib and were assessed for response. Eighteen percent (13/74) of patients achieved or had an improved response (CR 11% or PR 7%) with combination treatment.

Randomized, Open-Label, Phase 3 Clinical Study in Relapsed Multiple Myeloma comparing Bortezomib to 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 β2-microglobulin levels (≤2.5 mg/L versus >2.5 mg/L).

Baseline patient and disease characteristics are summarized in **Table 15**.

Table 15: Summary of Baseline Patient and Disease Characteristics in the Phase 3 Trial

Patient Characteristics Median age in years (range)	**Bortezomib N=333** 62.0 (33, 84)	**Dexamethasone N=336** 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 10⁹/L	6%	4%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	60% / 23% / 12%	59% / 24% / 13%
Median β2-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%
All Patients	(N=333)	(N=336)
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. Within each 3-week treatment cycle, Bortezomib 1.3 mg/m²/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/m²/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 *Posology and Method of Administration*).

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. At this time of study termination, a final statistical analysis was performed. Due to this early termination of the study, the median duration of follow-up for surviving patients (n=534) is limited to 8.3 months.

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 phase 3 multiple myeloma study are presented in **Table 16**. Response and progression were assessed using the European Group for Blood and Marrow Transplantation (EBMT) criteria.[1] 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 16: Summary of Efficacy Analyses in the Phase 3 Study

	All Patients		**1 Prior Line of Therapy**		**> 1 Prior Line of Therapy**	
	Bortezomib	**Dex**	**Bortezomib**	**Dex**	**Bortezomib**	**Dex**
Efficacy Endpoint	**n=333**	**n=336**	**n=132**	**n=119**	**n=200**	**n=217**
Time to Progression Events n (%)	147 (44)	196 (58)	55 (42)	64 (54)	92 (46)	132 (61)
Median [a] (95% CI)	6.2 mo (4.9, 6.9)	3.5 mo (2.9, 4.2)	7.0 mo (6.2, 8.8)	5.6 mo (3.4, 6.3)	4.9 mo (4.2, 6.3)	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	
Median Response Duration						
CR[f]	9.9 mo	NE[i]	9.9 mo	NE	6.3 mo	NA[j]
nCR[f]	11.5 mo	9.2 mo	NE	NE	11.5 mo	9.2 mo
CR + PR[f]	8.0 mo	5.6 mo	8.1 mo	6.2 mo	7.8 mo	4.1 mo

[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.
[i] Not Estimable.
[j] Not Applicable, no patients in category.

Randomized, Open-Label Clinical Study in Relapsed Multiple Myeloma comparing Bortezomib IV and SC

An open-label, randomized, phase 3 non-inferiority study compared the efficacy and safety of the subcutaneous administration (SC) of Bortezomib versus the intravenous administration (IV). This study included 222 patients with relapsed multiple myeloma, who were randomized in a 2:1 ratio to receive 1.3 mg/m² of Bortezomib by either the SC or IV 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 dexamethasone 20 mg daily on the day of and after Bortezomib administration. Patients with baseline grade ≥ 2 peripheral neuropathy or platelet counts < 50000/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 beta2-microglobulin and albumin levels; Stages I, II, or III)

Baseline patient and disease characteristics are summarized in **Table 17**.

Table 17: Summary of Baseline Patient and Disease Characteristics in the Phase 3 Trial of Bortezomib IV vs SC

Patient Characteristics	**IV N = 74**	**SC N = 148**
Median age in years (range)	64.5 (38,86)	64.5 (42,88)
Gender: male/female	64% / 36%	50% / 50%
Race: Caucasian/Asian	96% / 4%	97% / 3%
Karnofsky performance status score ≤70	16%	22%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	72% / 19% / 8%	65% / 26% / 8%
ISS staging[a] I/II/III (%)	27/41/32	27/41/32
Median β2-microglobulin (mg/l)	4.25	4.20
Median albumin (g/l)	3.60	3.55
Creatinine clearance ≤ 30 ml/min [n (%)]	2 (3%)	5 (3%)
Median Duration of Multiple Myeloma Since Diagnosis (Years)	2.93	2.68
Number of Prior Therapeutic Lines of Treatment		
1 prior line	65%	62%
> 1 prior line	35%	38%

[a] ISS Staging is derived from baseline central laboratory data.

