360 mm

390 mm

50 mm

MIBZO C03286-00

MIBZO C03286-00

MIBZO (Bortezomib powder for solution for injection 3.5 mg/vial)

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Name of the medicinal product
Product Name : MIBZO (Bortezomib Powder for Solution for Injection 3.5 mg/vial)
Strength : 3.5 mg/vial
Pharmaceutical Dosage Form : Lyophilized powder for injection

List of Excipients
Mannitol.

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.

Pharmaceutical form
Powder for solution for injection.

Before reconstitution
White to off-white lyophilized cake or powder in 10mL tubular USP Type -I clear vial with 13 mm bromobutyl double slotted rubber stopper and sealed with 13 mm aluminium seal having polypropylene disc.

After reconstitution
Clear colorless solution free from visible particulate matter.

Clinical particulars

Therapeutic indications
Bortezomib is indicated for the treatment of patients with multiple myeloma.
Bortezomib is indicated for the treatment of patients with mantle cell lymphoma.

Recommended dose

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 may be administered in-travenously at a concentration of 1 mg/ml, or subcutaneously at a concentration of 2.5mg/ml.
Bortezomib retreatment may be considered for patients with multiple myeloma who had previously responded to treatment with Bortezomib and who have relapsed at least 6 months after completing prior Bortezomib treatment. Treatment may be started at the last tolerated dose.
When administered intravenously, administer Bortezomib as a 3 to 5 second bolus intravenous injection.

Dosage in Previously Untreated Multiple Myeloma
Bortezomib is administered in combination with oral melphalan and oral prednisone for 9, sixweek 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 (60 mg/m²)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period

Dose Modification Guidelines for Bortezomib when given in Combination with Melphalan and Prednisone
Prior to initiating any cycle of therapy with Bortezomib in combination with melphalan and prednisone:
- Platelet count should be at least 70 x 10⁹/L and the absolute neutrophil count (ANC) should be at least 1.0 x 10⁹/L
- Nonhematological toxicities should have resolved to Grade 1 or baseline

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

Toxicity	**Dose Modification or Delay**
Hematological toxicity during a cycle: If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25% in the next cycle
If platelet count is not above 30 × 10⁹/L or ANC is not above 0.75 x 109/L on a BORTEZOMIB dosing day (other than day 1)	Withhold BORTEZOMIB dose
If several BORTEZOMIB doses in consecutive cycles are withheld due to toxicity	Reduce BORTEZOMIB dose by 1 dose level (from 1.3 mg/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²)
Grade 3 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 neuropathic pain and/or peripheral neuropathy, hold or modify BORTEZOMIB as outlined in **Table 6**.

For information concerning melphalan and prednisone, see manufacturer's prescribing information.
Dose modifications guidelines for peripheral neuropathy are provided.

Posology for previously untreated multiple myeloma patients eligible for haematopoietic stem cell transplantation (induction therapy)
Combination therapy with dexamethasone
Bortezomib 3.5 mg powder for solution for injection is administered via intravenous or subcutane-ous injection at the recommended dose of 1.3 mg/m² body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of Bortezomib .
Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4, 8, 9, 10 and 11 of the Bortezomib treatment cycle.
Four treatment cycles of this combination therapy are administered.

Combination therapy with dexamethasone and thalidomide
Bortezomib 3.5 mg powder for solution for injection is administered via intravenous or subcutane-ous injection at the recommended dose of 1.3 mg/m² body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 28-day treatment cycle. This 4-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of Bortezomib.
Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4, 8, 9, 10 and 11 of the Bortezomib treament cycle.
Thalidomide is administered orally at 50 mg daily on days 1-14 and if tolerated the dose is in-creased to 100 mg on days 15-28, and thereafter may be further increased to 200 mg daily from cycle 2 (see table 3).
Four treatment cycles of this combination are administered. It is recommended that patients with at least partial response receive 2 additional cycles.

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

Bc+ Dx	**Cycles 1 to 4**			
	Week	1	2	3
	Bc (1.3 mg/m²)	Day 1, 4	Day 8, 11	Rest Period
	Dx 40 mg	Day 1, 2, 3, 4	Day 8, 9, 10, 11	-
Bc+Dx+T	**Cycle 1**			
	Week	**1**	**2**	**3**	**4**
	Bc (1.3 mg/m²)	Day 1, 4	Day 8, 11	Rest Period	Rest Period
	T 50 mg	Daily	Daily	-	-
	T 100 mg[a]	-	-	Daily	Daily
	Dx 40 mg	Day 1, 2, 3, 4	Day 8, 9, 10, 11	-	-
	Cycles 2 to 4b				
	Bc (1.3 mg/m²)	Day 1, 4	Day 8, 11	Rest Period	Rest Period
	T 200 mg[a]	Daily	Daily	Daily	Daily
	Dx 40 mg	Day 1, 2, 3, 4	Day 8, 9, 10, 11	-	-

