For the use only of a Registered Medicial Practitioner or a Hospital or a Laboratory

Bortezomib for Injection

Bortezomib 2 mg

**COMPOSITION**

Each vails contains:

Bortezomib..... 2 mg

Bortezomib 3.5mg

**COMPOSITION**

Each vials contains:

Bortezomib..... 3.5 mg

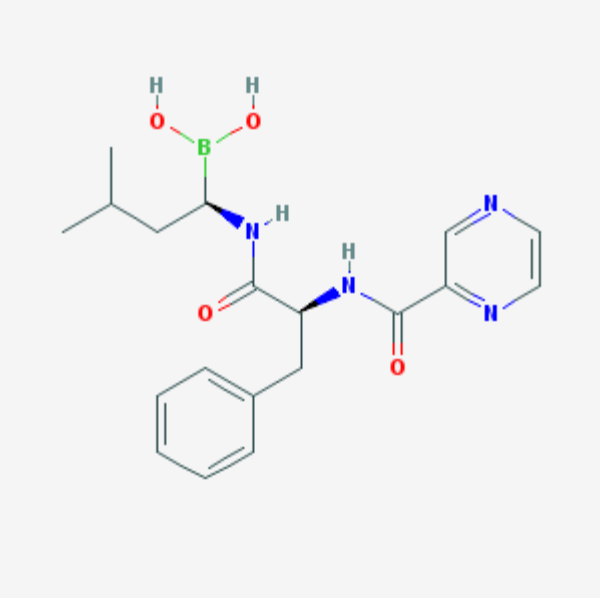
**DESCRIPTION**

Bortezomib for injection is an antineoplastic agent available for Intravenous Injection (IV) use only.

Each single use vials contains 2 mg of bortezomib as a sterile lyophilized powder. Bortezomib id modified dipeptidyl boronic acid. The Product is provided as a mannitol boronic ester which, in reconstituted from, consist of the mannitol ester in equilibrium with its chydrolysis product, the Monomeric boronic acid. The substance exits in its cyclic anhydride from as a trimericboroxine.

The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1[(2S)-1-oxo-3-phenyl-222-(pyrazinycarbony) amino]propyl]butyl] boronic acid.

Bortezomib has the following chemical structure:



The molecular weight is 384.24. The molecular formula is C19H25BN404. The solubility of bortezomib, as the monomeric boronic acid, in water is 3.3 to 3.8 mg/ml in a pH range of 2 to 6.5

**CLINICAL PHARMACOLOGY**

Mechanism of Actions: 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 ubiqutinated protein. The unbiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby mainatining homeostasis within cells. Inhabition of the 26S proteasome prevent this targeted proteolysis, which can affect multiple signallingcascedes with the cell.ThisDistruption of normal homeostatics mechanisms can lead to cell death. Experiments have demostrated that bortezomib id cytotoxic to a variety of cancer cell types in vitro. Bortezomib cause a dealay in turnor growth in vivo in nonclinical turnormodels,include multiple myeloma.3

**Pharmacodynamics:** Following twice weekly administration of 1 mg/m2 and 1.3 mg/m2 borttezomib doses (n=12 per each doses level),the madium inhibition of 20S proteasome activity (relative to baseline)ubn whole blood was obseverd5 minutes after drug administration . Comparable maximum inhibition of the 26S proteasome activity was obseverd between 1 and 1.3 mg/m2 doses . Maximal inhibitonranged from 70% to 84% and from 73% to 83% for the 1 mg/m2 and 1.3 mg/m2 dose regimens, respectively.

**Pharmacokinetics:**Following intravenous administration of 1 mg/m2 and 1.3 mg/m2 doses to 24 patients with multiple myeloma (n=2, per each dose level), the maximum plasma cincentration of bortezomib (Cmax) after first dose (Day 1) were 57 and 112 mg/ml, respectively. In subsequent doses, when adnministered twice weekly , the mean maximum observed plasma concentration rangs from 67 to 106 mg/ml for the 1 mg/m2 dose and 89 to 120 mg/ml for the 1.3 mg/m2 dose.The mean elimination half-life of bortezomib upon multiple dosing range from 40 to 193 hours after the 1 mg/m2 dose and 76 to 108 hours after the 1.3 mg/m2 doses. The mean total body clearance was 102 and 112 L/h following the frist doses of 1 mg/m2 and 1.3 mg/m2, respectively.