This study met its primary objective of non-inferiority for response rate (CR + PR) after 4 cycles of single agent Bortezomib for both the SC and IV routes, 42% in both groups. In addition, secondary response-related and time to event related efficacy endpoints showed consistent results for SC and IV administration (**Table 18**).

Table 18: Summary of efficacy analyses for the SC administration of Bortezomib compared to IV

Response-Evaluable Population[a] Response Rate at 4 cycles	**IV Bortezomib**		**SC Bortezomib**
	N = 73		**N = 145**
ORR (CR+PR)	31 (42)		61 (42)
p-value[b]		0.00201	
CR n (%)	6(8)		9(6)
PR n (%)	25(34)		52(36)
nCR n (%)	4(5)		9(6)
Response Rate at 8 cycles			
ORR (CR+PR)	38(52)		76(52)
p-value[b]		0.0001	
CR n (%)	9 (12)		15 (10)
PR n (%)	29(40)		61(42)
nCR n (%)	7(10)		14(10)
Intent to Treat Population[c]	**N = 74**		**N = 148**
Median Time to Progression, months	9.4		10.4
(95% CI)	(7.6,10.6)		(8.5,11.7)
Hazard ratio (95% CI)[d]		0.839 (0.564,1.249)	
p-value (d)		0.38657	
Progression Free Survival, months	8.0		10.2
(95% CI)	(6.7,9.8)		(8.1,10.8)
Hazard ratio (95% CI)[d]		0.824 (0.574,1.183)	
p-value[e] **1-year Overall Survival (%)[f]**	76.7	0.295	72.6
(95% CI)	(64.1,85.4)		(63.1,80.0)

[a] All randomized subjects who received at least 1 non-zero dose of study medication and had measurable disease at study entry
[b] P-value is for the non-inferiority hypothesis that the SC arm retains at least 60% of the response rate in the IV arm.
[c] 222 subjects were enrolled into the study; 221 subjects were treated with Bortezomib
[d] Hazards ratio estimate is based on a Cox model adjusted for stratification factors: ISS staging and number of prior lines.
[e] Log-rank test adjusted for stratification factors: ISS staging and number of prior lines.
[f] Median duration of follow up is 11.8 months

Table 19 presents a cross-tabulation summary of best response by algorithm after 4 cycles versus after 8 cycles for patients who received dexamethasone. Eighty-two subjects in the SC treatment group and 39 subjects in the IV treatment group received dexamethasone after cycle 4.

Dexamethasone had a similar effect on improvement of response on both treatment arms:

- 30% (SC) and 30% (IV) of patients with no response at end of Cycle 4 obtained a response later.
- 13% (SC) and 13% (IV) of patients with PR at end of Cycle 4 obtained a CR later.

Table 19: Cross-tabulation of Summary of Best Response After 4 Cycles vs. After 8 Cycles for patients who received dexamethasone