Bc=Bortezomib; Dx=dexamethasone; T=thalidomide
[a] Thalidomide dose is increased to 100 mg from week 3 of Cycle 1 only if 50 mg is tolerated and to 200 mg from cycle 2 onwards if 100 mg is tolerated.
[b] Up to 6 cycles may be given to patients who achieve at least a partial response after 4 cycles

Dosage adjustments for transplant eligible patients

For Bortezomib dosage adjustments, as described under **"Dosage and Dose Modifications for Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma" and "Dose Modifications for Peripheral Neuropathy" should be followed.**
In addition, when Bortezomib is given in combination with other chemotherapeutic medicinal products, appropriate dose reductions for these products should be considered in the event of toxicities according to the recommendations in the local package inserts.

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

Table 4: Dosage Regimen for Patients with Previously Untreated Mantle Cell Lymphoma

Twice Weekly BORTEZOMIB (6, Three Week Cycles)*								
Week	**1**				**2**		**3**	
Bortezomib (1.3 mg/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 2 more cycles (for a total of 8 cycles) if response is first seen at cycle 6.
Dose Modification Guidelines for Bortezomib When Given in Combination with Rituximab, Cyclophosphamide, Doxorubicin and Prednisone.
Prior to the first day of each cycle (other than Cycle 1):
- Platelet count should be at least 100 x 10⁹/L and absolute neutrophil count (ANC) should be at least 1.5 x 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 and Special warnings and special precautions for use].

For dose adjustments, see Table 5 below.

Table 5: Dose Modifications on Days 4, 8, and 11 during Cycles of Combination BORTEZOMIB, Rituximab, Cyclophosphamide, Doxorubicin and Prednisone Therapy

Toxicity	**Dose modification or delay**
Hematological toxicity	
Grade 3 or higher neutropenia, or a platelet count not at or above 25 x 10⁹/L	**Withhold BORTEZOMIB therapy for up to 2 weeks until the patient has an ANC at or above 0.75 x 10⁹/L and a platelet count at or above 25 x 10⁹/L.** • If, after BORTEZOMIB has been withheld, the toxicity does not resolve, discontinue BORTEZOMIB. • If toxicity resolves such that the patient has an ANC at or above 0.75 x 10⁹/L and a platelet count at or above 25 x 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 as outlined in Table 6.

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

Dosage and Dose Modifications for Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma
Bortezomib (1.3 mg/m²/dose) is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a tenday rest period (Days 12 to 21). For extended therapy of more than eight cycles, Bortezomib may be administered on the standard schedule or, for relapsed multiple myeloma, on a maintenance schedule of once weekly for four weeks (Days 1, 8, 15, and 22) followed by a 13 day rest period (Days 23 to 35). At least 72 hours should elapse between consecutive doses of Bortezomib.
Patients with multiple myeloma who have previously responded to treatment with Bortezomib (ei-ther 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 ad-ministered either as a single agent or in combination with dexamethasone.
Bortezomib therapy should be with held 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 mg/m²/dose; 1 mg/m²/dose reduced to 0.7mg/m²/dose.
For dose modifications guidelines for peripheral neuropathy, see Dose modifications for peripheral neuropathy below.

Dose Modifications for Peripheral Neuropathy
Starting Bortezomib subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy. Patients with pre-existing severe neuropathy should be treated with Bortezomib only after careful riskbenefit assessment.
Patients experiencing new or worsening peripheral neuropathy during Bortezomib therapy may require a decrease in the dose and/or a less dose-intense schedule.
For dose or schedule modification guidelines for patients who experience Bortezomib related neuropathic pain and/or peripheral neuropathy see Table 6.

Table 6: Recommended Dose Modification for BORTEZOMIB related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms*	**Modification of Dose and Regimen**
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesias) 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 Toxicity 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

Special Populations

Patients with Renal Impairement
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. For patients with moderate or severe hepatic impairment, see Table 7 below, (also, see Pharmacokinetic Properties)

Table 7: Recommended Starting Dose Modification for BORTEZOMIB in Patients with Hepatic Impairment

	Bilirubin Level	**SGOT (AST) Levels**	**Modification of Starting Dose in Multiple Myeloma and Relapsed Mantle Cell Lymphoma (1.3 mg/m² twice weekly)**
Mild	≤ 1.0x ULN	> ULN	None
	> 1.0x–1.5x ULN	Any	None
Moderate	> 1.5x–3x ULN	Any	Reduce BORTEZOMIB to 0.7 mg/m² in the first cycle. Consider dose escalation to 1.0 mg/m² or further dose reduction to 0.5 mg/m² in subsequent cycles based on patient tolerability.
Severe	> 3x ULN	Any	

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

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.

