Hepatobiliary disorders: Cholestasis, hepatic hemorrhage, hyperbilirubinemia, portal vein thrombosis, hepatitis, liver failure
Immune system disorders: Anaphylactic reaction, drug hypersensitivity, immune complex mediated hypersensitivity, angioedema, laryngeal edema
Infections and infestations: Aspergillosis, bacteremia, urinary tract infection, herpes viral infection, listeriosis, septic shock, toxoplasmosis, oral candidiasis, sinusitis, catheter related infection
Injury, poisoning and procedural complications: Catheter related complication, skeletal fracture, subdural hematoma
Metabolism and nutrition disorders: Hypocalcemia, hyperuricemia, hypokalemia, hyperkalemia, hyponatremia, hypernatremia
Nervous system disorders: Ataxia, coma, dysarthria, dysautonomia, encephalopathy, cranial palsy, grand mal convulsion, hemorrhagic stroke, motor dysfunction, spinal cord compression, paralysis, postherpetic neuralgia, transient ischemic attack
Psychiatric disorders: Agitation, confusion, mental status change, psychotic disorder, suicidal ideation
Renal and urinary disorders: Calculus renal, bilateral hydronephrosis, bladder spasm, hematuria, hemorrhagic cystitis, urinary incontinence, urinary retention, renal failure (acute and chronic), glomerular nephritis proliferative
Respiratory, thoracic and mediastinal disorders: Acute respiratory distress syndrome, aspiration pneumonia, atelectasis, chronic obstructive airways disease exacerbated, dysphagia, dyspnea, dyspnea exertional, epistaxis, hemoptysis, hypoxia, lung infiltration, pleural effusion, pneumonitis, respiratory distress, pulmonary hypertension
Skin and subcutaneous tissue disorders: Urticaria, face edema, rash (which may be pruritic), leukocytoclastic vasculitis
Vascular disorders: Cerebrovascular accident, cerebral hemorrhage, deep venous thrombosis, peripheral embolism, pulmonary embolism, pulmonary hypertension

DRUG INTERACTIONS

Ketoconazole
Co-administration of ketoconazole, a potent CYP3A inhibitor, increased the exposure of **Bortezomib.** Therefore, patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).
Melphalan-Prednisone
Co-administration of melphalan-prednisone increased the exposure of **Bortezomib**.
Omeprazole
Co-administration of omeprazole, a potent inhibitor of CYP2C19, had no effect on the exposure of **Bortezomib**.
Cytochrome P450
Patients who are concomitantly receiving **Bortezomib** and drugs that are inhibitors or inducers of cytochrome P450 3A4 should be closely monitored for either toxicities or reduced efficacy.

OVERDOSAGE

There is no known specific antidote for **bortezomib** overdose. In the event of an overdose, 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.

DIRECTIONS

Store below 30°C, Protect from direct light, To be sold on prescription only.
Keep out of the reach of children.

PRESENTATION

EGYBORT 1mg:is available in 5 ml vial in a plastic tray in unit carton along with package insert.
EGYBORT 3.5mg: is available in10 ml vial in a plastic tray in unit carton along with package insert.

Marketed by:
Revive healthcare
503, 5th Floor, Eden Heights, 6 Main Gulberg, Jail Road, Lahore - Pakistan 54600.

Manufactured by:
United Biotech (P) Limited
Bagbania, Baddi-Nalagarh Road, Distt. Solan (HP) - 174 101 - India

ایگیبورٹ

(بورٹیزومب) انجکشن
۳.۵ ملی گرام

دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
دوا کو روشنی سے محفوظ رکھیں۔
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
بچوں کی پہنچ سے دور رکھیں۔

EDa01-01

Rx Bortezomib for Injection 1mg/3.5mg

EGYBORT

(Lyophilized)
For Bolus Intravenous Injection

PHARMACEUTICALS WORLDWIDE
UNITED BIOTECH
The Emergence of a New Standard

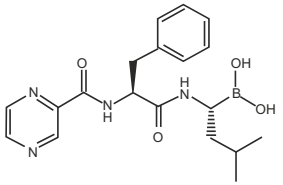
COMPOSITION

EGYBORT 1mg
Each Vial contains:
Bortezomib 1.0mg
(As per Innovator's Specs.)

