SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BORTERO (Bortezomib for Injection 3.5mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 3.5 mg of Bortezomib

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Injection

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

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Multiple Myeloma

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

Mantle Cell Lymphoma

Bortezomib is indicated for the treatment of adult patients with mantle cell lymphoma.

4.2 Posology and Method of administration

Important Dosing Guidelines

Bortezomib is for intravenous or subcutaneous use only. Do not administer Bortezomib by any other route. Because each route of administration has a different reconstituted concentration, use caution when calculating the volume to be administered.

The recommended starting dose of Bortezomib is 1.3 mg/m2. Bortezomib is administered intravenously at a concentration of 1 mg/mL, or subcutaneously at a concentration of
2.5 mg/mL [see Dosage and Administration (2.10)].

Bortezomib retreatment may be considered for patients with multiple myeloma who had previously responded to treatment with Bortezomib and who have relapsed at least six months after completing prior Bortezomib treatment. Treatment may be started at the last tolerated dose [see Dosage and Administration (2.6)].

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

Dosage in Previously Untreated Multiple Myeloma

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

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

Twice Weekly Bortezomib (Cycles 1 to 4)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
Bortezomib (1.3 mg/m2)	Day 1	--	--	Day 4	Day 8	Day 11	rest period	Day 22	Day 25	Day 29	Day 32	rest period
Melphalan (9 mg/m2) Prednisone (60 mg/m2)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period
Once Weekly Bortezomib (Cycles 5 to 9 when used in combination with Melphalan and Prednisone)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
Bortezomib (1.3 mg/m2)	Day 1	--	--		Day 8		rest period	Day 22		Day 29		rest period
Melphalan (9 mg/m2) Prednisone	Day 1	Day 2	Day 3	Day 4	--	--	rest	--	--	--	--	rest

Dose Modification Guidelines for Bortezomib When Given in Combination with Melphalan and Prednisone

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

Table 2: Dose Modifications During Cycles of Combination Bortezomib, Melphalan and Prednisone Therapy

Toxicity	Dose Modification or Delay
Hematological toxicity during a cycle: If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the	Consider reduction of the melphalan dose by 25% in the next cycle

If platelet count is not above 30 × 109/L or ANC is not above 0.75 × 109/L on a Bortezomib dosing day (other than	Withhold Bortezomib dose
If several Bortezomib doses in consecutive cycles are withheld due to toxicity	Reduce Bortezomib dose by one dose level (from 1.3 mg/m2 to 1 mg/m2, or from 1 mg/m2 to 0.7 mg/m2)

Grade 3 or higher non-hematological toxicities	Withhold Bortezomib therapy until symptoms of toxicity have resolved to Grade 1 or baseline. Then, Bortezomib may be reinitiated with one dose level reduction (from 1.3 mg/m2 to 1 mg/m2, or from 1 mg/m2 to 0.7 mg/m2). For Bortezomib -related

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

Dose modifications guidelines for peripheral neuropathy are provided *[see Dosage and Administration (2.7)]*.

Dosage in Previously Untreated Mantle Cell Lymphoma

Bortezomib (1.3 mg/m2) is administered intravenously in combination with intravenous rituximab, cyclophosphamide, doxorubicin and oral prednisone (VcR-CAP) for 6, three-week treatment cycles as shown in Table 3. Bortezomib is administered first followed by rituximab. Bortezomib is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a ten-day rest period on Days 12 to 21. For patients with a response first documented at Cycle 6, two additional VcR-CAP cycles are recommended. At least 72 hours should elapse between consecutive doses of Bortezomib .

Table 3: Dosage Regimen for Patients with Previously Untreated Mantle Cell Lymphoma

Twice Weekly Bortezomib (6, Three Week Cycles)*								
Week	**1**					**2**		**3**
Bortezomib (1.3 mg/m2)	Day 1	--	--	Day 4	--	Day 8	Day 11	rest period

Rituximab (375 mg/m2) Cyclophosphamide (750 mg/m2) Doxorubicin (50 mg/m2)	Day 1	--	--			--	--	rest period
Prednisone (100 mg/m2)	Day 1	Day 2	Day 3	Day 4	Day 5	--	--	rest period

* Dosing may continue for two more cycles (for a total of eight cycles) if response is first seen at Cycle 6.