Contraindications
Bortezomib is contraindicated in patients with hypersensitivity to Bortezomib, boron or mannitol.

Warnings and Precautions
Bortezomib should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.
There have been fatal cases of inadvertent intrathecal administration of Bortezomib. Bortezomib is for IV and subcutaneous use only. **DO NOT ADMINISTER Bortezomib INTRATHE-CALLY.**
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
MIBZO teatment 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 during treatment with MIBZO. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness.
Patients with pre-existing PN or at high risk of peripheral neuropathy may benefit from starting MIBZO subcutaneously.
Patients experiencing new or worsening peripheral neuropathy may require a change in dose schedule or route of administration. Following dose adjustments, improvement in or resolution of peripheral neuropathy was reported in patients with peripheral neuropathy. Improvement in or resolution of peripheral neuropathy was reported in patients who discontinued due to neuropathy or who had peripheral neuropathy
The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

Hypotension
Caution should be used when treating patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, or administration of mineralocorticoids and/or sympathomimetics

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.

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 diagnostic evaluation should be performed and patients treated appropriately.

Laboratory Tests
Complete blood counts (CBC) should be frequently monitored throughout treatment with MIBZO.

Thrombocytopenia/Neutropenia
MIBZO is associated with thrombocytopenia and neutropenia.
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 MIBZO. MIBZO therapy should be held when the platelet count is <25,000/uL. There have been reports of gastrointestinal and intracerebral hemorrhage in association with MIBZO. Transfusion and supportive care may be considered

Gastrointestinal Adverse Events
Bortezomib treatment can cause nausea, diarrhea, constipation, and vomiting sometimes requiring use of antiemetics and antidiarrheal medications. Fluid and electrolyte replacement should be ad-ministered to prevent dehydration. Since patients receiving Bortezomib therapy may experience vomiting and/or diarrhea, patients should be advised regarding appropriate measures to avoid dehy-dration. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light headedness or fainting spells.

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

Patients with Hepatic Impairment
Bortezomib is metabolized by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with Bortezomib at reduced starting doses and closely monitored for toxicities.

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.

Interactions with other Medicaments
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. 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 .
A drug-drug interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of Bortezomib showed a mean Bortezomib AUC decreased .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 pharmacokinetics.
A drug-drug interaction study assessing the effect of melphalan-prednisone on Bortezomib showe increased in mean Bortezomib AUC.
The 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 decrease in blood pressure.

Drug Laboratory Test Interactions
None known.

Pregnancy and Lactation
Women of child bearing potential should avoid becoming pregnant while being treated with bortezomib.
No placental transfer studies have been conducted with bortezomib. There are no adequate and well controlled studies in pregnant women. If bortezomib is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.
Patients should be advised to use effective contraceptive measures to prevent pregnancy and to avoid breast feeding during treatment with bortezomib.

Nursing Mothers
It is not known whether bortezomib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from bortezomib, women should be advised against breast feeding while being treated with Bortezomib.

Undesirable effects
Nervous system disorders: Frequency 'rare': Guillain-Barré syndrome, Demyelinating polyneuropathy
Summary of the safety profile
Serious adverse reactions uncommonly reported during treatment with bortezomib include cardiac failure, tumour lysis syndrome, pulmonary hypertension, posterior reversible encephalopathy syndrome, acute diffuse infiltrative pulmonary disorders and rarely autonomic neuropathy.
The most commonly reported adverse reactions during treatment with bortezomib are nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia.

Tabulated summary of adverse reactions
Multiple Myeloma
Undesirable effects in Table 8 were considered by the investigators to have at least a possible or probable causal relationship to bortezomib.
Adverse reactions are listed below by system organ class and frequency grouping. Frequencies are defined as: Very common; common; uncommon; rare; very rare, not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 8: Adverse reactions in patients with Multiple Myeloma treated with bortezomib

System Organ Class	**Incidence**	**Adverse reaction**
Infections and infestations	Common	Herpes zoster (inc disseminated & ophthalmic), Pneumonia*, Herpes simplex*, Fungal infection*
	Uncommon	Infection*, Bacterial infections*, Viral infections*, Sepsis (inc septic shock)*, Bronchopneumonia, Herpes virus infection*, Meningoencephalitis herpetic#, Bacteraemia (inc staphylococcal), Hordeolum, Influenza, Cellulitis, Device related infection, Skin infection*, Ear infection*, Staphylococcal infection, Tooth infection*
	Rare	Meningitis (inc bacterial), Epstein-Barr virus infection, Genital herpes, Tonsillitis, Mastoiditis, Post viral fatigue syndrome
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Rare	Neoplasm malignant, Leukaemia plasmacytic, Renal cell carcinoma, Mass, Mycosis fungoides, Neoplasm benign*

