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APPLICATION NUMBER:

209191Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology Memo

NDA Number	209191 (SDN 30)
Submission Date	05/16/2018
Submission Type	505(b)(2), resubmission
Brand Name	Bortezomib for injection
Generic Name	Bortezomib
Dosage Form and Strength	1.3 mg/m ² administered either as a 3 to 5 second bolus injection or subcutaneous injection; 2.5 mg/vial
Route of Administration	Intravenous or subcutaneous injection
Proposed Indication	Treatment of multiple myeloma
Applicant	Hospira Inc.
OCP Review Team	Guoxiang Shen, Ph.D. and Olanrewaju Okusanya, Pharm.D., MS
OCP Final Signatory	Olanrewaju Okusanya, Pharm.D., MS

This resubmission is an amendment to NDA 209191 for Bortezomib for Injection, 2.5 mg/vial, single dose vial. This amendment provides a response to the Agency's Complete Response Letter dated February 22, 2018. The applicant provided responses to the Agency's comments regarding product quality, prescribing information, carton and container labeling and safety update.

The resubmission contains no new clinical pharmacology information for review. This memo finalizes our review of this NDA.

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/s/

GUOXIANG SHEN
06/25/2018

OLANREWAJU OKUSANYA
06/30/2018

Office of Clinical Pharmacology Memo

NDA Number	209191 (SDN 25)
Submission Date	12/22/2017
Submission Type	505(b)(2), resubmission
Brand Name	Bortezomib for injection
Generic Name	Bortezomib
Dosage Form and Strength	1.3 mg/m ² administered either as a 3 to 5 second bolus injection or subcutaneous injection; 2.5 mg/vial
Route of Administration	Intravenous or subcutaneous injection
Proposed Indication	Treatment of multiple myeloma
Applicant	Hospira
OCP Review Team	Guoxiang Shen, Ph.D. and Gene Williams, Ph.D.
OCP Final Signatory	Gene Williams, Ph.D.

This is a resubmission to address the deficiencies identified in the Agency's Complete Response Letter dated November 3, 2017. The applicant provided responses to the Agency's comments regarding facility inspections, prescribing information, carton and container labeling and safety update.

The resubmission contains no new clinical pharmacology information for review. This memo finalizes our review of this NDA.

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/s/

GUOXIANG SHEN
02/09/2018

GENE M WILLIAMS
02/09/2018
I concur with the recommendations

Office of Clinical Pharmacology Memo

NDA or BLA Number	NDA 209191
Link to EDR	\\CDSESUB1\evsprod\NDA209191\0018
Applicant	Hospira
Submission Date	09/07/17
Submission Type	Resubmission/Class 1
Brand Name	Bortezomib for injection
Generic Name	Bortezomib
Dosage Form and Strength	1.3 mg/m ² administered either as a 3 to 5 second bolus injection or subcutaneous injection; 2.5 mg/vial
Route of Administration	Intravenous or subcutaneous injection
Indication	Treatment of multiple myeloma
OCP Review Team	Yuhong Chen, MD & Ph.D.; Stacy Shord, Pharm.D.
OCP Final Signatory	Stacy Shord, Ph.D. Team Leader Division of Clinical Pharmacology V

Bortezomib for injection (Bortezomib) was tentatively approved for the treatment of patients with multiple myeloma on 04/26/2017. The recommended dose for bortezomib is 1.3 mg/m² administered either as a 3 to 5 second bolus injection or subcutaneous injection with strength of 2.5 mg/vial. In the tentative approval letter, the Agency stated "To obtain final approval of this application, submit an amendment two or six months prior to the: 1.) expiration of the patent or 2.) date you believe that your NDA will be eligible for final approval, as appropriate." The applicant submitted the request for final approval according to the Agency's requirement. The labeling was revised to be consistent with the current labeling practices as outline in the Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format. in the original NDA 209191 submission on 06/30/2016.

The Office of Clinical Pharmacology will not be reviewing this application as there is no updated clinical pharmacology information.

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/s/

YUHONG CHEN
11/01/2017

BRIAN P BOOTH
11/01/2017

Clinical Pharmacology Review	
NDA	209190
Type/Category	Original 505(b)(2) New Drug Application
Brand Name	Bortezomib for Injection
Generic name	Bortezomib
Proposed Indications	Treatment of multiple myeloma
Dosage Form	Lyophilized Powder
Route of Administration	Intravenous or Subcutaneous
Dosing Regimen and Strength	1.3 mg/m ² administered either as a 3 to 5 second bolus injection; 2.5 mg/vial
Applicant	Hospira
OCP Division	DCPV
OND Division	DHP
Submission Date	June 30, 2016
PDUFA	April 2, 2017

EXECUTIVE SUMMARY

The Applicant submitted a New Drug Application (NDA) for Bortezomib for Injection in accordance with Section 505(b)(2) of the Federal Food, Drugs, and Cosmetic Act. The Applicant developed a 2.5 mg per vial strength as a means to reduce drug waste. Velcade, the listed drug, is currently available as a 3.5 mg/vial presentation. The Applicant states that the concentration per millimeter of active ingredient on reconstitution remains the same at the Velcade drug product. No new clinical pharmacology information was included in this application. The proposed labeling included the same content as listed in the Velcade labeling. The proposed labeling was modified in accordance with current labeling practices and Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (December 2016).

RECOMMENDATION

This original application is acceptable from a clinical pharmacology perspective provided that the applicant and FDA come to an agreement regarding the labeling.