Dose Modification Guidelines for Bortezomib **When Given in Combination with Rituximab, Cyclophosphamide, Doxorubicin and Prednisone**

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

Platelet count should be at least 100 × 109/L and absolute neutrophil count (ANC) should be at least 1.5 × 109/L

Hemoglobin should be at least 8 g/dL (at least 4.96 mmol/L) Non-hematologic toxicity should have recovered to Grade 1 or baseline

Interrupt Bortezomib treatment at the onset of any Grade 3 hematologic or non-hematological toxicities, excluding neuropathy [see Table 5, Warnings and Precautions (5)]. For dose adjustments, see Table 4 below.

Table 4: Dose Modifications on Days 4, 8, and 11 during Cycles of Combination Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin and Prednisone Therapy

Toxicity	Dose Modification or Delay
Hematological Toxicity	
Grade 3 or higher	Withhold Bortezomib therapy for up to 2 weeks until the patient has an ANC at or above 0.75 × 109/L and a platelet count at or above 25 × 109/L. If, after Bortezomib has been withheld, the toxicity does not resolve, discontinue
neutropenia, or a platelet count not at or above 25 × 109/L	Bortezomib. If toxicity resolves such that the patient has an ANC at or above 0.75 × 109/L and a platelet count at or above 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).

Grade 3 or higher non-hematological toxicities	Withhold Bortezomib therapy until symptoms of the toxicity have resolved to Grade 2 or better. Then, Bortezomib may be reinitiated with one dose level reduction (from 1.3 mg/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 or modify Bortezomib

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

Dosage and Dose Modifications for Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma

Bortezomib (1.3 mg/m2/dose) is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a ten day rest period (Days 12 to 21). For extended therapy of more than eight cycles, Bortezomib may be administered on the standard schedule or, for relapsed multiple myeloma, on a maintenance schedule of once weekly for four weeks (Days 1, 8, 15, and 22) followed by a 13 day rest period (Days 23 to 35) [see Clinical Studies (14)]. At least 72 hours should elapse between consecutive doses of Bortezomib.

Patients with multiple myeloma who have previously responded to treatment with Bortezomib (either alone or in combination) and who have relapsed at least six months after their prior Bortezomib therapy may be started on Bortezomib at the last tolerated dose. Retreated patients are administered Bortezomib twice weekly (Days 1, 4, 8, and 11) every three weeks for a maximum of eight cycles. At least 72 hours should elapse between consecutive doses of Bortezomib. Bortezomib may be administered either as a single agent or in combination with dexamethasone [see Clinical Studies (14.1)].

Bortezomib therapy should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematological toxicities excluding neuropathy as discussed below [see Warnings and Precautions (5)]. 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 mg/m2/dose; 1 mg/m2/dose reduced to 0.7 mg/m2/dose).

Dose Modifications for Peripheral Neuropathy

Starting Bortezomib subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy. Patients with pre-existing severe neuropathy should be treated with Bortezomib only after careful risk-benefit assessment.

Patients experiencing new or worsening peripheral neuropathy during Bortezomib therapy may require a decrease in the dose and/or a less dose-intense schedule.

For dose or schedule modification guidelines for patients who experience Bortezomib - related neuropathic pain and/or peripheral neuropathy, see Table 5.

Table 5: Recommended Dose Modification for Bortezomib - Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms*	Modification of Dose and Regimen
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL)†)	Reduce Bortezomib to 1 mg/m2
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL‡)	Withhold Bortezomib therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of Bortezomib at 0.7 mg/m2 once per week.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue Bortezomib

** Grading based on NCI Common Terminology Criteria CTCAE v4.0*

† Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc.