**Distrubition:** The mean distrubition volume of bortezomib ranged from approximately 498 to 1884 L/m2 following single- or –repeat –doses administration of 1 mg/m2 or 1.3 mg/m2 to patients with multiples myeloma. This suggest bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma protiens averaged 83% over the concentration range of 100 to 1000 mg/mL.

**Metalbolism:** In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metalbolized via cytochrome P450 enzymes 3A4, 2C19 and 1A2. Bortezomib Metabolism bt CYP 206 and 2CP enzymes is minor. The major

metabolic pathway is deboronation to form 2 deboronated metabolites that subsequently undergo hydroxylation to several metabolies.Doeboronated bortezomib are inactive as 26S proteasome inhibitor. 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.

**Age:** Analyses of data after the first dose of cycle 1 (Day 1) in 39 multiples myeloma patients who had received intravenous doses of 1 mg/m2 showed that both dose- normalized AUC and Cmaxtand to be less I n younger patients. Patients < 65 years of age (n=26) had about 25% lower means dose – normalized AUC and Cmax than those ≥ 65 year of age (n=3)

**Gender:**Means dose- normalized AUC and Cmax value were comparable between male(n=22) and female (n=17) patients after the first dose of cycle 1 for the 1 and 1.3 mg/m2 doses

**Race:**The effect of race on exposure to bortezomib could not be assessed as most of the patients were Caucasian.

**Hepatic Impairment:** The effect of hepatic impalrment (see Tablet 4 for definition of hepatic ompairment) on the Pharmacokinetics of bortezomib was assessed in 51 cancer patients at bortezomib doses ranging from 0.5 to 1.3 mg/m2.when compared to patients with normal hepatic function ,mild hepatic impairment did not alter dose-normalized bortezomib AUC. However ,the dose-normalized mean AUC value 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 monitored closely.

**Renal Impairment:** A pharmacokinetics study was conducted in patients with various degress of renal impairment who were classified according to their creatinine clearance value (CrCl) into the following group: Normal (CrCl≥60ml/min/1.73m2,N=12), Mild (CrCL=40-59ml/min/1.73m2,N=10), Moderate (CrCl=20-39ml/min/1.73m2N=9), and Severe (CrCL<20ml/min/1.73m2,N=3).A group of dialysis patients who were dosed after dialysis was also included in the study (N=8).Patients were administered intravenous doses of 0.7 to 1.3 mg/m2 of bortezomib twice weekly. Exposure of bortezomib (dose –normalized AUC and Cmax) was comparable among all the groups .

**Paedlatric :**There are no pharmacokinetic data in pediatric Patients.

**Effect of Ketoconazole:** Co-administration of Ketoconazole,a potent CYP3A inhibitor, showed a 35% increase in mean bortezomib AUC,based on data from 12 patients.

**Effect of Omeprazole:** Co-administration of melphalan-prednisone on ZORTEMIB showed a 17% increase in mean bortezomib AUC based on data from 21 patients. This increase is unlikely to be clinically relevant.

**Effect of Omeprazole:** Co-administration of omeprazole, a potent inhibitor of CYP2C19, had no significant effect on the pharmacokinetic ofbortezomib, based on data from 17 patients.

**CytochromeP450:** Bortezomib is a poor inhibitor of human liver microsome cytochrome P4501A2,

2C9, 2D6, and 3A4, with IC50 value of >30um (>11.5µg/ml).Bortezomib may inhibit 2C19 activity (IC50=18 µM, 6.9µg/ml) and increase exposure to drugs that are substrates for this enzymes.

Bortezomib did not induce the activities of cytochrome P450 3A4 and 1A2 in primary cultured human hepatocytes.

**INDICATIONS AND USAGE**

**Multiple Myeloma:** (bortezomib) for injection is indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

**Mantle 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**

Dosage in Previously Untreated Multiple Myeloma

(bortezomib) is administered as a 3-5 second bolus IV injection in combination with oral melphalan and oral prednisone for nine 6 week treatment cycles as shown in Tablet 1. In Cycle 1-4, is administered twice weekly (days 1, 4,8,11,22,25,29 and 32). In Cycle 5-9 is administered once weekly (day 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 1-4) | | | | | | | | | | | | |
| 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 (60mg/m2) | Day 1 | Day 2 | Day 3 | Day 4 | - | - | Rest Period | - | - | - | - | Rest Period |
| Once weekly Bortezomib (cycles 5-9 When used in combination with Melphalan and Prednisone | | | | | | | | | | | | |
| Week | 1 | | | | 2 | | 3 | 4 | | 5 | | 6 |
| Bortezomib (1.3mg/m2) | Day 1 | `- | - | | Day 8 | | Rest Period | Day 22 | | Day 29 | | Rest Period |
| Melphalan (9 mg/m2) Prednisone (60mg/m2) | Day 1 | Day 2 | Day 3 | Day 4 | - | - | Rest Period | - | - | - | - | Rest Period |