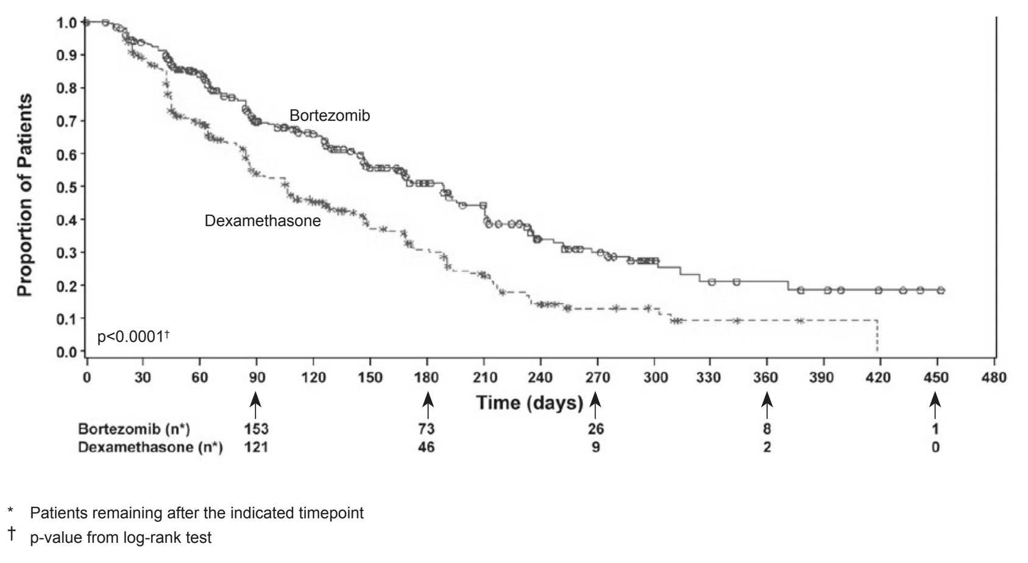
	-------------------- Best Response After 8 Cycles -------------------- (N = 121)			
Treatment Group	Total	-------------------- Category, n (%) --------------------		
Cycle 4 Best Response[a]	n (%)	CR	PR	Non-responder
IV	39 (32)	3 (8)	20 (51)	16 (41)
CR	1 (1)	1 (100)	0	0
PR	15 (12)	2 (13)	13 (87)	0
Non-responder	23 (19)	0	7 (30)	16 (70)
SC	82 (68)	8 (10)	41 (50)	33 (40)
CR	4 (3)	4 (100)	0	0
PR	31 (26)	4 (13)	27 (87)	0
Non-responder	47 (39)	0	14 (30)	33 (70)

[a] Response assessment by validated computer algorithm. This algorithm incorporates a consistent assessment of all data required for response by the modified EBMT criteria.

Relative to previously reported outcomes, the ORR after 8 cycles of treatment (52% in both treatment groups) and time to progression (median 10.4 months and 9.4 months in SC and IV treatment groups, respectively), including the effect of the addition of dexamethasone from cycle 5 onwards, were higher than observed in prior registration study with single agent IV Bortezomib 38% ORR and median TTP of 6.2 months for the Bortezomib arm). Time to Progression and ORR was also higher compared to the subgroup of patients that received only 1 prior line of therapy (43% ORR and median TTP of 7.0 months) (**Table 16**).

TTP was statistically significantly longer on the Bortezomib arm (see Figure 1).

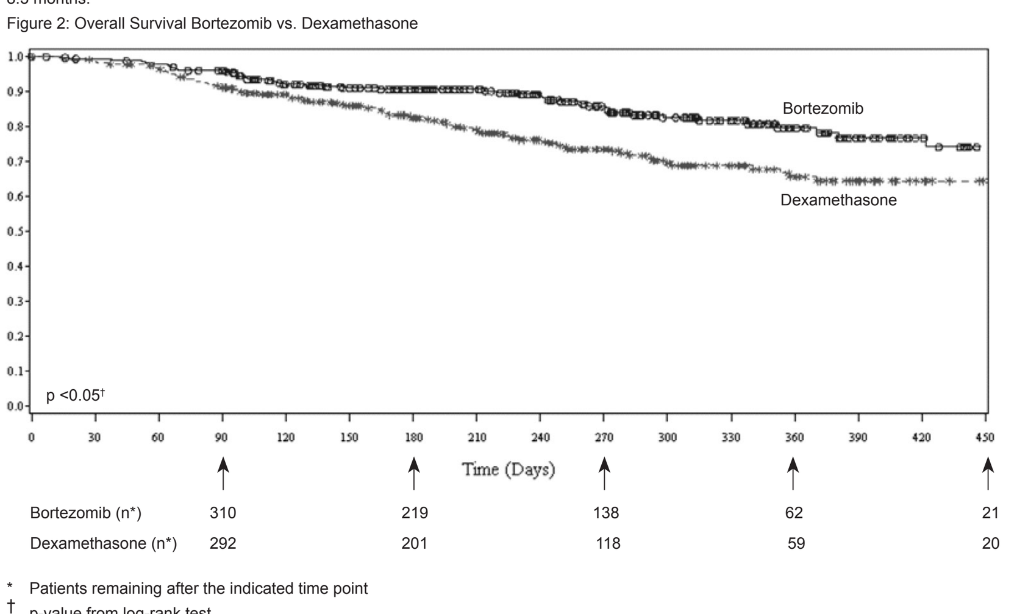
Figure 1: Time to Progression Bortezomib vs. Dexamethasone