‡ Self care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

Dosage in Patients with Hepatic Impairment

Do not adjust the starting dose for patients with mild hepatic impairment.

Start patients with moderate or severe hepatic impairment at a reduced dose of 0.7 mg/m2 per injection during the first cycle, and consider subsequent dose escalation to 1 mg/m2 or further dose reduction to 0.5 mg/m2 based on patient tolerance (see Table 6) [see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

Table 6: Recommended Starting Dose Modification for Bortezomib in Patients with Hepatic Impairment

	Bilirubin Level	SGOT (AST) Levels	Modification of Starting Dose
Mild	Less than or equal to 1× ULN	More than ULN	None
	More than 1× to 1.5× ULN	Any	None
Moderate	More than 1.5× to 3× ULN	Any	Reduce Bortezomib to 0.7 mg/m2 in the first cycle.

Severe	More than 3× ULN	Any	Consider dose escalation to 1 mg/m2 or further dose reduction to 0.5 mg/m2 in subsequent cycles based on patient tolerability

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

Administration Precautions

The drug quantity contained in one vial (3.5 mg) may exceed the usual dose required. Caution should be used in calculating the dose to prevent overdose [see Dosage and Administration (2.10)].

When administered subcutaneously, sites for each injection (thigh or abdomen) should be rotated. New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous, or indurated.If local injection site reactions occur following Bortezomib administration subcutaneously, a less concentrated Bortezomib solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously [see Dosage and Administration (2.10)]. Alternatively, consider use of the intravenous route of administration [see Dosage and Administration (2.10)].Bortezomib is a hazardous drug. Follow applicable special handling and disposal procedures.1

Reconstitution/Preparation for Intravenous and Subcutaneous Administration

Use proper aseptic technique. Reconstitute only with 0.9% sodium chloride. The reconstituted product should be a clear and colorless solution.

Different volumes of 0.9% sodium chloride are used to reconstitute the product for the different routes of administration. The reconstituted concentration of bortezomib for subcutaneous administration (2.5 mg/mL) is greater than the reconstituted concentration of bortezomib for intravenous administration (1 mg/mL). Because each route of administration has a different reconstituted concentration, use caution when calculating the volume to be administered [see Dosage and Administration (2.9)].

For each 3.5 mg single-dose vial of bortezomib, reconstitute with the following volume of 0.9% sodium chloride based on route of administration (Table 7):

Table 7: Reconstitution Volumes and Final Concentration for Intravenous and Subcutaneous Administration

Route of Administration	**Bortezomib (mg/vial)**	**Diluent (0.9% Sodium**	**Final Bortezomib Concentration**
Intravenous	3.5 mg	3.5 mL	1 mg/mL

Subcutaneous	3.5 mg	1.4 mL	2.5 mg/mL

Dose must be individualized to prevent overdosage. After determining patient body surface area (BSA) in square meters, use the following equations to calculate the total volume (mL) of reconstituted Bortezomib to be administered:

Intravenous Administration [1 mg/mL concentration]

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

Subcutaneous Administration [2.5 mg/mL concentration]

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

Stickers that indicate the route of administration are provided with each Bortezomib vial. These stickers should be placed directly on the syringe of Bortezomib once Bortezomib is prepared to help alert practitioners of the correct route of administration for Bortezomib .

Parenteral drug products should be inspected visual y for particulate matter and discoloration prior to administration whenever solution and container permit. If any discoloration or particulate matter is observed, the reconstituted product should not be used.

Stability

Unopened vials of Bortezomib are stable until the date indicated on the package when stored in the original package protected from light.

Bortezomib contains no antimicrobial preservative. Administer reconstituted Bortezomib within eight hours of preparation. When reconstituted as directed, Bortezomib may be stored at 25°C (77°F). The reconstituted material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for up to eight hours in a syringe; however, total storage time for the reconstituted material must not exceed eight hours when exposed to normal indoor lighting.