Front Page

MSN LABORATORIES PRIVATE LIMITED — PACKAGING DEVELOPMENT

Artwork Information		**Specification for Printed Leaflet**	
		Test	**Specification**
Brand Name	MIBZO	**Substrate**	Maplitho Paper
Generic Name	Bortezomib for injection 3.5 mg/vial	**GSM**	60 ± 5% GSM
Open Dimension	360 x 390 ± 2 mm	**Mode of supply**	Tray pack with suitable quantity
Folding Dimension	50 x 30 ± 2 mm	* **Pharma Code**	Front side 7646 & Back side 7647
Folding Type	Booklet type with gluing	**Font Type**	Arial Narrow
Item Code	C03286-00	**Font Size**	6 pt
Supersede Code	NA	**Perforation/Non-Perforation**	Non-Perforation
Country	Malaysia	**Developed by**	K.Prasad
Customer	MEGA LIFESCIENCES	**Reviewed by**	J.Srikanth
Version	02	**Colours**	Black P 485 C
Date & Time	29.01.2021 & 16:20		

*Note: Pharma code & Product name position and direction is not fixed and may vary based on the printer's requirement/ Machine suitability.

360 mm

50 mm

390 mm

Blood and lymphatic system disorders	Very Common	Thrombocytopenia*, Neutropenia*, Anaemia*
	Common	Leukopenia*, Lymphopenia*
	Uncommon	Pancytopenia*, Febrile neutropenia, Coagulopathy*, Leukocytosis*, Lymphadenopathy, Haemolytic anaemia#
	Rare	Disseminated intravascular coagulation, Thrombocytosis*, Hyperviscosity syndrome, Platelet disorder NOS, Thrombotic microangiopathy (inc thrombocytopenic purpura) #, Blood disorder NOS, Haemorrhagic diathesis, Lymphocytic infiltration
Immune system disorders	Uncommon	Angioedema#, Hypersensitivity*
	Rare	Anaphylactic shock, Amyloidosis, Type III immune complex mediated reaction
Endocrine disorders	Uncommon	Cushing's syndrome*, Hyperthyroidism*, Inappropriate antidiuretic hormone secretion
	Rare	Hypothyroidism
Metabolism and nutrition disorders	Very Common	Decreased appetite
	Common	Dehydration, Hypokalaemia*, Hyponatraemia*, Blood glucose abnormal*, Hypocalcaemia*, Enzyme abnormality*
	Uncommon	Tumour lysis syndrome, Failure to thrive*, Hypomagnesaemia*, Hypophosphataemia*, Hyperkalaemia*, Hypercalcaemia*, Hypernatraemia*, Uric acid abnormal*, Diabetes mellitus*, Fluid retention
	Rare	Hypermagnesaemia*, Acidosis, Electrolyte imbalance*, Fluid overload, Hypochloraemia*, Hypovolaemia, Hyperchloraemia*, Hyperphosphataemia*, Metabolic disorder, Vitamin B complex deficiency, Vitamin B12 deficiency, Gout, Increased appetite, Alcohol intolerance
Psychiatric disorders	Common	Mood disorders and disturbances*, Anxiety disorder*, Sleep disorders and disturbances*
	Uncommon	Mental disorder*, Hallucination*, Psychotic disorder*, Confusion*, Restlessness
	Rare	Suicidal ideation*, Adjustment disorder, Delirium, Libido decreased
Nervous system disorders	Very Common	Neuropathies*, Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia*
	Common	Motor neuropathy*, Loss of consciousness (inc syncope), Dizziness*, Dysgeusia*, Lethargy, Headache*
	Uncommon	Tremor, Peripheral sensorimotor neuropathy, Dyskinesia*, Cerebellar coordination and balance disturbances*, Memory loss (exc dementia)*, Encephalopathy*, Posterior Reversible Encephalopathy Syndrome#, Neurotoxicity, Seizure disorders*, Post herpetic neuralgia, Speech disorder*, Restless legs syndrome, Migraine, Sciatica, Disturbance in attention, Reflexes abnormal*, Parosmia
	Rare	Cerebral haemorrhage*, Haemorrhage intracranial (inc subarachnoid)*, Brain oedema, Transient ischaemic attack, Coma, Autonomic nervous system imbalance, Autonomic neuropathy, Cranial palsy*, Paralysis*, Paresis*, Presyncope, Brain stem syndrome, Cerebrovascular disorder, Nerve root lesion, Psychomotor hyperactivity, Spinal cord compression, Cognitive disorder NOS, Motor dysfunction, Nervous system disorder NOS, Radiculitis, Drooling, Hypotonia