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

As shown in Figure 2, Bortezomib had a significant survival advantage relative to dexamethasone (p<0.05). The median follow-up was 8.3 months.

Figure 2: Overall Survival Bortezomib vs. Dexamethasone



* Patients remaining after the indicated time point
† 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 β2-microglobulin levels at baseline.

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/m² or 1.3 mg/m² 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/m² and 38% (10/26) at 1.3 mg/m².

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 *Undesirable Effects*).

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 (1.3 mg/m²) in combination with melphalan (9 mg/m²) and prednisone (60 mg/m²) resulted in improvement in time to progression (TTP) when compared to melphalan (9 mg/m²) and prednisone (60 mg/m²) in patients with previously untreated multiple myeloma. This study included patients who were not candidates for stem cell transplant. Treatment was administered for a maximum of 9 cycles (approximately 54 weeks) and was discontinued early for disease progression or unacceptable toxicity. Baseline demographics and patient characteristics are summarized in **Table 20**.

Table 20: Summary of Baseline Patient and Disease Characteristics in the VISTA Study

Patient Characteristics	**VMP N=344**	**MP N=338**
Median age in years (range)	71.0 (57, 90)	71.0 (48, 91)
Gender: male/female	51% / 49%	49% / 51%
Race: Caucasian/asian/black/other	88% / 10% / 1% / 1%	87% / 11% / 2% / 0%
Karnofsky performance status score ≤70	35%	33%
Hemoglobin <100 g/L	37%	36%
Platelet count <75 x 10⁹/L	<1%	1%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	64% / 24% / 8%	62% / 26% / 8%
Median β2-microglobulin (mg/L)	4.2	4.3
Median albumin (g/L)	33.0	33.0
Creatinine clearance ≤30 mL/min [n (%)]	20 (6%)	16 (5%)

At the time of a pre-specified interim analysis, the primary endpoint, time to progression, was met and patients in the MP arm were offered VcMP treatment. Median follow-up was 16.3 months. The final survival update was performed with a median duration of follow-up at 60.1 months. A statistically significant survival benefit in favor of the VcMP treatment group was observed (HR=0.695; p=0.00043) despite subsequent therapies that included Bortezomib based regimens. The median survival in MP treatment group has been estimated at 43.1 months, and the median survival on the VcMP treatment group has been estimated at 56.4 months. Efficacy results are presented in **Table 21**.