4.3 Contraindications

Bortezomib is contraindicated in patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol. Reactions have included anaphylactic reactions [see Adverse Reactions (6.1)].
Bortezomib is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of Bortezomib.

4.4 Special warnings and precautions for use

Peripheral Neuropathy
Bortezomib treatment causes a peripheral neuropathy that is predominantly sensory; however, cases of severe sensory and motor peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral neuropathy (including ≥Grade 3) during treatment with Bortezomib. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness. In the Phase 3 relapsed multiple myeloma trial comparing Bortezomib subcutaneous vs intravenous, the incidence of Grade ≥2 peripheral neuropathy was 24% for subcutaneous and 39% for intravenous. Grade ≥3 peripheral neuropathy occurred in 6% of patients in the subcutaneous treatment group, compared with 15% in the intravenous treatment group [see Adverse Reactions (6.1)]. Starting Bortezomib subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy.
Patients experiencing new or worsening peripheral neuropathy during Bortezomib therapy may require a decrease in the dose and/or a less dose-intense schedule [see Dosage and Administration (2.7)]. In the Bortezomib vs dexamethasone Phase 3 relapsed multiple myeloma study, improvement in or resolution of peripheral neuropathy was reported in 48% of patients with ≥Grade 2 peripheral neuropathy following dose adjustment or interruption. Improvement in or resolution of peripheral neuropathy was reported in 73% of patients who discontinued due to Grade 2 neuropathy or who had ≥Grade 3 peripheral neuropathy in the Phase 2 multiple myeloma studies. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.
Hypotension

The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 8% [see Adverse Reactions (6.1)]. These events are observed throughout therapy. Patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated may be at increased risk of hypotension. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetic.
Cardiac Toxicity

Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have occurred during Bortezomib therapy, including reports in patients with no risk factors for decreased left ventricular ejection fraction [see Adverse Reactions (6.1)]. Patients with risk factors for, or existing heart disease should be frequently monitored. In the relapsed multiple myeloma study of Bortezomib vs dexamethasone, the incidence of any treatment-related cardiac disorder was 8% and 5% in the Bortezomib and dexamethasone groups, respectively. The incidence of adverse reactions suggestive of heart failure (acute pulmonary edema, pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock) was ≤1% for each individual reaction in the Bortezomib group. In the dexamethasone group the incidence was ≤1% for cardiac failure and congestive cardiac failure; there were no reported reactions of acute pulmonary edema, pulmonary edema, or cardiogenic shock. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.

Pulmonary Toxicity

Acute Respiratory Distress Syndrome (ARDS) and acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration have occurred in patients receiving Bortezomib. Some of these events have been fatal.
In a clinical trial, the first two patients given high-dose cytarabine (2 g/m2 per day) by continuous infusion with daunorubicin and BORTEZOMIB for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy.
There have been reports of pulmonary hypertension associated with BORTEZOMIB administration in the absence of left heart failure or significant pulmonary disease.
In the event of new or worsening cardiopulmonary symptoms, consider interrupting BORTEZOMIB until a prompt and comprehensive diagnostic evaluation is conducted.

Posterior Reversible Encephalopathy Syndrome (PRES)

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

Gastrointestinal Toxicity

Bortezomib treatment can cause nausea, diarrhea, constipation, and vomiting [see Adverse Reactions (6.1)] sometimes requiring use of antiemetic and antidiarrheal medications. Ileus can occur. Fluid and electrolyte replacement

should be administered to prevent dehydration. Interrupt BORTEZOMIB for severe symptoms.

Thrombocytopenia/Neutropenia

Bortezomib is associated with thrombocytopenia and neutropenia that follow a cyclical pattern with nadirs occurring following the last dose of each cycle and typical y recovering prior to initiation of the subsequent cycle. The cyclical pattern of platelet and neutrophil decreases and recovery remain consistent in the studies of multiple myeloma and mantle cell lymphoma, with no evidence of cumulative thrombocytopenia or neutropenia in the treatment regimens studied. Monitor complete blood counts (CBC) frequently during treatment with Bortezomib. Measure platelet counts prior to each dose of Bortezomib. Adjust dose/schedule for thrombocytopenia [see Dosage and Administration (2.6)]. Gastrointestinal and intracerebral hemorrhage has occurred during thrombocytopenia in association with Bortezomib . Support with transfusions and supportive care, according to published guidelines.