EGYBORT 3.5mg
Each Vial contains:
Bortezomib 3.5mg
(As per Innovator's Specs.)

DESCRIPTION

EGYBORT (bortezomib for Injection) is an antineoplastic agent available for Intravenous Injection use only. The molecular formula is $C_{19}H_{25}BN_4O_4$.
The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) amino] propyl] amino] butyl] boronic acid.
Bortezomib has the following chemical structure:



CLINICAL PHARMACOLOGY

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.

Pharmacokinetics
Absorption: Following intravenous administration of 1.0 mg/m^2 and 1.3 mg/m^2 doses to 24 patients with multiple myeloma (n=12, per each dose level), the mean maximum plasma concentrations of **bortezomib** (C_{max}) after the first dose (Day 1) were 57 and 112 ng/mL, respectively. In subsequent doses, when administered twice weekly, the 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.
Distribution: The mean distribution volume of **bortezomib** ranged from approximately 498 to 1884 L/m^2 following single- or repeat-dose administration of 1.0mg/m^2 or 1.3mg/m^2 to patients with multiple myeloma. This suggests **bortezomib** distributes widely to peripheral tissues. The binding of **bortezomib** to human plasma proteins averaged 83% over the concentration range of 100 to 1000 ng/mL.
Metabolism: In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes 3A4, 2C19, and 1A2. Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor. The major metabolic pathway is deboronation to form 2 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.
Excretion: The mean elimination half-life of **bortezomib** upon multiple dosing ranged from 40 to 193 hours after the 1.0 mg/m^2 dose

and 76 to 108 hours after the 1.3mg/m^2 dose. The mean total body clearances was 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 and 1.3 mg/m^2, respectively.

Special Populations

Age: Analyses of data after the first dose of Cycle 1 (Day 1) in 39 multiple myeloma patients who had received intravenous doses of 1 mg/m^2 and 1.3 mg/m^2 showed that both dose-normalized AUC and Cmax tend to be less in younger patients. Patients < 65 years of age (n=26) had about 25% lower mean dose-normalized AUC and Cmax than those ≥65 years of age (n=13).

Pediatric Use: The safety and effectiveness of Bortezomib in children have not been established

Renal Impairment : The pharmacokinetics of Bortezomib are not influenced by the degree of renal impairment. Therefore, dosing adjustments of Bortezomib are not necessary for patients with renal insufficiency. Since dialysis may reduce Bortezomib concentrations, Bortezomib should be administered after the dialysis procedure

Hepatic Impairment: The exposure of bortezomib is increased in patients with moderate (bilirubin 1.5 – 3x ULN) and severe (bilirubin > 3 x ULN) hepatic impairment. Starting dose should be reduced in those patients

INDICATIONS

Multiple Myeloma

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

Mantle Cell Lymphoma

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

DOSAGE AND ADMINISTRATION

Mantle cell lymphoma

Usual dosage: 1.3mg/m2 dose twice weekly for 2 weeks (days 1,4,8,11) followed by a 10-day rest period (days 12-21).

Maintenance dosage: For extended therapy of more than 8 cycles, bortezomib may be administered on the standard schedule or on a maintenance schedule of once weekly for 4 weeks (days 1,8,10 and 22) followed by a 13-day rest period (days 23 to 35). At least 72 hours should elapse between consecutive doses of bortezomib.

