Reconstitution/Preparation for Intravenous Administration:
Each vial of NEOMIB® 3.5 mg must be reconstituted with 3.5 mL of 0.9% sodium chloride injection IP and NEOMIB® 2 mg must be reconstituted with 2 mL of 0.9% sodium chloride injection IP
Reconstitute solution should be clear and colorless solution.
Product should be inspected for particulate matter and discoloration prior to administration. If any particulate matter or discoloration has been observed during any point of time, the reconstituted product should not be used.

Stability
Bortezomib contains no antimicrobial preservatives. When reconstituted as directed, Bortezomib may be stored at 25°C (77°F). Reconstituted Bortezomib should be administered within 8 hours of preparation. the reconstituted material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for upto 8 hours in a syringe; however total storage time for the reconstituted material must not exceed 8 hours when exposed to normal indoor lighting.

HOW SUPPLIED
NEOMIB® (Bortezomib for Injection) 3.5mg and 2mg is supplied as individually cartoned 15 ml vials containing Bortezomib as a white to off-white cake or powder.

STORAGE
Store at controlled room temperature 25°C (77°F). Protect from light.

REFERENCES

1. Blade J, Samson D, Reece D, Apperley J, Bjorkstrand B, Gahrton et al. Criteria for evaluating disease response and progression inpatients with multiple myeloma treated by high dose therapy and hematopoietic stem cell transplantation. Myeloma subcommittee of the EBMT. European group for Blood and Marrow Transplant. British Journal of Haematology
1998;102(5):1115-123.
2. Salmon SE, Haut A, Bonnet JD, Amare M, Weick JK, Durie BG et al. Alternating combination chemotherapy and levamisole improves survival in multiple myeloma: a South West Oncology Group Study. Journal of Clinical Oncology 1983;1(8):453-461.
3. Elliott PJ, Zollner TM, Boehncke WH. Proteasome inhibition: a new anti-inflammatory strategy. J Mol Med. 2003 Apr;81(4):235-45.
4. Lenz HJ. Clinical update: proteasome inhibitors in solid tumors. Cancer Treat Rev. 2003 May;29 Suppl 1:41-8.
5. Bortezomib (Or) High Dose Dexamethasone for relapsed Multiple Myeloma
NEJM : June 2005, 352; 24.

Marketed by:
Getwell Oncology Pvt. Ltd.
(A unit of Getwell)
464, Udyog Vihar, Phase-V, Gurgaon - 122016, Haryana, India

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0700NIDM0215

GETWELL

For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

Bortezomib for Injection

NEOMIB®

LYOPHILIZED

FOR I.V INFUSION ONLY

WARNING

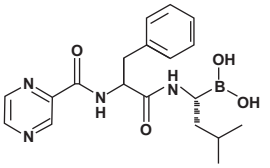
NEOMIB® should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

Pregnancy Category D
NEOMIB® should be avoided in women of childbearing potential and Bortezomib was not teratogenic when toxicity studies were conducted on rats and rabbits.

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

DESCRIPTION
NEOMIB® (Bortezomib) for injection is an antineoplastic agent available for Intravenous (Rapid bolus) use only.
Bortezomib is a modified dipeptidyl boronic acid which is in the form of mannitol boronic ester, reconstituted form, consists of the mannitol ester in equilibrium with its hydrolysis product, the monomeric boronic acid
The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-(pyrazinylcarbonyl) amino]propyl]amino] buty] boronic acid.

Bortezomib has the following chemical structure:



The molecular weight is 384.24. The molecular formula is $C_{19}H_{25}BN_4O_4$. The solubility of bortezomib, as the monomeric boronic acid, in water is 3.3-3.8 mg/ml in a pH range of 2.0-6.5.

COMPOSITION

Each vial of NEOMIB® 3.5mg contains	
Bortezomib IP	3.5 mg
Mannitol IP	35 mg
Each vial of NEOMIB® 2mg contains	
Bortezomib IP	2 mg
Mannitol IP	20 mg

CLINICAL PHARMACOLOGY
Mechanism of action
Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells.
Bortezomib is a novel synthetic dipeptide boronic acid with a high specificity for the 26S proteasome and a first-in-class proteasome inhibitor with antitumor activity. The consequence of inhibiting the proteasome is the matter of some speculation: the P27 protein is a critical regulator of the cell cycle, and the degradation of P27 is actually prevented by proteasome inhibition.

Pharmacokinetics
Following IV administration of a 1.3mg/m^2 dose, the median estimated maximum plasma concentrations of bortezomib was 509 ng/ml (range=109 to 1300 ng/ml) in patients with multiple my-eloma and creatinine clearence values ranging from 31 to 169 ml/min. The mean elimination half-life of bortezomib after first dose ranged from 9 to 15 hours at doses ranging from 1.45 to 2.00 mg/m^2 in patients with advanced malignancies. The pharmacokinetics of bortezomib as a single agent has not been fully characterized at the recommended dose in multiple myeloma patients.

Distribution
The distribution volume of bortezomib as a single agent was not assessed at the recommended dose in patients with multiple myeloma. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100 to 1000 ng/mL.