Eye disorders	Common	Eye swelling*, Vision abnormal*, Conjunctivitis*
	Uncommon	Eye haemorrhage*, Eyelid infection*, Chalazion#, Blepharitis#, Eye inflammation*, Diplopia, Dry eye*, Eye irritation*, Eye pain, Lacrimation increased, Eye discharge
	Rare	Corneal lesion*, Exophthalmos, Retinitis, Scotoma, Eye disorder (inc. eyelid) NOS, Dacryoadenitis acquired, Photophobia, Photopsia, Optic neuropathy#, Different degrees of visual impairment (up to blindness)*
Ear and labyrinth disorders	Common	Vertigo*
	Uncommon	Dysacusis (inc tinnitus)*,Hearing impaired (up to and inc deafness), Ear discomfort*
	Rare	Ear haemorrhage, Vestibular neuronitis, Ear disorder NOS
Cardiac disorders	Uncommon	Cardiac tamponade#, Cardio-pulmonary arrest*, Cardiac fibrillation (inc atrial), Cardiac failure (inc left and right ventricular)*, Arrhythmia*, Tachycardia*, Palpitations, Angina pectoris, Pericarditis (inc pericardial effusion)*, Cardiomyopathy*, Ventricular dysfunction*, Bradycardia
	Rare	Atrial flutter, Myocardial infarction*, Atrioventricular block*, Cardiovascular disorder (inc cardiogenic shock), Torsade de pointes, Angina unstable, Cardiac valve disorders*, Coronary artery insufficiency, Sinus arrest
Vascular disorders	Common	Hypotension*, Orthostatic hypotension, Hypertension*
	Uncommon	Cerebrovascular accident#, Deep vein thrombosis*, Haemorrhage*, Thrombophlebitis (inc superficial), Circulatory collapse (inc hypovolaemic shock), Phlebitis, Flushing*, Haematoma (inc perirenal)*, Poor peripheral circulation*, Vasculitis, Hyperaemia (inc ocular)*
	Rare	Peripheral embolism, Lymphoedema, Pallor, Erythromelalgia, Vasodilatation, Vein discolouration, Venous insufficiency
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea*, Epistaxis, Upper/lower respiratory tract infection*, Cough*
	Uncommon	Pulmonary embolism, Pleural effusion, Pulmonary oedema (inc acute), Pulmonary alveolar haemorrhage#, Bronchospasm, Chronic obstructive pulmonary disease*, Hypoxaemia*, Respiratory tract congestion*, Hypoxia, Pleurisy*, Hiccups, Rhinorrhoea, Dysphonia, Wheezing
	Rare	Respiratory failure, Acute respiratory distress syndrome, Apnoea, Pneumothorax, Atelectasis, Pulmonary hypertension, Haemoptysis, Hyperventilation, Orthopnoea, Pneumonitis, Respiratory alkalosis, Tachypnoea, Pulmonary fibrosis, Bronchial disorder*, Hypocapnia*, Interstitial lung disease, Lung infiltration, Throat tightness, Dry throat, Increased upper airway secretion, Throat irritation, Upper-airway cough syndrome
Gastrointestinal disorders	Very Common	Nausea and vomiting symptoms*, Diarrhoea*, Constipation
	Common	Gastrointestinal haemorrhage (inc mucosal)*, Dyspepsia, Stomatitis*, Abdominal distension, Oropharyngeal pain*, Abdominal pain (inc gastrointestinal and splenic pain)*, Oral disorder*, Flatulence
	Uncommon	Pancreatitis (inc chronic)*, Haematemesis, Lip swelling*, Gastrointestinal obstruction (inc small intestinal obstruction, ileus)*, Abdominal discomfort, Oral ulceration*, Enteritis*, Gastritis*, Gingival bleeding, Gastrooesophageal reflux disease*, Colitis (inc clostridium difficile)*, Colitis ischaemic#, Gastrointestinal inflammation*, Dysphagia, Irritable bowel syndrome, Gastrointestinal disorder NOS, Tongue coated, Gastrointestinal motility disorder*, Salivary gland disorder*
	Rare	Pancreatitis acute, Peritonitis*, Tongue oedema*, Ascites, Oesophagitis, Cheilitis, Faecal incontinence, Anal sphincter atony, Faecaloma*, Gastrointestinal ulceration and perforation*, Gingival hypertrophy, Megacolon, Rectal discharge, Oropharyngeal blistering*, Lip pain, Periodontitis, Anal fissure, Change of bowel habit, Proctalgia, Abnormal faeces