Table 21: Summary of Efficacy Analyses in the VISTA study

Efficacy Endpoint	**VMP n=344**	**MP n=338**
Time to Progression – Events n (%)	101 (29)	152 (45)
Median[a] (95% CI)	20.7 mo (17.6, 24,7)	15.0 mo (14.1, 17.9)
Hazard ratio[b] (95% CI)	0.54 (0.42, 0.70)	
p-value [c]	0.000002	
Progression-free Survival Events n (%)	135 (39)	190 (56)
Median[a] (95% CI)	18.3 mo (16.6, 21.7)	14.0 mo (11.1, 15.0)
Hazard ratio[b] (95% CI)	0.61 (0.49, 0.76)	
p-value [c]	0.00001	
Overall Survival[h] Events (deaths) n (%)	176 (51.2)	211 (62.4)
Median[a] (95% CI)	56.4 mo (52.8, 60.9)	43.1 mo (35.3, 48.3)
Hazard ratio[b] (95% CI)	0.695 (0.567, 0.852)	
p-value [c]	0.00043	
Response Rate population[e] n = 668	n=337	n=331
CR[f] n (%)	102 (30)	12 (4)
PR[f] n (%)	136 (40)	103 (31)
nCR n (%)	5 (1)	0
CR + PR[f] n (%)	238 (71)	115 (35)
p-value[d]	$<10^{-10}$	
Reduction in Serum M-protein population[g] n=667	n=336	n=331
>=90% n (%)	151 (45)	34 (10)
Time to First Response in CR + PR		
Median	1.4 mo	4.2 mo
Median[a] Response Duration		
CR[f]	24.0 mo	12.8 mo
CR + PR[f]	19.9 mo	13.1 mo
Time to Next Therapy Events n (%)	224 (65.1)	260 (76.9)
Median[a] (95% CI)	27.0 mo (24.7, 31.1)	19.2 mo (17.0, 21.0)
Hazard ratio[b] (95% CI)	0.557 (0.462, 0.671)	
p-value [c]	(< 0.000001)	

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 VMP
[c] Nominal p-value based on the stratified log-rank test adjusted for stratification factors: beta2-microglobulin, albumin, and region
[d] p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors
[e] Response population includes patients who had measurable disease at baseline
[f] EBMT criteria
[g] All randomized patients with secretory disease
[h] Survival update based on a median duration of follow-up at 60.1 months
NE: Not estimable

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 [M34103-053 (PINNACLE)] of 155 patients with progressive disease who had received at least 1 prior therapy. Bortezomib was administered at the recommended dose of 1.3 mg/m². The median number of cycles administered across all patients was 4 (range 1-17); and 8 in responding patients. Response rates to Bortezomib are described in **Table 22**.

Table 22: Summary of Disease Outcomes in a Phase 2 Mantle Cell Lymphoma Study

[a]Response Analyses (N = 141)	N (%)	95% CI
Overall Response Rate (IWRC) (CR + CRu + PR)	47 (33)	(26, 42)
Complete Response (CR + CRu)	11 (8)	(4, 14)
CR	9 (6)	(3, 12)
Cru	2 (1)	(0, 5)
Partial Response (PR)	36 (26)	(19, 34)
Time to Event Analyses	Median	95% CI
Kaplan-Meier Estimated Duration of Response		
CR + CRu + PR (N = 47)	9.2 months	(4.9, 13.5)
CR + CRu (N = 11)	13.5 months	(13.5, NE)
Kaplan-Meier Estimated Time to Progression (N = 155)	6.2 months	(4.0, 6.9)
**Kaplan-Meier Estimated Treatment Free Interval, CR + CRu (N = 11)	13.8 months	(13.4, NE)
Median Time to Next Treatment CR + CRu + PR (N = 47) CR+CRu (N=11)	12.7 months 19.4 months	(9.33, NE) (17.8, NE)

[a] Based on International Response Workshop Criteria (IRWC).

CRu = Complete Response unconfirmed NE=not estimable**Additional analyses

With a median duration of follow-up of more than 13 months in surviving patients, the median survival had not yet been reached and the Kaplan-Meier estimate of 1-year survival was 69%. The Kaplan-Meier estimate of 1-year survival was 94% in responders and 100% in those achieving CR or CRu.

Previously Untreated Mantle Cell Lymphoma

A randomized, open-label, Phase 3 study (LYM-3002) was conducted in 487 adult patients with previously untreated mantle cell lymphoma (Stage II, III or IV) 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 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/m²) administered intravenously on Days 1, 4, 8, and 11 (rest period Days 12-21); rituximab (375 mg/m²) on Day 1; cyclophosphamide (750 mg/m²) on Day 1; doxorubicin (50 mg/m²) on Day 1; and prednisone (100 mg/m²) 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 given.