Metabolism
In vitro studies indicate that Bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes. The major metabolic pathway is through deboronation to form deboronated metabolites, that subsequently undergo hydroxylation to several metabolites these deboronated Bortezomib metabolites are inactive.

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

INDICATIONS AND USAGE
NEOMIB® (Bortezomib for injection) is indicated for the treatment of multiple myeloma patients who have received at least 1 prior therapy.

CONTRAINDICATIONS
NEOMIB® is contraindicated in patients with hypersensitivity to Bortezomib, Boron, or Mannitol.

PRECAUTIONS

Peripheral Neuropathy:
Bortezomib treatment causes peripheral neuropathy that is predominantly sensory, although cases of motor neuropathy have also been reported. Patients with preexisting symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral neuropathy (including >/= Grade 3) during treatment.

So all the Patients on Bortezomib should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, discomfort or neuropathic pain. Patients experiencing new or worsening peripheral neuropathy may require changes in the dose and schedule of bortezomib (see dosage and administration)

Hypotension:
Caution should be exercised when treating patients with a history of hypotension, syncope and patients who are dehydrated. Management of hypotension may include adjustment of antihypertensive medications, hydration and administration of mineralocortiocids (see Adverse Reactions)

Cardiac Disorders:
Patients with risk factors for, or existing heart disease should be closely monitored, particularly for the Q-T interval prolongation.

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

Gastrointestinal Adverse Events:
Treatment with Bortezomib leads to nausea, constipation, diarrhea, and vomiting (see adverse events): this can be taken care by anti-emetic and anti-diarrheal medications. Fluid and electrolyte replacement should be administered to prevent dehydration.

Thrombocytopenia:
Bortezomib is associated with thrombocytopenia usually platelets were lowest at Day 11 of each cycle and recovers to the basline by the next cycle. The platelet count decrease and recovery remained consistent over the treatment and there was no evidence of cummulative thrombocytopenia
Treatment should be held when the platelet count is <25,000/μL and reinitiated at a reduced dose (see dosage and administration and adverse events).

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

Hepatic Events
Patients who are on multiple concomitant medication and with serious medical conditions have to be monitored for liver failure (Rare cases of acute liver failure have been reported). Other reported hepatic events include asymptomatic increase in liver enzymes, hyperbillirubinemia, and hepatitis. Such changes may be reversible upon discontinuation of Bortezomib.

Patients with Hepatic Impairment:
Liver enzymes metabolize Bortezomib and Bortezomib's clearance may decrease in patients with hepatic impairment. These patients should be closely monitored for toxicities when treated with Bortezomib.

Patients with Renal Impairment:
No clinical information is available on the use of Bortezomib in patients with creatinine clearance values less than 13 mL/min and patients on hemodialysis. Patients with renal impairment should be closely monitored for toxicities when treated with Bortezomib.

Information of Patients
Ability to Driver or Operate Machinery or Impairment of Mental Ability:
Since Bortezomib may be associated with fatigue, dizziness, syncope, orthostatic/postural hypotension, diplopia or blurred vision, patients should be cautious when operating machinery, including automobiles.

Dehydration/Hypotension: Patients receiving Bortezomib therapy may experience vomiting and/or diarrhea, patients should be advised regarding appropriate measures to avoid dehydration. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light headedness or fainting spells.

Drug Interactions
In vitro studies indicate that Bortezomib is primarily is a substrate for cytochrome P450 3A4, 2C19, and 1 A2. Patients who are concomitantly receiving Bortezomib and other drugs which either induces or inhibitors of cytochrome P450 should be closely monitored for either toxicity or reduced efficacy. Patients on diabetic drugs receiving Bortezomib treatment may require close monitoring of their blood glucose levels and adjustments of the dose of antidiabetic medication. No formal drug interaction studies have been conducted with Bortezomib.

Carcinogenesis, Mutagenesis, Impairment of fertility
No studies have been reported for carcinogenicity with Bortezomib.
Bortezomib could have a potential effect on either male (or) female fertility.

Pregnancy Category D (see WARNINGS)
Pregnancy/Nursing:
Patients should be advised to use effective contraceptive measures to prevent pregnancy.

Nursing Mothers
It is not known whether Bortezomib is excreted in human milk. Women should be advised against breast-feeding while receiving Bortezomib therapy.

Paediatric Use
The safety and effectiveness of Bortezomib in children has not been established.

Geriatric Use
No overall differences in safety of effectiveness were observed between patients >/= age 65 and younger patients receiving Bortezomib; but greater sensitivity of some older individuals can not be ruled out.

ADVERSE EVENTS

Table 3. Adverse Events during Treatment Reported by 15 percent more of patients Receiving Bortezomib or Dexamethasone, Including Grade 3 and Grade 4 Events.