Hepatobiliary disorders	Common	Hepatic enzyme abnormality*
	Uncommon	Hepatotoxicity (inc liver disorder), Hepatitis*, Cholestasis
	Rare	Hepatic failure, Hepatomegaly, Budd-Chiari syndrome, Cytomegalovirus hepatitis, Hepatic haemorrhage, Cholelithiasis
Skin and subcutaneous tissue disorders	Common	Rash*, Pruritus*, Erythema, Dry skin
	Uncommon	Erythema multiforme, Urticaria, Acute febrile neutrophilic dermatosis, Toxic skin eruption, Toxic epidermal necrolysis#, Stevens-Johnson syndrome#, Dermatitis*, Hair disorder*, Petechiae, Ecchymosis, Skin lesion, Purpura, Skin mass*, Psoriasis, Hyperhidrosis, Night sweats, Decubitus ulcer#, Acne*, Blister*, Pigmentation disorder*
	Rare	Skin reaction, Jessner's lymphocytic infiltration, Palmar-plantar erythrodysaesthesia syndrome, Haemorrhage subcutaneous, Livedo reticularis, Skin induration, Papule, Photosensitivity reaction, Seborrhoea, Cold sweat, Skin disorder NOS, Erythrosis, Skin ulcer, Nail disorder
Musculoskeletal and connective tissue disorders	Very Common	Musculoskeletal pain*
	Common	Muscle spasms*, Pain in extremity, Muscular weakness
	Uncommon	Muscle twitching, Joint swelling, Arthritis*, Joint stiffness, Myopathies*,Sensation of heaviness
	Rare	Rhabdomyolysis, Temporomandibular joint syndrome, Fistula, Joint effusion, Pain in jaw, Bone disorder, Musculoskeletal and connective tissue infections and inflammations*, Synovial cyst
Renal and urinary disorders	Common	Renal impairment*
	Uncommon	Renal failure acute, Renal failure chronic*, Urinary tract infection*, Urinary tract signs and symptoms*, Haematuria*, Urinary retention, Micturition disorder*, Proteinuria, Azotaemia, Oliguria*, Pollakiuria
	Rare	Bladder irritation
Reproductive system and breast disorders	Uncommon	Vaginal haemorrhage, Genital pain*, Erectile dysfunction,
	Rare	Testicular disorder*, Prostatitis, Breast disorder female, Epididymal tenderness, Epididymitis, Pelvic pain, Vulval ulceration
Congenital, familial and genetic disorders	Rare	Aplasia, Gastrointestinal malformation, Ichthyosis
General disorders and administration site conditions	Very Common	Pyrexia*, Fatigue, Asthenia
	Common	Oedema (inc peripheral), Chills, Pain*, Malaise*
	Uncommon	General physical health deterioration*, Face oedema*, Injection site reaction*, Mucosal disorder*, Chest pain, Gait disturbance, Feeling cold, Extravasation*, Catheter related complication*, Change in thirst*, Chest discomfort, Feeling of body temperature change*, Injection site pain*
	Rare	Death (inc sudden), Multi-organ failure, Injection site haemorrhage*, Hernia(inc hiatus)*, Impaired healing*, Inflammation, Injection site phlebitis*, Tenderness, Ulcer, Irritability, Non-cardiac chest pain, Catheter site pain, Sensation of foreign body
Investigations	Common	Weight decreased
	Uncommon	Hyperbilirubinaemia*, Protein analyses abnormal*, Weight increased, Blood test abnormal*,C-reactive protein increased
	Rare	Blood gases abnormal*, Electrocardiogram abnormalities (inc QT prolongation)*, International normalised ratio abnormal*, Gastric pH decreased, Platelet aggregation increased, Troponin I increased, Virus identification and serology*, Urine analysis abnormal*
Injury, poisoning and procedural complications	Uncommon	Fall, Contusion
	Rare	Transfusion reaction, Fractures*, Rigors*, Face injury, Joint injury*, Burns, Laceration, Procedural pain, Radiation injuries*
Surgical and medical procedures	Rare	Macrophage activation

