Bortezomib for Injection

**INDICATIONS AND USE**

Bortezomib for injection is a selective proteasome inhibitor indicated for:

- Treatment of patients with multiple myeloma (1.1)
- Treatment of mantle cell lymphoma (1.2)

**DOSAGE AND ADMINISTRATION**

- Do not use injection in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min).
- For patients with renal impairment, adjust the dose of bortezomib to maintain plasma concentrations at the lower end of the normal range.
- For patients with severe renal impairment, the recommended starting dose of bortezomib for injection is 1 mg/m² (0.5 mg/m² in the rat and 0.05 mg/kg; 0.6 mg/m² in the rabbit) at the recommended dose and schedule.
- For patients with moderate renal impairment (creatinine clearance 31-60 mL/min), reduce the dose to 1 mg/m² (0.5 mg/m² in the rat and 0.05 mg/kg; 0.6 mg/m² in the rabbit) at the recommended dose and schedule.

**CONTRAINDICATIONS**

- Patients with hypersensitivity to bortezomib or any of its components.
- Patients with thrombocytopenia (ANC not above 1,500 cells/μL) are not candidates for bortezomib injection.

**WARNINGS AND PRECAUTIONS**

- Peripheral Neuropathy: Manage dose reduction if dose reduction or discontinuation is required due to neuropathy. Monitor patients for peripheral neuropathy and dose reduction or discontinuation as necessary.
- Cardiac Toxicity: Assessing and monitoring patients for cardiac failure is recommended.
- Pulmonary Toxicity: Assessing and monitoring patients for infiltrative pulmonary disease is recommended.
- Gastrointestinal Toxicity: Assessing and monitoring patients for gastrointestinal toxicity is recommended.
- Hypertension: Assessing and monitoring patients for hypertension is recommended.
- Renal and Urinary Disorders: Assessing and monitoring patients for renal and urinary disorders is recommended.
- Nervous System Disorders: Assessing and monitoring patients for nervous system disorders is recommended.
- Gastrointestinal Disorders: Assessing and monitoring patients for gastrointestinal disorders is recommended.

**ADVERSE REACTIONS**

- Most commonly reported adverse reactions (incidence ≥ 20% in clinical studies or postmarketing surveillance) are:
  - Neutropenia
  - Thrombocytopenia
  - Diarrhea
  - Nausea
  - Fatigue

**DRUG INTERACTIONS**

- Avoid concurrent use with strong CYP3A4 inhibitors. (7.3)
- Bortezomib may be administered intravenously at a concentration of 100 to 1,000 ng/mL.

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DOSAGE FORMS AND STRENGTHS
For injection, 3.5 mg of bortezomib as a white or off-white lyophilized powder in a single-dose vial for reconstitution (see Dose and Administration, 2.8).

CONTRAINDICATIONS
Bortezomib is contraindicated in patients with hypersensitivity to bortezomib, Bortezomib for Injection, or any component of the formulation. Patients must be monitored for anaphylactic reactions during and after reconstitution and administration. See Adverse Reactions (6.6).

2.6 Dosage in Patients with Hepatic Impairment

For patients with moderate hepatic impairment, administer bortezomib at a reduced dosage of 0.7 mg/m² based on body surface area (see Dose and Administration, 2.8).

5.1 Peripheral Neuropathy

Overall, peripheral neuropathies occurred in 38% of patients. The most common adverse reactions from the relapsed multiple myeloma trials were sensory peripheral neuropathy (25%), with an additional 12% experiencing a sensory and motor peripheral neuropathy. The adverse reactions occurred both during treatment and after treatment had been discontinued. Median time to onset was 3 months (range, 1 to 46 months) from the start of bortezomib treatment. Patients with symptomatic neuropathy should receive symptomatic treatment (see Management of Toxicity, 5.1).

8.6 Patients with Renal Impairment

In the relapsed multiple myeloma and relapsed acute myelogenous leukemia trials, bortezomib treatment did not result in an increased incidence of adverse reactions compared to patients with normal renal function. However, patients with renal impairment, particularly those on dialysis or with severe renal impairment (creatinine clearance of < 30 mL/min), should be dosed with caution (see Dose and Administration, 2.8).

5.6 Gastrointestinal Toxicity

Gastrointestinal adverse reactions were less common in bortezomib-treated patients compared to melphalan-prednisone patients. The most common adverse reactions in bortezomib-treated patients were abdominal pain (23%) and diarrhea (11%), whereas in melphalan-prednisone patients the most common adverse reactions were vomiting (33%) and abdominal pain (15%).

6.2 Postmarketing Experience

In the postmarketing experience, neoplastic disorders were reported in 3.6% of patients treated with bortezomib. These included solid tumors (1.2%), non-Hodgkin lymphomas (1.2%), Hodgkin lymphoma (0.7%), and multiple myeloma (0.3%).