Event	Bortezomib(N=331) [n (%)]			Dexamethasone (N=332) [n (%)]		
	All Adverse Events	Grade 3 Events	Grade 4 Events*	All Adverse Events	Grade 3 Events	Grade 4 Events*
	Number (percent)					
1 Event	331 (100)	203 (61)	45 (14)	327 (98)[†]	146 (44)[†]	52 (16)
Diarrhea	190 (57)	24 (7)	0	69 (21)[†]	6 (2)	0
Nausea	190 (57)	8 (2)	0	46 (14)[†]	0[†]	0
Fatigue	140 (42)	17 (5)	1(<1)	106(32)[†]	12(4)	0
Constipation	140 (42)	7 (2)	0	49 (15)[†]	4 (1)	0
peripheral neuropathy	120 (36)	24 (7)	2 (1)	29 (9)[†]	1(<1)[†]	1(<1)
Vomiting	117 (35)	11 (3)	0	20 (6)[†]	4 (1)	0
Pyrexia	116 (35)	6 (2)	0	54 (16)[†]	4 (1)	1 (<1)
Thrombocytopenia	115 (35)	85 (26)	12 (4)	36 (11)[†]	18 (5)[†]	4 (1)[§]
Anemia	87 (26)	31 (9)	2 (1)	74 (22)	32 (10)[†]	3 (1)
Headache	85 (26)	3 (1)	0	43 (13)[†]	2 (1)	0
Anorexia	75 (23)	9 (3)	0	14 (4)[†]	1 (<1)[§]	0
Cough	70 (21)	2 (1)	0	35 (11)[†]	1 (<1)	0
Paresthesia	68 (21)	5 (2)	0	27 (8)[†]	0[§]	0
Dyspnea	65 (20)	16 (5)	1 (<1)	58 (17)	9 (3)	2 (1)
Neutropenia	62 (19)	40 (12)	8 (2)	5 (2)[†]	4 (1)[†]	0[†]
Rash	61 (18)	4 (1)	0	20 (6)[†]	0	0
Insomnia	60 (18)	1 (<1)	0	90 (27)[†]	5 (2)	0
Abdominal Pain	53 (16)	6 (2)	0	12 (4)[†]	1 (<1)	0
Bone pain	52 (16)	12 (4)	0	50 (15)	9 (3)	0
Pain in limb	50 (15)	5 (2)	0	24 (7)[†]	2 (1)	0
muscle Cramps	41 (12)	0	0	50 (15)	3 (1)	0

*More than one patient in the bortezomib group had additional grade 4 adverse events Including hypercalcemia, hyponatremia, sepsis, disease progression, renal failure and gastrointestinal hemorrhage.
[†]More than one patient in the dexamethasone group had additional grade 4 adverse events, including hyperglycemia, sepsis, septicshok , dyspnea, respiratory failure, renal failure. cerebrovas cular accident, pulmonary embolism, psychotic disorder, and death.
[‡]P<0.01 Proportions were compared with the use of Fisher's exact test.
[§]P<0.05. Proportions were compared with the use of Fisher's exact test.

OVERDOSAGE

Pharmacological studies in animals showed that the lethal IV doses are associated with decrease in blood pressure, increase in heart rate, increase in contractility, and ultimately terminal hypotension and at dose of 3.0 mg/m^2 and greater resulted in hypotension and slowly progressed to death by 12 to 14 hours following drug administration.
Overdosage more than twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fetal outcomes.

DOSAGE AND ADMINISTRATION

The recommended dose of NEOMIB® is 1.3 mg/m^2 /dose administrated as a 3 to 5 second bolus intravenous injection twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12-21). For extended therapy of more than 8 cycles, NEOMIB® may be administered on the standard schedule or on a maintenance schedule of once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35). At least 72 hours should elapse between consecutive doses of NEOMIB®

Dose Modification and Re-Initiation of Therapy
Bortezomib therapy should be withheld at the onset of any grade 3 non-hematological or grade 4 hematological toxicities excluding neuropathy as discussed below. Once the symptoms of the toxicity have resolved, Bortezomib therapy will be reinitiated at a 25% reduced (1.3 mg/m^2/dose reduced to 1.0 mg/m^2/dose: 1.0 mg/m^2/dose reduced to 0.7 mg/m^2/dose).
Table 2 contains the recommended dose modification for the management of patients who experienced Bortezomib related neuropathic pain and/or peripheral neuropathy. Patients with preexisting severe neuropathy should be treated with Bortezomib only after careful risk/benefit assessment.

Table 2: Recommended Dose Modification for BORTEZOMIB related Neuropathic Pain and/or Peripheral Sensory Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms	Modification of Dose and Regimen
Grade 1 (Paresthesias and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce BORTEZOMIB TO 1.0 mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold BORTEZOMIB therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of BORTEZOMIB at 0.7 mg/m^2 and change treatment schedule to once per week.
Grade 4 (disabling)	Discontinue BORTEZOMIB
Grading based on NCI Common Toxicity Criteria CTCAE v3.0 -	

Administration:
BORTEZOMIB is an antoneoplastic agent. Care should be taken during preparation and handling.
During the progress aseptic technique has to be used.
Use of gloves and other protective clothing to prevent skin contact is recommended.