In the single agent, relapsed multiple myeloma study of Bortezomib vs dexamethasone, the mean platelet count nadir measured was approximately 40% of baseline. The severity of thrombocytopenia related to pretreatment platelet count is shown in Table 8. The incidence of bleeding (≥Grade 3) was 2% on the Bortezomib arm and was <1% in the dexamethasone arm.

Table 8: Severity of Thrombocytopenia Related to Pretreatment Platelet Count in the Relapsed Multiple Myeloma Study of Bortezomib vs Dexamethasone

Pretreatment Platelet Count*	Number of Patients (N=331)†	Number (%) of Patients with Platelet Count <10,000/µL	Number (%) of Patients with Platelet Count 10,000 to 25,000/µL
≥75,000/µL	309	8 (3%)	36 (12%)
≥50,000/µL to <75,000/µL	14	2 (14%)	11 (79%)
≥10,000/µL to <50,000/µL	7	1 (14%)	5 (71%)

** A baseline platelet count of 50,000/µL was required for study eligibility*

† Data were missing at baseline for one patient

In the combination study of Bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone (VcR-CAP) in previously untreated mantle cell lymphoma patients, the incidence of thrombocytopenia (≥Grade 4) was 32% vs 1% for the rituximab, cyclophosphamide, doxorubicin, vincristine, and

prednisone (R-CHOP) arm as shown in Table 12. The incidence of bleeding events (≥Grade 3) was 1.7% in the VcR-CAP arm (four patients) and was 1.2% in the R-CHOP arm (three patients).
Platelet transfusions were given to 23% of the patients in the VcR-CAP arm and 3% of the patients in the R-CHOP arm.
The incidence of neutropenia (≥Grade 4) was 70% in the VcR-CAP arm and was 52% in the R-CHOP arm. The incidence of febrile neutropenia (≥Grade 4) was 5% in the VcR- CAP arm and was 6% in the R-CHOP arm. Myeloid growth factor support was provided at a rate of 78% in the VcR-CAP arm and 61% in the R-CHOP arm.

Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with Bortezomib therapy. Patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor patients closely and take appropriate precautions.

Hepatic Toxicity

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

Thrombotic Microangiopathy

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

Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, Bortezomib can cause fetal harm when administered to a pregnant woman. Bortezomib administered to rabbits during organogenesis at a dose approximately

0.5 times the clinical dose of 1.3 mg/m2 based on body surface area caused postimplantation loss and a decreased number of live fetuses [see Use in Specific Populations (8.1)].
Advise females of reproductive potential to use effective contraception during treatment with BORTEZOMIB and for seven months following treatment. Advise males with female partners of reproductive potential to use effective contraception during treatment with Bortezomib and for four months following treatment. If Bortezomib is used during pregnancy or if the patient becomes pregnant during Bortezomib treatment, the patient should be apprised of the potential risk to the fetus [see Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)].

4.5 Interaction with other medicinal products and other forms of interaction

Effects of Other Drugs on Bortezomib
Strong CYP3A4 Inducers

Coadministration with a strong CYP3A4 inducer decreases the exposure of bortezomib [see Clinical Pharmacology (12.3)] which may decrease Bortezomib efficacy. Avoid coadministration with strong CYP3A4 inducers.

Strong CYP3A4 Inhibitors

Coadministration with a strong CYP3A4 inhibitor increases the exposure of bortezomib

[see Clinical Pharmacology (12.3)] which may increase the risk of Bortezomib toxicities. Monitor patients for signs of bortezomib toxicity and consider a bortezomib dose reduction if bortezomib must be given in combination with strong CYP3A4 inhibitors.