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, 35% of patients had an International Prognostic Index (IPI) score of 3 (high-intermediate) and 74% had Stage IV disease. 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 majority of the patients in both groups received 6 or more cycles of treatment, 83% in the R-CHOP group and 84% in the VcR-CAP group.

The primary efficacy endpoint was progression-free survival based on Independent Review Committee (IRC) assessment. Secondary endpoints included, time to progression (TTP), time to next anti-lymphoma treatment (TNT), duration of treatment free interval (TFI), overall response rate (ORR) and complete response (CR/CRu) rate, overall survival (OS) and response duration. The response criteria used to assess efficacy were based on the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma (IWRC)[6].

A statistically significant benefit in favor of the VcR-CAP treatment group was observed for PFS, TTP, TNT, TFI overall complete response rate, and overall survival. At a median follow-up of 40 months, a 59% improvement in the primary endpoint of PFS (Hazard Ratio [HR]=0.63; p < 0.001) was observed in the Vc-RCAP group (median=24.7 months) as compared to the R-CHOP group (median=14.4 months). The median duration of complete response was more than double in the VcR-CAP group (42.1 months) compared with the R-CHOP group (18 months) and the duration of overall response was 21.4 months longer in the VcR-CAP group. At a median follow-up of 40 months, median OS (56.3 months in the R-CHOP group, and not reached in the VcR-CAP group) favored the VcR-CAP group, (estimated HR=0.80; p=0.173). There was a trend towards prolonged overall survival favoring the VcR-CAP group; the estimated 4-year survival rate was 53.9% in the R-CHOP group and 64.4% in the VcR-CAP group.

The final analysis for OS was performed after a median follow-up of 82 months. Median OS in the VR-CAP group was 90.7 months, almost three years more than the OS achieved in the R- CHOP group, which was 55.7 months (HR=0.66; p=0.001).

Efficacy results are presented in **Table 23**.

Table 23: Summary of Efficacy Outcomes in a Phase 3 Mantle Cell Lymphoma Study in Previously Untreated Patients (LYM-3002)

Efficacy endpoint	**VcR-CAP**	**R-CHOP**	
n: ITT patients	243	244	
Progression free survival (IRC)[a]			
Events n (%)	133 (54.7)	165 (67.6)	HR[d] (95% CI)=0.63 (0.50;0.79)
Median[c] (95% CI) (months)	24.7 (19.8; 31.8)	14.4 (12; 16.9)	p-value[e] < 0.001
Progression free survival (Investigator)[b]			
Events n (%)	128 (52.7)	179 (73.4)	HR[d] (95% CI)=0.51 (0.41; 0.65) p-value[e] < 0.001
Median[c] (95% CI) (months)	30.7 (25.1; 37.3)	16.1 (14.0; 18.4)	
Time to Progression[a]			
Events n (%)	114 (46.9)	148 (60.7)	HR[d] (95% CI)=0.58 (0.45;0.74) p-value[e] < 0.001
Median[c] (95% CI) (months)	30.5 (22.9; 40.9)	16.1(13.7;18.1)	
Time to Next Anti-lymphoma Therapy			
Events n (%)	94 (38.7)	145 (59.4)	HR[d] (95% CI)=0.50 (0.38;0.65) p-value[e] < 0.001
Median[c] (95% CI) (months)	44.5 (38.8; NE)	24.8 (22.1; 27.5)	
Treatment Free Interval			
n :All Treated Patients	240	242	
Events n (%)	93 (38.8)	145 (59.9)	HR[d] (95% CI)=0.50 (0.38; 0.65) p-value[e] < 0.001
Median[c] (95% CI) (months)	40.6 (33.6; NE)	20.5 (17.8; 22.8)	
Overall survival at a median follow-up of 82 months			
n :ITT patients	243	244	
Events n (%)	103 (42.4)	138 (56.6)	HR[d] (95% CI)=0.66 (0.51; 0.85) p-value[e] =0.001
Median[c] (95% CI) (months)	90.7 (71.4; NE)	55.7 (47.2; 68.9)	
Response Rate			
n : response-evaluable patients	229	228	
Overall complete response (CR+CRu)[h] n(%)	122 (53.3)	95(41.7)	OR[f] (95% CI)=1.688 (1.148; 2.481) p-value[g] =0.007
Overall radiological response (CR+CRu+PR) [i] n(%)	211 (92.1)	204 (89.5)	OR[f] (95% CI)=1.428 (0.749; 2.722) p-value[g] =0.275
Response Duration			
Duration of complete response (CR+CRu)[j]			
n = response-evaluable patients	122	95	
Median[c] (95% CI) (months)	42.1 (30.7; 49.1)	18.0 (14.0; 23.4)	
Duration of Response (CR+CRu+PR)[k]			
n: response-evaluable subjects	211	204	
Median[c] (95% CI) (months)	36.5 (26.7; 46.7)	15.1 (12.5; 17.0)	