Dose Modification Guidelines for Combination Therapy with Zortemib, Melphalan and Prednisone

Prior to initating any cycle of therapy with Bortezomib in combination with melphalan and prednisone

Platelet count should be 270 × 109/L and the ANC should be ≥ 1.0 × 109/L
Non – hematological toxicities should have resolved to grade 1 or baseline

| Table 2-Dose Modification During Cycles of Combination Bortezomib, Melphalan and Prednisons Therapy | |
|---|---|
| Toxicity | Dose modification or delay |
| For information concerning melphalan and prednisone, see manufacturing prescribing information | |

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

**Dosage in Relapased Multiple Myeloma and Mantle cell Lymphome:**Boetezomib (1.3mg/m2/dose) is administered as a 3 to 5 second bolus intravenous injection twice weekly for 2 weeks (Day 1, 2, 8 and 11) followed by a 10-day rest period (Days 12-21). For extended therapy of more than 8 cycles weekly for 4 weeks (Days 1, 8, 15 and 22) followed by a 13-days rest period (Days 23 to 35). At least 72 hours should elapse between consecutive doses of Bortezomib.

Dose Modification Guidelines for Relapsed Multiple Myeloma and Mantle Cell Lymphoma:

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 may be reinitiated at a 25% reduced dose (1.3 mg/m2/dose reduce to 1mg/m2/dose reduced to 0.7 mg/m2/dose)

For the management of patients who experience. Bortezomib related neuropathic pain and/or peripheral neuropathy see Table 3. Patients should be treated with Bortezomib only after careful risk – benefit assessment.

| Table 3. Recommended Dose Modification for Bortezomib related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy | |
|---|---|
| Severity of peripheral Neuropathy sign and Symptoms | Modification of Dose and Regimen |
| Grading based on NCI Common Toxicity Criteria CTCAE v3.0 | |
| Grade 1 (paresthesisias , weakness and/or loss of reflexes ) without pain or loss of function | No action |
| Grade 1 with pain or Grad 2 (interfering with function but not with activities of daily living) | Reduce Bortezomib to 1 mg/m2 |

| | |
|---|---|
| Grade 2 with pain or Grade 3 (interfering with activities of daily living) | Withheld Bortezomib therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of Bortezomib at 0.7 mg/m2 and change treatment schedule to once per week |
| Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life treating or leads to paralysis) | Discontinue Bortezomib |

**Dosage in Patients with Hepatic Impairment:**Patients with mild hepatic impairment do not required a starting dose adjustment and should be treated per the recommended Bortezomib dose. Patients with moderate pr severe hepatic impairment should be started on Bortezomib at a reduced dose of 0.7 mg/m2 per injection during the first cycle, and a subsequent dose escalation to 1.0 mg/m2 or further dose reduction to 0.5 mg/m2 may be considered based on patients tolerance (see Table)

Table 4: Recommended Stating Dose Modification for Bortezomib in Patients with Hepatic impairment

Abbreviation: S60T = serum glutamic oxaloacetic transaminase;
AST = aspartate aminotransferase ; ULN = upper limit the normal range

| | Bilirubin Level | S60T(AST ) Level | Modification of starting Dose |
|---|---|---|---|
| Mild | ≤ 1.0x ULN | >ULN | None |
| | >1.0x UNL 1.5x UNL | Any | None |
| Moderate | >1.5x-3.0 X UNL | Any | Reduce Bortezomib to 0.7mg/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 patients tolerability |
| Severe | >3x UNL | Any | |

**Administration Precautions:**The drugs quality contained in one vial (3.5mg) may exceed the usal dose required. Caution should be used in calculating the dose to prevent overdose. ZORTEMIB is an antineoplastic. Procedure for proper handling and disposal should be considered .In clinical trials local skin irritation was reported in 5% of patients, but extravasation of ZORTEMIB was not associated with tissue damage.