NOS=not otherwise specified
* Grouping of more than one MedDRA preferred term.
# Post-marketing adverse reaction

Mantle Cell Lymphoma (MCL)

The safety profile of bortezomib in MCL patients treated with bortezomib at 1.3 mg/m^2 in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (BcR-CAP) versus patients treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] was relatively consistent to that observed in patients with multiple myeloma with main differences described below. Additional adverse drug reactions identified associated with the use of the combination therapy (BcR-CAP) were hepatitis B infection and myocardial ischaemia. The similar incidences of these events in both treatment arms, indicated that these adverse drug reactions are not attributable to bortezomib alone. Notable differences in the MCL patient population as compared to patients in the multiple myeloma studies were higher incidence of the haematological adverse reactions (neutropenia, thrombocytopenia, leukopenia, anemia, lymphopenia), peripheral sensory neuropathy, hypertension, pyrexia, pneumonia, stomatitis, and hair disorders.

Adverse drug reactions identified as those with similar or higher incidence in the BcR-CAP arm and with at least a possible or probable causal relationship to the components of the BcR-CAP arm, are listed in Table 9 below. Also included are adverse drug reactions identified in the BcR-CAP arm that were considered by investigators to have at least a possible or probable causal relationship to bortezomib based on historical data in the multiple myeloma studies.

Adverse reactions are listed below by system organ class and frequency grouping. Frequencies are defined as: Very common; common; uncommon; rare; very rare, not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 9: Adverse reactions in patients with Mantle Cell Lymphoma treated with BcR-CAP

System Organ Class	Incidence	Adverse reaction
Infections and infestations	Very Common	Pneumonia*
	Common	Sepsis (inc septic shock)*, Herpes zoster (inc disseminated & ophthalmic), Herpes virus infection*, Bacterial infections*, Upper/lower respiratory tract infection*, Fungal infection*, Herpes simplex*
	Uncommon	Hepatitis B, Infection*, Bronchopneumonia
Blood and lymphatic system disorders	Very Common	Thrombocytopenia*, Febrile neutropenia, Neutropenia*, Leukopenia*, Anaemia*, Lymphopenia*
	Uncommon	Pancytopenia*
Immune system disorders	Common	Hypersensitivity*
	Uncommon	Anaphylactic reaction
Metabolism and nutrition disorders	Very Common	Decreased appetite
	Common	Hypokalaemia*, Blood glucose abnormal*, Hyponatraemia*, Diabetes mellitus*, Fluid retention
	Uncommon	Tumour lysis syndrome
Psychiatric disorders	Common	Sleep disorders and disturbances*
Nervous system disorders	Very Common	Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia*
	Common	Neuropathies*, Motor neuropathy*, Loss of consciousness (inc syncope), Encephalopathy*, Peripheral sensorimotor neuropathy, Dizziness*, Dysgeusia*, Autonomic neuropathy
	Uncommon	Autonomic nervous system imbalance
Eye disorders	Common	Vision abnormal*
Ear and labyrinth disorders	Common	Dysacusis (inc tinnitus)*
	Uncommon	Vertigo*, Hearing impaired (up to and inc deafness)
Cardiac disorders	Common	Cardiac fibrillation (inc atrial), Arrhythmia*, Cardiac failure (inc left and right ventricular)*, Myocardial ischaemia, Ventricular dysfunction*
	Uncommon	Cardiovascular disorder (inc cardiogenic shock)
Vascular disorders	Common	Hypertension*, Hypotension*, Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea*, Cough*, Hiccups
	Uncommon	Acute respiratory distress syndrome, Pulmonary embolism, Pneumonitis, Pulmonary hypertension, Pulmonary oedema (inc acute)
Gastrointestinal disorders	Very Common	Nausea and vomiting symptoms*, Diarrhoea*, Stomatitis*, Constipation
	Common	Gastrointestinal haemorrhage (inc mucosal)*, Abdominal distension, Dyspepsia, Oropharyngeal pain*, Gastritis*, Oral ulceration*, Abdominal discomfort, Dysphagia, Gastrointestinal inflammation*, Abdominal pain (inc gastrointestinal and splenic pain)*, Oral disorder*
	Uncommon	Colitis (inc clostridium difficile)*
Hepatobiliary disorders	Common	Hepatotoxicity (inc liver disorder)
	Uncommon	Hepatic failure
Skin and subcutaneous tissue disorders	Very Common	Hair disorder*
	Common	Pruritus*, Dermatitis*, Rash*
Musculoskeletal and connective tissue disorders	Common	Muscle spasms*, Musculoskeletal pain*, Pain in extremity
Renal and urinary disorders	Common	Urinary tract infection*
General disorders and administration site conditions	Very Common	Pyrexia*, Fatigue, Asthenia
	Common	Oedema (inc peripheral), Chills, Injection site reaction*, Malaise*
Investigations	Common	Hyperbilirubinaemia*, Protein analyses abnormal*, Weight decreased, Weight increased

* Grouping of more than one MedDRA preferred term.

Retreatment of patients with relapsed multiple myeloma

In a study in which bortezomib retreatment was administered in patients with relapsed multiple myeloma, who previously had at least partial response on a bortezomib-containing regimen, the most common all-grade adverse events occurring in patients were thrombocytopenia, neuropathy, anaemia, diarrhoea, and constipation. All grade peripheral neuropathy and grade ≥ 3 peripheral neuropathy were observed in patients.