Drugs Without Clinically Significant Interactions with Bortezomib

No clinically significant drug interactions have been observed when Bortezomib was coadministered with dexamethasone, omeprazole, or melphalan in combination with prednisone [see Clinical Pharmacology (12.3)].

4.6 Pregnancy, lactation and Special population

Pregnancy
Risk Summary

Based on its mechanism of action [see Clinical Pharmacology (12.1)] and findings in animals, bortezomib can cause fetal harm when administered to a pregnant woman. There are no studies with the use of bortezomib in pregnant women to inform drug-associated risks. Bortezomib caused embryo-fetal lethality in rabbits at doses lower than the clinical dose (see Data). Advise pregnant women of the potential risk to the fetus.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinical y recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Lactation

Risk Summary

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

bortezomib and for two months after treatment.

Females and Males of Reproductive Potential

Based on its mechanism of action and findings in animals, bortezomib can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

Pregnancy Testing

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

Females

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

Males

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

Infertility

Based on the mechanism of action and findings in animals, bortezomib may have an effect on either male or female fertility [see Nonclinical Toxicology (13.1)].

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

The activity and safety of bortezomib in combination with intensive re-induction chemotherapy was evaluated in pediatric and young adult patients with lymphoid malignancies (pre-B cel ALL 77%, 16% with T-cel ALL, and 7% T-cel lymphoblastic lymphoma (LL)), al of whom relapsed within 36 months of initial diagnosis in a single-arm multicenter, nonrandomized cooperative group trial. An effective reinduction multiagent chemotherapy regimen was administered in three blocks. Block 1 included vincristine, prednisone, doxorubicin and pegaspargase; Block 2 included cyclophosphamide, etoposide and methotrexate; Block 3 included high-dose cytosine arabinoside and asparaginase. Bortezomib was administered at a dose of 1.3 mg/m2 as a bolus intravenous injection on Days 1, 4, 8, and 11 of Block 1 and Days 1, 4, and 8 of Block
2. There were 140 patients with ALL or LL enrolled and evaluated for safety. The median age was ten years (range: 1 to 26), 57% were male, 70% were white, 14% were black, 4% were Asian, 2% were American Indian/Alaska Native, 1% were Pacific Islander.

The activity was evaluated in a prespecified subset of the first 60 evaluable patients enrolled on the study with pre-B ALL ≤21 years and relapsed <36 months from diagnosis. The complete remission (CR) rate at day 36 was compared to that in a historical control set of patients who had received the identical backbone therapy without bortezomib. There was no evidence that the addition of bortezomibhad any impact on the CR rate.

No new safety concerns were observed when bortezomibwas added to a chemotherapy backbone regimen as compared with a historical control group in which the backbone regimen was given without bortezomib.
The BSA-normalized clearance of bortezomib in pediatric patients was similar to that observed in adults.

Geriatric Use

Of the 669 patients enrolled in the relapsed multiple myeloma study, 245 (37%) were 65 years of age or older: 125 (38%) on the bortezomib arm and 120 (36%) on the dexamethasone arm. Median time to progression and median duration of response for patients ≥65 were longer on bortezomib compared to dexamethasone [5.5 mo vs 4.3 mo, and 8.0 mo vs 4.9 mo, respectively]. On the bortezomib arm, 40% (n=46) of evaluable patients aged ≥65 experienced response (CR + PR) vs 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 to 64 and ≥65 years old, respectively [see Adverse Reactions (6.1), Clinical Studies (14.1)].
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.

Renal Impairment

No starting dosage adjustment of bortezomib is recommended for patients with renal impairment. In patients requiring dialysis, bortezomib should be administered after the dialysis procedure [see Clinical Pharmacology (12.3)].