Reconstitution/Preparation for Intravenous Administration : Proper aseptic technique should be used. Reconstitute with 2ml of 0.9% Sodium Chloride resulting in a final concentration of 2mg/vial of bortezomib. 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. It any discoloration or particulate matter is observed the reconstituted product should not be used.

Stability : unopened vials of ZORTEMIB are stable until the date indicated on thepackage when stored in the original package protected from light.

ZORTEMIB contains no antimicrobial preservative. Reconstituted ZORTEMIB should be administered within 8 hours of preparation. When reconstituted as directe, ZORTEMIB may be stored at 25°C (77°F). The product may be stored for upto 8 hours in a syringe, however total storage time for the reconstituted material must not exceed 8hours when exposed to normal indoor lighting.

DOSAGE FORMS AND STRENGTHS: Each single us a vial of ZORTEMIB contains 2mg of bortezomib as a sterile lyophilized powder.

CONTRAINDICATIONS: ZORTEMIB is contraindicated in patients with hypersensitivity to bortezomib, boron or mannitol.

**WARNINGS :**ZORTEMIB should be administered under the supervision of a physician experienced in the used of antineoplastic therapy. Complete blood counts (CBC) should be monitored frequently during treatment with ZORTEMIB.

Use in Pregnancy

Pregnancy Category D: Women of childbearing potential should avoid becoming pregnant while being treated with ZORTEMIB. Bortezomib administered to rabbits during organogenesis at a dose approximately 0.5 time the clinical dose of 1.3 mg/m2 based on body surface area caused post implantation loss and a deceased number of live fetuses.

Peripheral Neuropathy: ZORTEMIB 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 ZORTEMIB. Patients should be monitored for symptoms of neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy may require change in the dose and schedule of ZORTEMIB. Following dose adjustments, improvement in or resolution of peripheral neuropathy was reported in 50% of patients with ≥ Grade 2 peripheral neuropathy in the relapsed multiple myeloma study. 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.

**PRECAUTIONS:**

**Hypotension:** The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 13%.

Theses event are observed throughout therapy, caution should be used when treating patients with a history of syncope, patients receiving medications know 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 sympathomimetic.

**Cardiac Disorder:** Acute development or exacerbation congestive heart failure and new onset of decreased left ventricular ejection fraction have been reported, including reports in patients with a

history of syncope, patients with risk factors for existing heart diseases should be closely monitored in the rerelapsed multiple myeloma study, the incidence of any treatment-emerged cardiac disorder was 15% and 13% in the Zortemib and dexamethasone group, respectively. The Incidence of heart failure event (acute pulmonary edema, cardiac failure, congestive cardiac failure. Cardiogenic shock, pulmonary edema) was similar in the Zortemib and dexamethasone group, 5% and 4% respectively .There have been isolated cases of Qt-interval prolongation in clinical studies, causality has not been established

**Pulmonary Disorder:** There have been reports of acute diffuse infiltrative pulmonary disease of unkown etiology such as Pnemounitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress syndrome (ARDS) in patients receiving Bortezomib. Some of these events have been fatal.

In a clinical trial, the first two patients given high-dose cytarabine (2mg/m2 per day) by continues infusion with daunorubicin and Zortemib for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy. There have been reports of pulmonary hypertension associated with ZORTEMIB administration in the absences of left heart failure or significant pulmonary diseases.

In the event of new worsening cardiopulmonary symptoms, a prompt comprehensive diagnostic evaluation should be conducted.

**Reversible Posterior Leukoencephalopathy syndrome (RPLS):** There have been reports of RPLS in patients receiving ZORTIMIB. RPLS is a rare, reversite, neurological disorder which can present with seizure ,hypertension, headache, lethargy, confusion blindness, and other visual and neurological disturbances brain imaging preferably MRI (Magnetic Rsonance Imaging), is used to confirm the diagnosis. In patients developing RPLS, discontinuous ZORTEMIB. The safety of reinitiating ZORTEMIB therapy in patients previously experiencing RPLS is not known.

**Gastrointestinal Adverse Event:** ZORTEMIB treatment can cause nausea, diarrhea, constipation and vomiting. Sometimes requiring use of antiemetic and anti diarrhea medications, lieus can occurs fluid and electrolyte replacement should be administered to prevent dehydration.