12.3 Pharmacokinetics

The plasma protein binding of bortezomib is approximately 15% in vitro. The plasma binding of bortezomib is similar in normal subjects and in plasma from patients with multiple myeloma, and is not significantly affected by the introduction of an anticoagulant. Bortezomib is extensively absorbed following oral administration, with peak plasma concentrations occurring within 1 to 4 hours. The volume of distribution of bortezomib is approximately 40 liters.

12.1 Mechanism of Action

The binding of bortezomib to human plasma proteins averaged 83% (N=1,008). The plasma binding of bortezomib is similar in normal subjects and in plasma from patients with multiple myeloma, and is not significantly affected by the introduction of an anticoagulant.

5.2 Cardiac Toxicity

In the relapsed multiple myeloma trial, 10% of patients experienced moderately severe (Grade 2) or severe (Grade 3 or 4) cardiac toxicity. The most common adverse reactions from the relapsed multiple myeloma trials were ventricular arrhythmia (1%), atrial fibrillation (1%), and myocardial infarction (1%).

6.3 Disposition

The systemic exposure of bortezomib is increased with increasing dose and duration of dosing. The systemic exposure of bortezomib decreases with increasing time from the last dose, likely due to the slow rate of complete absorption and distribution. The systemic exposure of bortezomib is increased in patients with hepatic impairment, and is decreased in patients with renal impairment.

7.4 Effect of Dexamethasone on Bortezomib

Coadministration of dexamethasone with bortezomib had no clinically significant effect on the pharmacokinetics of bortezomib in patients with relapsed multiple myeloma. The Cmax and AUC values of bortezomib were similar in patients treated with bortezomib alone and in patients treated with bortezomib plus dexamethasone.

5.3 Cardiac Toxicity

Cardiac arrhythmias were reported in 17% of patients receiving bortezomib. The most common adverse reactions were sinus tachycardia (7%), atrial fibrillation (4%), and ventricular tachycardia (2%). These findings are consistent with the known safety profile of both bortezomib and anti-myeloma agents.
Dosage and Dose Modifications for Relapsed Multiple Myeloma

- The recommended starting dose of bortezomib for injection is 1.3 mg/m².

5.6 Gastrointestinal Toxicity

- Bortezomib for Injection is contraindicated in patients with hyperlipidemia.

8.2 Lactation

- Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits at the highest dose tested (30 mg/kg in rats and 0.5 mg/kg in rabbits).

bortezomib, boron, boric acid, glycine, including anaphylactic reactions. Bortezomib for Injection is contraindicated in patients with hyperlipidemia.

5.10 Embryo-fetal Toxicity

- Cases of acute liver failure have been reported in patients receiving bortezomib.

Because many drugs are excreted in human milk, their potential effects on a breastfed infant must be considered when administering bortezomib to a nursing mother.

8.3 Females and Males of Reproductive Potential

- The binding of bortezomib to human plasma proteins averaged 83%.

The percentage of patients with neutropenia, 73% reported improvement or resolution of peripheral neuropathy, 73% reported improvement or resolution.
Fertility studies with bortezomib were not performed but evaluation of carcinogenicity studies have not been conducted with bortezomib.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Use in Specific Populations (8.6)

2.6.2 Dose-Ranging Study (see also Table 12)

2.6.3 Multiple Myeloma Study

Clinical Studies

14.1 Multiple Myeloma

A prospective, international, randomized (1:1), open-label clinical study in patients with relapsed multiple myeloma has been conducted with bortezomib. Patients were randomized to receive bortezomib in combination with melphalan (9 mg/m2) and prednisone (60 mg/m2) in patients with progressive multiple myeloma. The primary endpoint of the study was the difference in time to progression (TTP) compared to high-dose dexamethasone (90 mg/m2 daily for 14 days every 21 days) following the first dose. Ninety-eight percent of patients had prior bortezomib treatment, and 47% had prior lenalidomide treatment. TTP was statistically significantly longer on the bortezomib arm (see Figure 2). The median follow-up time was 2.9 months.

14.2 Multiple Myeloma: Renal Impairment

In an open-label, single-arm study, thirty-seven percent (37%) of patients had renal impairment (as defined by eGFR<60 mL/min/1.73 m2). Ninety-five percent of patients had at least one prior line of therapy. TTP was statistically significantly longer on the bortezomib arm. Overall survival was statistically significantly longer on the bortezomib arm compared to the high-dose dexamethasone arm (see Figure 3). The median follow-up was 6.1 months.

15 REFERENCES

http://www.osha.gov/SLTC/hazardousdrugs/index.html

A Randomized Phase 2 Dose-Response Study in Relapsed Myeloma

A prospective phase 2, international, randomized (1:1), stratified, open-label clinical study enrolling 184 patients was designed to compare the maximum effect of rifampin administered alone with the maximum effect of rifampin administered in combination with rifabutin. Decreases greater than or equal to 45% may occur, as the drug interaction may be additive in vitro.