Hepatic Impairment

No starting dosage adjustment of bortezomib is recommended for patients with mild hepatic impairment (total bilirubin ≤1× ULN and AST >ULN, or total bilirubin >1 to 1.5× ULN and any AST). The exposure of bortezomib is increased in patients with moderate (total bilirubin ≥1.5 to 3× ULN and any AST) and severe (total bilirubin >3× ULN and any AST) hepatic impairment. Reduce the starting dose in patients with moderate or severe hepatic impairment [see Dosage and Administration (2.8), Clinical Pharmacology (12.3)].

Patients with Diabetes

During clinical trials, hypoglycemia and hyperglycemia were reported in diabetic patients receiving oral hypoglycemic. 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.

4.7 Effects on ability to drive and use machines

The influence of bortezomib on the ability to drive or use machine is unknown.

4.8 Undesirable Effects

The following clinical y significant adverse reactions are also discussed in other sections of the labeling:

- Peripheral Neuropathy [see Warnings and Precautions (5.1)]
- Hypotension [see Warnings and Precautions (5.2)] Cardiac Toxicity [see Warnings and Precautions (5.3)]
- Pulmonary Toxicity [see Warnings and Precautions (5.4)]
- Posterior Reversible Encephalopathy Syndrome (PRES) [see Warnings and Precautions (5.5)]
- Gastrointestinal Toxicity [see Warnings and Precautions (5.6)] Thrombocytopenia/Neutropenia [see Warnings and Precautions (5.7)] Tumor Lysis Syndrome [see Warnings and Precautions (5.8)]
- Hepatic Toxicity [see Warnings and Precautions (5.9)]
- Thrombotic Microangiopathy [see Warnings and Precautions (5.10)]

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the Pharmacy and Poisons Board (PPB) through the Pharmacovigilance Electronic Reporting System (PvERS) at https://pv.pharmacyboardkenya.org/ or by using the approved PPB ADR reporting forms.

4.9 Overdose

There is no known specific antidote for BORTEZOMIB overdosage. In humans, fatal outcomes following the administration of more than twice the recommended therapeutic dose have been reported, which were associated with the acute onset of symptomatic hypotension (5.2) and thrombocytopenia (5.7). In the event of an overdosage, the patient's vital signs should be monitored and appropriate supportive care given.
Studies in monkeys and dogs showed that intravenous bortezomib doses as low as two times the recommended clinical dose on a mg/m2 basis were associated with increases in heart rate, decreases in contractility, hypotension, and death. In dog studies, a slight increase in the corrected QT interval was observed at doses resulting in death. In monkeys, doses of 3.0 mg/m2 and greater (approximately twice the recommended clinical dose) resulted in hypotension starting at one hour post administration, with progression to death in 12 to 14 hours following drug administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties *Pharmacotherapeutic group*:

Antineoplastic Agent *ATC code*: L01XX32.

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.
Following twice weekly administration of 1 mg/m2 and 1.3 mg/m2 bortezomib doses, the maximum inhibition of 20S proteasome activity (relative to baseline) in whole blood was observed five minutes after drug administration. Comparable maximum inhibition of 20S proteasome activity was observed between 1 and 1.3 mg/m2 doses. Maximal inhibition ranged from 70% to 84% and from 73% to 83% for the 1 mg/m2 and 1.3 mg/m2 dose regimens, respectively.

5.2 Pharmacokinetic properties

Following intravenous administration of 1 mg/m2 and 1.3 mg/m2 doses, the mean maximum plasma concentrations of bortezomib (Cmax) after the first dose (Day 1) were 57 and 112 ng/mL, respectively. When administered twice weekly, the mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1 mg/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, the total systemic exposure after repeat dose administration (AUClast) was equivalent for subcutaneous and intravenous administration. The AUClast geometric mean ratio (90% confidence interval) was 0.99 (0.80 to 1.23). The Cmax after subcutaneous administration (20.4 ng/mL) was lower than after intravenous administration (223 ng/mL) with repeat dose administration.
Distribution

The mean distribution volume of bortezomib ranged from approximately 498 to 1884

L/m2 following single- or repeat-dose administration of 1 mg/m2 or 1.3 mg/m2 to patients with multiple myeloma. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100 to 1000 ng/mL.
Elimination

The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours after the 1 mg/m2 dose and 76 to 108 hours after the 1.3 mg/m2 dose. The mean total body clearances were 102 and 112 L/h following the first dose for doses of 1 mg/m2 and 1.3 mg/m2, respectively, and ranged

from 15 to 32 L/h following subsequent doses for doses of 1 and 1.3 mg/m2, respectively.