**Thrombocytopenia/Neutropenia:** ZORTEMIB is associated with thrombocytopenia and neutropenia that allow a cyclical with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of the subsequent cycle. The cyclical patterns of platelet and neutrophiil decreases and recovery remaind consistent over the 8 cycle of twice weekly dosing. And there were no evidences of cumulative thrombocytopenia or neutropenia. The mean platelet count nadir measured was approximately 40% of baseline. The seventy of thrombocytopenia related to pretreatment platelet count is shown in Tablet 5. In the relapsed multiplies mymeloma study, the incidences of significant bleeding event (≥Grade 3) was similar on both the ZORTEMIB (4%) and dexamethasone (5%) arms. Platelet count should be monitored prior to each dose of ZORTEMIB. Patients experiencing thrombocytopenia may require change in the dose and schedule of ZORTEMIB. Transfusion may be considered .The incidence of febrile neutropenia was <1%

| Tablet 5 Severity of Thrombocytopenia Related to pretreatment patients count in the Relapsed Multiple Myeloma study | | | |
|---|---|---|---|
| Pretreatment Platelet Count * | Number of patients (N=331)** | Number (%) of patients with Platelet count <10,000/μL | Number (%) of patients with platelet count 10,000-25,000/-L |

| | | | |
|---|---|---|---|
| *A baseline platelet count of 50,000/μL. was required for study eligibility<br>**Data were missing at baseline for 1 patients | | | |
| ≥ 75,000/μL | 309 | 8(3%) | 36(12%) |
| ≥ 50,000/μL<br>≥75,000/μL | 14 | 2(14%) | 11(79%) |
| ≥10,000/μL | 7 | 1(14%) | 5(71%) |

**Tumor Lysis Syndrome:** Because Bortezomib is 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 mentioned closely and appropriate precaution taken.

**Hepatic event:** Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic event include increases in liver enzymes, hyperbilirubinemia, and hepatic. Such changes may be reversible upon discontinuation of BORTEZMIB. There is limited re-challenge information in these patients.

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

**ADVERSE REACTION:**

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

Peripheral Neuropathy
Hypotension
Cardiac Disorder
Pulmonary Disorder
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
Gastrointestinal Adverse Event
Thrombocytopenia/Neutropenia
Tumor Lysis Syndrome Hepatic Events

**Post marketing Experiences:** the following adverse drug reaction have been identified from worldwide post-marketing experiences with ZORTEMIB. Because these reaction are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate frequency or established a causal relationship to drugs exposure atrioventricular block complete cardic tamponande , ischemic colitis, encephalopathy, dysautonomia, deafness, bilateral, disseminated intravascular coagulation hepatitis , acute pancreatitis, acute diffuse infiltrative pulmonary diseases, toxic epidermal necrolysis , hepers , meningoencephalitis and ophthalmic herpes

**DRUG INTERRACTION:** Ketoconazole: co-administration of ketoconazole, a potent CYP3A inhibitor increased the exposure of bortezomib. Therefore patients should closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g. Ketoconazole, reltonavir)

**Melphalan- Prednisone**: Co-administration of melphalan –prednisone increased the exposure bortezomib . However, this increases is unlikely to be clinically relavant

**Omeprazole:** Co-administration of omeprazole, a potent inhibitors of CYP2C19, had no effect or exposure of bortezomib.

**Cytochrome P450:** Patients who are concomitantly receiving Bortezomib and drugs that are inhibitors or inducers of cytochrome P450 should be closely monitored for either toxicities or reduced efficiency

USE IN SPECIFIC POPULATIONS

**Pregnancy: Pregnancy Category D:** Bortezomib was not teratogenic in nonclinical development toxicity studies in rats and rabbits at the highest test(0.075mg/kg; 0.5mg/m2 in the rat 0.05mg/kg; 0.6 mg/m2 in the rabbits) When administered during organogenesis. These dosage are approximately half the clinical dose of 1.3 mg/m2 based on body surface area. Pregnant rabbits given bortezomib during organogenesis at a dose of 0.05mg/kg (0.6mg/m2) experienced significant post-implantation loss and decreased in fetal weight. The dose is approximately 0.5 times the clinical dose of 1.3 women. If Bortezomib is used during pregnancy ,or if the patients becomes pregnant while receiving this drug, the patients should be apprised of the potential hazard to the fetus.