Adverse Reactions (6.1)

Bortezomib is administered intravenously (1.3 mg/m2) in combination with melphalan (9 mg/m2) and prednisone (60 mg/m2) in patients with progressive multiple myeloma. The primary endpoint of the study was the difference in time to progression (TTP) compared to high-dose dexamethasone (90 mg/m2 daily for 14 days every 21 days) following the first dose. Ninety-eight percent of patients had prior bortezomib treatment, and 47% had prior lenalidomide treatment. TTP was statistically significantly longer on the bortezomib arm (see Figure 2). The median follow-up time was 2.9 months.

Overall survival was statistically significantly longer on the bortezomib arm compared to the high-dose dexamethasone arm (see Figure 3). The median follow-up was 6.1 months.

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Patients in the bortezomib treatment group were included in 258 patients treated with bortezomib. The median duration of follow-up was 6.1 months. The median overall survival for the bortezomib, melphalan and prednisone arm (see Figure 2) was 14.7 months (range 31 to 204 days). The median overall survival for the bortezomib arm (see Figure 2) was 18.0 months (range 2.5 to 212 days). See also Table 12.

For detailed drug information, please consult the references.

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In the bortezomib arm, 39% of patients received at least one dose of bortezomib. Four patients had a single dose and 24 patients had multiple doses. The median number of doses was 1 (range 1 to 14). The median overall survival for the bortezomib arm (see Figure 2) was 18.0 months (range 2.5 to 212 days). See also Table 12.

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Fertility studies with bortezomib were not performed but evaluation in vitro and the coadministration of Bortezomib for injection is not expected to decrease the exposure of bortezomib by at least 45%.

Decreases greater than 45% may occur, as the drug interaction expected to decrease the exposure of bortezomib by at least 45%.

omeprazole, a strong inhibitor of CYP2C19, had no effect on the CLINICAL STUDIES

p-value < 10^-10

nCR n (%) 5 (1) 0

Mediana (months) 18.3 14

(95% CI) (16.6, 21.7) (11.1, 15)

[225x719]the ovary were observed at doses of 1 mg/m2 (one-fourth of the OSHA recommended limit) starting at 7 days of age. At 12 weeks (end of the 6-month rat toxicity study), degenerative effects in the brain, eye, and heart were observed.

In the tissue and organ studies, it was noted that Bortezomib did not induce the CYP3A4 or 1A2 activity in vitro. Decreases greater than 45% may occur, as the drug interaction expected to decrease the exposure of bortezomib by at least 45%.

[14 CLINICAL STUDIES]

[188x637 to 383x739]

[Image 189x637 to 383x739]

[Image 190x787 to 380x884]

[242x900]Figure 3: Time to Progression

Borretizomib versus Melphalan and Prednisone (unplanned multiple myeloma study)

As shown in Figure 4, bortezomib had a significant survival advantage relative to the other groups (p < 0.05). The median follow-up time was 8.3 months.

[188x962]e   Response population includes patients who had measurable disease at baseline and received at least one dose in all 9 cycles.

d  Precise p-value cannot be rendered

Table 3: Summary of Efficacy Analyses in the Relapsed Multiple Myeloma Study

<table>
<thead>
<tr>
<th></th>
<th>p-value</th>
<th>Median (Range)</th>
</tr>
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<tr>
<td>Median Time to Progression (months)</td>
<td>18.3</td>
<td>14 (95% CI: 16.6, 21.7)</td>
</tr>
<tr>
<td>OR = 0.39 (0.22, 0.70)</td>
<td>4.9 mo</td>
<td>4.2 (0.4, 6.3)</td>
</tr>
<tr>
<td>OR = 0.38 (0.27, 0.54)</td>
<td>4.9 mo</td>
<td>6.3 (3.4, 10.6)</td>
</tr>
<tr>
<td>OR = 0.39 (0.27, 0.56)</td>
<td>4.9 mo</td>
<td>3.4 (2.1, 6.3)</td>
</tr>
<tr>
<td>OR = 0.38 (0.28, 0.54)</td>
<td>4.9 mo</td>
<td>6.3 (3.8, 9.8)</td>
</tr>
<tr>
<td>OR = 0.37 (0.26, 0.55)</td>
<td>4.9 mo</td>
<td>3.4 (2.1, 6.3)</td>
</tr>
</tbody>
</table>


16 HOW SUPPLIED/STORAGE AND HANDLING

Bortezomib for injection is supplied in a 1-mL vial containing 3.5 mg of bortezomib as a white to off-white cake or powder in a single-use vial for reconstitution (after reconstitution the solution is colorless and clear).