Overdose

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.

Effects on Ability to Drive and Use Machine

Bortezomib for injection may have a moderate influence on the ability to drive and use machines.

Bortezomib for injection 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

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.

Pharmacokinetics

Absorption:

Following intravenous bolus administration of a 1.0 mg/m^2 and 1.3 mg/m^2 dose to patients with multiple myeloma, the mean first dose maximum plasma concentrations of bortezomib were 57 and 112 ng/mL, respectively.

In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/ml for the 1.0 mg/m^2 dose and 89 to 120 ng/ml for the 1.3 mg/m^2 dose.The mean elimination half-life of Bortezomib upon multiple dosing ranged from 40 – 193 hours. Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses. Mean total body clearances were 102 and 112 L/h following the first dose for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively.

Following an IV bolus or subcutaneous (SC) injection of a 1.3 mg/m^2 dose to multiple myeloma patients, the total systemic exposure after repeat dose administration (AUClast) was equivalent for SC and IV administration. The Cmax after SC administration (20.4 ng/mL) was lower than IV (223 ng/mL). The AUClast geometric mean ratio was 0.99 and 90% confidence intervals were 80.18% - 122.80%.

Distribution:

The mean distribution volume of bortezomib ranged from 1659 liters to 3294 liters single or repeat dose IV administration of 1.0 mg/m^2 or 1.3 mg/m^2 to patients with multiple myeloma.

This suggests that Bortezomib distributes widely to peripheral tissues. The binding of Bortezomib to human plasma proteins averaged 83% over the concentration range of 100 - 1000 ng/mL.

Biotransformation:

Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-Bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent drug.

Elimination:

The pathways of elimination of Bortezomib have not been characterized in humans.

Special Populations

Age, Gender, and Race

After correcting for the BSA effect, other demographics such as age, body weight and sex did not have significant effects on Bortezomib clearance. The effects of gender, and race on the pharmacokinetics of Bortezomib have not been evaluated.

Hepatic Impairment:

When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-normalised 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.

Renal Impairment

In patients with various degrees of renal impairment who were classified according to their creatinine clearance values (CrCL) into the following groups: Normal (CrCL ≥ 60 mL/min/1.73 m^2,), Mild (CrCL = 40 - 59 mL/min/1.73 m^2,), Moderate (CrCL = 20 - 39 mL/min/1.73 m^2,), and Severe (CrCL < 20 mL/min/1.73 m^2). A group of dialysis patients who were dosed after dialysis was also included. Patients were administered intravenous doses of 0.7 to 1.3 mg/m^2 of bortezomib twice weekly. Exposure of bortezomib (dose-normalized AUC and Cmax) was comparable among all the groups.

Instructions for Use and Handling and Disposal

PROCEDURE:

Bortezomib is an antineoplastic. Caution should be used during handling and preparation. Prope-raseptic technique should be used. Use of gloves and other protective clothing to prevent skin contact is recommended, but extravasation of Bortezomib was not associated with tissue damage.

When administered subcutaneously, alternate sites for each injection (thigh or abdomen).

New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, red or hard.

There have been fatal cases of inadvertent intrathecal administration of Bortezomib.

Bortezomib is for IV and subcutaneous use only. **DO NOT ADMINISTER BORTEZOMIB IN-TRATHECALLY.**

Reconstitution/Preparation for Intravenous and Subcutaneous Administration

The contents of each vial should be reconstituted only with normal (0.9%) saline according to the following instructions based on route of administration:

	IV	SC
	3.5 mg Bortezomib	3.5 mg Bortezomib
Volume of diluent (0.9% Sodium Chloride) added to reconstitute one vial	3.5 mL	1.4 mL
Final Concentration after reconstitution (mg/mL)	1.0 mg/mL	2.5 mg/mL

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

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

Compatibilities:

The product is compatable with 0.9% Sodium chloride solution.

Incompatibilities:

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

Storage Condition

Do not store above 30°C

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

For storage condition after reconstituted:

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.

Shelf Life

Shelf life : 36 months.

For single use only

Before reconstitution

Do not store above 30°C. Keep the vial in the outer carton in order to protect from light.

After reconstitution

Solution is stable for 8 hours at 25°C.

Caution: Cytotoxic agent.

Product Registration Holder:
MEGA LIFESCIENCES SDN. BHD.
B-28-02, The Ascent, Paradigm No. 1,
Jalan SS7/26A, Kelana Jaya,
47301 Petaling Jaya, Selangor,
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Manufactured by:
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Formulation Division, Unit-II,
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