Metabolism

Bortezomib is primarily oxidatively metabolized to several inactive metabolites in vitro via cytochrome P450 (CYP) enzymes 3A4, CYP2C19, and CYP1A2, and to a lesser extent by CYP2D6 and CYP2C9.

Excretion

The pathways of elimination of bortezomib have not been characterized in humans. Specific Populations

No clinical y significant differences in the pharmacokinetics of bortezomib were observed based on age, sex, or renal impairment (including patients administered BORTEZOMIB after dialysis). The effect of race on bortezomib pharmacokinetics is unknown.

Patients with Hepatic Impairment

Following administration of bortezomib doses ranging from 0.5 to 1.3 mg/m2, mild (total bilirubin ≤1× ULN and AST >ULN, or total bilirubin >1 to 1.5× ULN and any AST) hepatic impairment did not alter dose-normalized bortezomib AUC when compared to patients with normal hepatic function. Dose normalized mean bortezomib AUC increased by approximately 60% in patients with moderate (total bilirubin >1.5 to 3× ULN and any AST) or severe (total bilirubin >3× ULN and any AST) hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment.

Drug Interaction Studies Clinical Studies

No clinical y significant differences in bortezomib pharmacokinetics were observed when coadministered with dexamethasone (weak CYP3A4 inducer), omeprazole (strong CYP2C19 inhibitor), or melphalan in combination with prednisone.

Strong CYP3A4 Inhibitor

Coadministration with ketoconazole (strong CYP3A4 inhibitor) increased bortezomib exposure by 35%.

Strong CYP3A4 Inducer

Coadministration with rifampin (strong CYP3A4 inducer) decreased bortezomib exposure by approximately 45%.

In Vitro Studies

Bortezomib may inhibit CYP2C19 activity and increase exposure to drugs that are substrates for this enzyme.

5.3 Pre-clinical safety data

NONCLINICAL PROPERTIES

Animal Toxicology or Pharmacology

Cardiovascular Toxicity

Studies in monkeys showed that administration of dosages approximately twice the recommended clinical dose resulted in heart rate elevations, followed by profound progressive hypotension, bradycardia, and death 12 to 14 hours postdose. 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 two weeks followed by one week rest), toxicities observed included severe anemia and thrombocytopenia, and gastrointestinal, neurological and lymphoid system toxicities. Neurotoxic effects of bortezomib in animal studies included axonal swelling and degeneration in peripheral nerves, dorsal spinal roots, and tracts of the spinal cord. Additional y, multifocal hemorrhage and necrosis in the brain, eye, and heart were observed.

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 six 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients:

Mannitol Ph. Eur. (Perlitol PF) Tertiary butyl alcohol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30°C and protect from light.

6.5 Nature and contents of pack's

1x21's Vials

6.6 Instructions for use, handling and disposal

No studies on the effects on the ability to drive and use machines have been performed. As somnolence and dizziness are known undesirable effects, this should be taken into account when driving or using machinery

7. Marketing Authorization Holder

Hetero Labs Limited
7-2-A2, Hetero Corporate Industrial Estates
Sanath Nagar, Hyderabad-500 018 Telangana, India
Tel. No.: +91 40 23704923/ 24/25
Fax: +91 40 23704035, 23813359
Email: contact@heterodrugs.com

8. Marketing Authorization Number

H2025/CTD11248/23952

9. Date of first authorisation/renewal of the authorisation

2025 May 01

10. Date of revision of the text

2025 May 01