**Nursing Mother:** It is not know whether bortezomib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactors discontinuous the drug taking into account the importance of the drug to the mother

**Pediatric Use:** the safety and effectiveness of ZORTEMIB in children have not been established

**Geriatrics Use:** of the 669 patients enrolled in the relapsed multiple myeloma study. 245(37%) 65 year of age or elders. 125(38%) on the Zortemib arm and 12(36%) on the dexamethasone arm. Median time to progression and median during of response for patients ≥65 were longer on Bortezomib compared to dexamethesone [5.5 mo versus 4.3 mo, and 8.0 mo versus 4.9 mo respectively ). On the Bortezomib arm, 40% (n=46) of evaluable patients aged ≥65 experienced response (CR+PR) versus 18% (n=21) on the dexamethsone arm. The incidence of Grade 3 and 4 events was 64%, 78% and 75% for bortezomib patients ≤50,51-64 and ≥65 year old , respectively. No overall differences in safety or effectiveness were observed between patients ≥ age 65 younger patients receiving ZORTEMIB but greater sensitivity of some older individual cannot be ruled out

**Patients with Renal Impairment:** The pharmacokinetics of ZORTEMIB are not influenced by degree of renal impairment. Therefore , dosing adjustment of ZORTEMIB are not necessary patients with renal insufficiency. Since dialysis may reduce ZORTEMIB concentrations, the drugs should be administered after the dialysis procedure. For information concerning dosing of melphalan in patients with renal impairment see manufacturing prescribing information

**Patients with Hepatic Impairment :** The exposure of bortezomib is increased in patients moderate and severe hepatic impairment. Starting dose should be reduce in those patients.

**Patients with Diabetes:** During clinical trials, hypoglycemia and hyperglycemia were reported in diabetic patients receiving oral hypoglycemia. Patients on oral antidiabetic agent receiving ZORTEMIB treatment may required close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medication

**OVERDOSAGE:**

There is no Known specific antidote for ZORTEMIB overdosage . in human , fatal outcomes followings the administration of more than twice the recommended therapeutic dose have been reported, which were associated with the acute onset of symptomatic hypotension thrombocytopenia. In the event of an overdosage , the patients vital signs should be monitored appropriate supportivecare given.

Studies in monkeys and dogs showed that IV bortezmib doses as low as 2 times the recommended clinical dose on mg/m2 basis were associated with increases in heart rate , decreases in contractility, hypotension, and death. In dog studies , a slight increases in the corrected QT intervals was observed at doses resulting in death. In monkey , doses of 3.0mg/m2 and greater (approxin twice recommended clinical doses) resulted in hypotension starting at 1 hours post –administration with progression to death in 12 to 14 hours following drug administration

**NON CLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of fertility:** Carcinogenically studies have not been conducted with bortezomib showed clastogenic activity (structure chromosomal aberrations) in the in vitro chromosomal aberration assay using. Chinese hamster overy cells. Bortezomib was not genotoxic when tested in the vitro mutagenicity assay (Ames test) and in vivo micronucleus tissue has been performed in the general toxicity studies. In the 6 month rat toxicity study, degenerative effect in the ovary were observed at doses ≥0.3mg/m2 (one –fourth of the recommended clinical dose ) and degenerative changes in the testes occurred at 1.2 mg/m2 Bortezomib could have ba potential effect on either male or female fertility

**Animal Toxicology:** Cardiovascular toxicity: Stuudies in Monkey showed that administration dosage approximately twice the recommended clinical doses resulted in heart rate elevations, followed by profound progressive hypotension , bradycardia, and death 12 to 14 hours post doses. Doses ≥1.2 mg/m2 induced dose- proportional change in cardiac parameters. Bortezomib ha s been shown to distribute the most tissues in the body, including the myocardium . In a repeated dosing toxicity study in the monkey , myocardial hemorrhage, information and necrosis were also observed. Chronic Administration: In animals studies at a dose and schedule similar to that recommended for patients (twice weekly dosing for 2 week followed by 1- week rest). Toxicities observed included severe anemia and thrombocytopenia and gastrointestinal, neurological and lymphoid system toxicities. Neurotoxic effect of bortezomib in animal studies included axonal additionally,multifocal hemorrhage and necrosis in the brain, eye, and heart were observed.

**Storage:** Store between 15°C & 30°C. Protection light

**PRESENTATION:** Bortezomib is available as vials containing 2 mg & 3.5 mg of Bortezomib as lyophilized Powder

Manufactured in India by:

**ZUVIUS LIFESCIENCES PVT. LTD.**
**A WHO-GMP CERTIFIED COMPANY**
B/111, 112, 113, Kanara Business Centre,
Link Road, Ghatkopar (East), Mumbai 400075.
**www.zuviuslifesciences.in**