Multiple Myeloma

Usual dosage:

Administration Precautions

Bortezomib Dosage Regimen for Previously Untreated Multiple Myeloma

Week	1				2		3	4		5		6
Twice-weekly Bortezomib (Cycles 1 through 4)												
Bortezomib 1.3mg/m^2	Day 1	-	-	Day 4	Day 8	Day 11	Rest Period	Day 22	Day 25	Day 29	Day 32	Rest Period
Melphalan 9mg/m^2 Prednisone 60 mg/m^2	Day 1	Day 2	Day 3	Day 4	-	-	Rest Period	-	-		-	Rest Period
Once weekly Bortezomib (Cycles 5 through 9 when used in combination with Melphalan and Prednisolone)												
Bortezomib 1.3mg/m^2	Day 1	-	-		Day 8		Rest Period	Day 22		Day 29		Rest Period
Melphalan 9mg/m^2 Prednisone 60 mg/m^2	Day 1	Day 2	Day 3	Day 4	-	-	Rest Period	-	-		-	Rest Period

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

- **Bortezomib** is an antineoplastic. Caution should be used during handling and preparation.
- Proper aseptic technique should be used.
- Use of gloves and other protective clothing to prevent skin contact is recommended

Reconstitution/Preparation for Intravenous Administration: Prior to use, the contents of each vial must be reconstituted with 3.5 mL (for 3.5mg vial) and 2ml (for 2mg vial) of normal (0.9%) saline, Sodium Chloride Injection. The reconstituted product should be a clear and colorless solution.

Stability: **Bortezomib** contains no antimicrobial preservative. 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 up to 8 hours in a syringe; however total storage time for the reconstituted material must not exceed 8 hours when exposed to normal indoor lighting.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Warnings

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

Precautions

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. Patients experiencing new or worsening peripheral neuropathy may require change in the dose and schedule of **bortezomib**.

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

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.

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.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): There have been rare reports of RPLS in patients receiving bortezomib. RPLS 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 RPLS, discontinue **bortezomib**.

Laboratory Tests: Complete blood counts (CBC) should be frequently monitored during treatment with **bortezomib**.

Gastrointestinal Adverse Events: Bortezomib treatment can cause nausea, diarrhea, constipation, and vomiting sometimes requiring use of antiemetic and antidiarrheal medications. Fluid and electrolyte replacement should be administered to prevent dehydration.

Thrombocytopenia / Neutropenia: Bortezomib is associated with thrombocytopenia and neutropenia. Platelets and neutrophils 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 and neutrophil decreases and recovery remained consistent over the 8 cycles of twice weekly dosing, and there was no evidence of cumulative thrombocytopenia or neutropenia. Platelet counts should be monitored prior to each dose of bortezomib. Bortezomib therapy should be held when the platelet count is <25,000/µL and reinitiated at a reduced dose. There have been reports of gastrointestinal and intracerebral hemorrhage in association with **bortezomib**.

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

Hepatic Events: 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**.

Patients with Hepatic Impairment: Bortezomib is metabolized by liver enzymes 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: Patients with renal impairment should be closely monitored for toxicities when treated with bortezomib.

PREGNANCY & LACTATION

Pregnancy 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.

Lactation It is not known whether **bortezomib** is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from **bortezomib**, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE EFFECTS

Blood and lymphatic system disorders: Disseminated intravascular coagulation, lymphopenia, leukopenia

Cardiac disorders: Angina pectoris, atrial fibrillation aggravated, atrial flutter, bradycardia, sinus arrest, cardiac amyloidosis, complete atrioventricular block, myocardial ischemia, myocardial infarction, pericarditis, pericardial effusion, Torsades de pointes, ventricular tachycardia

Ear and labyrinth disorders: Hearing impaired, vertigo

Eye disorders: Diplopia and blurred vision, conjunctival infection, irritation

Gastrointestinal disorders: Ascites, dysphagia, fecal impaction, gastroenteritis, gastritis hemorrhagic, hematemesis, hemorrhagic duodenitis, ileus paralytic, large intestinal obstruction, paralytic intestinal obstruction, peritonitis, small intestinal obstruction, large intestinal perforation, stomatitis, melena, pancreatitis acute, oral mucosal petechiae, gastroesophageal reflux

General disorders and administration site conditions: Injection site erythema, neuralgia, injection site pain, irritation, phlebitis