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

[a] Based on IRC assessment (radiological data only).
[b] Based on Investigator assessment.
[c] Based on Kaplan-Meier product limit estimates.
[d] 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.
[e] Based on Log-rank test stratified with IPI risk and stage of disease.
[f] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used, with IPI risk and Stage of Disease as stratification factors. An odds ratio (OR) > 1 indicates an advantage for VcR-CAP.
[g] P-value from the Cochran Mantel-Haenszel Chi-Squared test, with IPI and Stage of Disease as stratification factors.
[h] Include all CR + CRu, by IRC, bone marrow and LDH.
[i] Include all radiological CR+CRu+PR by IRC regardless the verification by bone marrow and LDH.
[j] Calculated from first date of complete response (CR+CRu by IRC, bone marrow and LDH) to date of PD or death due to PD.
[k] Calculated from first date of response (include all radiological CR+CRu+PR by IRC) to date of PD or death due to PD.

IRC=Independent Review Committee; IPI=International Prognostic Index; LDH = Lactate dehydrogenase; CR=Complete Response; CRu= Complete response unconfirmed; PR=Partial Response; CI=Confidence Interval, HR=hazard ratio; OR= odds ratio; ITT= intent to treat; PD=Progressive disease

nterval, HR=hazard ratio; OR= odds ratio; ITT= intent to treat; PD=Progressive disease

Patients with Previously Treated Light-Chain (AL) Amyloidosis

A Phase 1/2 study was conducted to determine the safety and efficacy of Bortezomib in patients with previously treated light-chain (AL) Amyloidosis. No new safety concerns were observed during the study, and in particular Bortezomib did not exacerbate target organ damage (heart, kidney and liver). In 49 evaluable patients treated at 1.6 mg/m² weekly or 1.3 mg/m² twice weekly, a 67.3% response rate (including a 28.6% CR rate) as measured by haematological response (M- protein) was reported. For these dose cohorts, the combined 1-year survival rate was 88.1%.

Pediatric Use

The safety and effectiveness of Bortezomib in pediatric patients has not been established for multiple myeloma and mantle cell lymphoma.

Geriatric Use

Of the 669 patients enrolled in the phase 3 multiple myeloma study, 245 (37%) were 65 years of age or older: 125 (38%) on the Bortezomib arm and 120 (36%) on 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 *Clinical Trials*).

In the phase 2 clinical study of 202 patients with relapsed multiple myeloma, 35% of patients were 65 years of age or older, the incidence of Grade ≥3 events was 74%, 80%, and 85% for Bortezomib patients ≤50, 51 to 65, and >65 years old, respectively (see *Clinical Trials*).

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.

5.2 Pharmacokinetic properties

<u>Absorption</u>

Following intravenous bolus administration of a 1.0 mg/m² and 1.3 mg/m² dose to 11 patients with multiple myeloma and creatinine clearance values greater than 50 ml/min, 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/m² dose and 89 to 120 ng/ml for the 1.3 mg/m² dose.

Following an intravenous bolus or subcutaneous injection of a 1.3 mg/m² dose to patients with multiple myeloma (n=14 in the intravenous group, n=17 in the subcutaneous group), the total systemic exposure after repeat dose administration (AUC_{last}) was equivalent for subcutaneous and intravenous administrations. 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%.

<u>Distribution</u>

The mean distribution volume (Vd) of Bortezomib ranged from 1,659 Liters to 3,294 Liters following single- or repeated-dose intravenous administration of 1.0 mg/m² or 1.3 mg/m² to patients with multiple myeloma. This suggests that Bortezomib distributes widely to peripheral tissues. Over a Bortezomib concentration range of 0.01 to 1.0 µg/ml, the in vitro protein binding averaged 82.9% in human plasma. The fraction of Bortezomib bound to plasma proteins was not concentration-dependent.

<u>Biotransformation</u>

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that Bortezomib is primarily oxidatively metabolised via cytochrome P450 enzymes, 3A4, 2C19, and 1A2. 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.

<u>Elimination</u>

The mean elimination half-life (t1/2) 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/h following the first dose for doses of 1.0 mg/m² and 1.3 mg/m², respectively, and ranged from 15 to 32 l/h and 18 to 32 l/h following subsequent doses for doses of 1.0 mg/m² and 1.3 mg/m², respectively.

<u>Special populations</u>

Age, Gender, and Race

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/hr/m², volume of distribution at steady-state was 834 (39%) L/m², 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 pharmacokinetics of bortezomib have not been evaluated.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of IV bortezomib was assessed in 60 cancer patients at bortezomib doses ranging from 0.5 to 1.3 mg/m². 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 5**).

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 m², n=12), Mild (CrCL=40-59 mL/min/1.73 m², n=10), Moderate (CrCL=20-39 mL/min/1.73 m², n=9), and Severe (CrCL < 20 mL/min/1.73 m², 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/m² of bortezomib twice weekly. Exposure of bortezomib (dose-normalized AUC and Cmax) was comparable among all the groups (see *Posology and Method of Administration*).

5.3 Preclinical safety data

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/m² (one-fourth of the recommended clinical dose), and degenerative changes in the testes occurred at 1.2 mg/m². Bortezomib could have a potential effect on either male or female fertility.

Animal Toxicity Findings

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/m² 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.

6. Pharmaceutical particulars

6.1 List of excipients

Mannitol

Nitrogen

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

<u>Unopened vial</u>

2 years

<u>Reconstituted solution</u>

The reconstituted solution should be used immediately after preparation. If 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. The total storage time for the reconstituted medicinal product should not exceed 8 hours prior to administration.

6.4 Special precautions for storage

Do not store above 30°C.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass 10 ml-vial with a grey bromobutyl stopper and an aluminium seal, with a PP disc containing 3.5 mg Bortezomib.

Each pack contains 1 single-use vial.

6.6 Special precautions for disposal and other handling

<u>General precautions</u>

Bortezomib is a cytotoxic agent. Therefore, caution should be used during handling and preparation of Bortezomib. Use of gloves and other protective clothing to prevent skin contact is recommended.

Aseptic technique must be strictly observed throughout the handling of Bortezomib, since it contains no preservative.

There have been fatal cases of inadvertent intrathecal administration of Bortezomib. Bortezomib 1 mg powder for solution for injection is for intravenous use only, while Bortezomib 3.5 mg powder for solution for injection is for intravenous or subcutaneous use. **DO NOT ADMINISTER BORTEZOMIB INTRATHECALLY.**

<u>Instructions for reconstitution</u>

BORTEZOMIB must be reconstituted by a healthcare professional.

Intravenous injection

Each 10 ml vial of Bortezomib must be carefully reconstituted with 3.5 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

After reconstitution, each ml solution contains 1 mg Bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7.

The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

Subcutaneous injection

Each 10 ml vial of BORTEZOMIB must be carefully reconstituted with 1.4 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

After reconstitution, each ml solution contains 2.5 mg Bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7. The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

<u>Disposal</u>

Bortezomib is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Product Owner:

AUROBINDO

Aurobindo Pharma Ltd.,
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8. Date of revision of the text

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