Signatures:

Yuhong Chen, MD, Ph.D
 Primary Reviewer
 Division of Clinical Pharmacology V

Stacy S. Shord, Pharm.D.
 Team Leader
 Division of Clinical Pharmacology V

Cc: DHP: RPM – K Kolibab; MO – B Kanapuru; MTL – N Gormley
 DCPV: DDD – B Booth; DD – NA Rahman

SUMMARY OF CLINICAL PHARMACOLOGY LABELING

The Applicant submitted a New Drug Application (NDA) for Bortezomib for Injection in accordance with Section 505(b)(2) of the Federal Food, Drugs, and Cosmetic Act. No new clinical pharmacology information was included in this application. The proposed labeling included the same content as listed in the Velcade labeling. The proposed labeling was modified in accordance with current labeling practices and Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (December 2016). The table below provides a side by side comparison of the proposed labeling and the FDA recommended labeling.

Labeling Section	Applicant Proposed Labeling	FDA Proposed Labeling
<p>2 DOSAGE AND ADMINISTRATION</p>	<p>(b) (4) Dosage in Patients with Hepatic Impairment</p> <p>(b) (4)</p>	<p>2.6 Dosage in Patients with Hepatic Impairment</p> <p>Do not adjust the starting dose for patients with mild hepatic impairment.</p> <p>Start patients with moderate or severe hepatic impairment at a reduced dose of 0.7 mg/m² per injection during the first cycle, and consider subsequent dose escalation to 1 mg/m² or further dose reduction to 0.5 mg/m² based on patient tolerance (Table 4) [see <i>Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)</i>].</p>
<p>7 DRUG INTERACTIONS</p>	<p>7 DRUG INTERACTIONS</p> <p>(b) (4)</p> <p>7.1 CYP3A4 inhibitors</p> <p>(b) (4)</p>	<p>7 DRUG INTERACTIONS</p> <p>7.1 Effect of Strong CYP3A4 Inhibitors on Bortezomib</p> <p>Monitor patients for signs of bortezomib toxicity and consider a bortezomib dose reduction if bortezomib must be given with strong CYP3A4 inhibitors (b) (4)</p> <p>7.2 Effect of Strong CYP3A4 Inducers on Bortezomib</p> <p>Avoid strong CYP3A4 inducers. The coadministration of a strong CYP3A4 inducer is expected to decrease the exposure of bortezomib (b) (4)</p> <p>Efficacy may be reduced when</p>

	<p>7.2 CYP2C19 inhibitors</p> <p>(b) (4)</p> <p>7.3 (b) (4)</p> <p>(b) (4)</p> <p>7.4 (b) (4)</p> <p>(b) (4)</p>	<p>Bortezomib for Injection is coadministered with strong CYP3A4 inducers.</p> <p>Avoid St. John’s Wort (<i>Hypericum perforatum</i>), as it may decrease bortezomib exposure unpredictably.</p> <p>7.3 Effect of Dexamethasone on Bortezomib</p> <p>The coadministration of dexamethasone, (b) (4) had no effect on bortezomib exposure.</p> <p>7.4 Effect of Melphalan-Prednisone on Bortezomib</p> <p>The coadministration of melphalan-prednisone had no clinically important effect on bortezomib exposure.</p>
<p>8 USE IN SPECIFIC POPULATIONS</p>	<p>8.6 Patients with Renal Impairment</p> <p>The pharmacokinetics of bortezomib for injection is not influenced by the degree of renal impairment. (b) (4) dosing adjustments of bortezomib for injection are not necessary for patients with renal</p>	<p>8.6 Patients with Renal Impairment</p> <p>The pharmacokinetics of bortezomib for injection is not influenced by the degree of renal impairment. Dosing adjustments of bortezomib for injection are not necessary for patients with renal impairment. Since</p>

	<p>(b) (4). Since dialysis may reduce bortezomib concentrations, (b) (4) (b) (4) [see <i>Clinical Pharmacology (12.3)</i>].</p> <p>8.7 Patients with Hepatic Impairment</p> <p>(b) (4)</p>	<p>dialysis may reduce bortezomib concentrations, administer Bortezomib for Injection after the dialysis procedure [see <i>Clinical Pharmacology (12.3)</i>].</p> <p>8.7 Patients with Hepatic Impairment</p> <p>Reduce starting dose in patients with moderate (bilirubin greater than 1.5 to 3 times upper limit of normal (ULN) and any AST) and severe (bilirubin greater than 3 times ULN and any AST) hepatic impairment [see <i>Dosage and Administration (2.6)</i>, <i>Clinical Pharmacology (12.3)</i>].</p>
<p>12 CLINICAL PHARMACOLOGY</p>	<p>12.3 Pharmacokinetics</p> <p>Following intravenous administration of 1 mg/m² and 1.3 mg/m² (b) (4) (b) (4)</p>	<p>12.3 Pharmacokinetics</p> <p>Following intravenous administration of 1 mg/m² and 1.3 mg/m², the mean maximum plasma concentrations of bortezomib (C_{max}) after the first dose (Day 1) were 57 ng/mL and 112 ng/mL, respectively. When administered twice weekly, the mean maximum observed plasma concentrations ranged from 67 ng/mL to 106 ng/mL following a 1 mg/m² dose and 89 ng/mL to 120 ng/mL following a 1.3 mg/m² dose.</p> <p>Following an intravenous bolus or subcutaneous injection of a 1.3 mg/m² dose, AUC_{last} after multiple-dose administration was similar for subcutaneous and intravenous administration. The C_{max} after subcutaneous administration (20.4 ng/mL) was lower than intravenous administration (223 ng/mL).</p> <p>Distribution</p> <p>The mean distribution volume of bortezomib ranged from approximately 498 L/m² to 1884 L/m² following single- or multiple-dose administration of 1 mg/m² or 1.3</p>

	<p>(b) (4)</p> <p>Distribution: The mean distribution volume of bortezomib ranged from approximately 498 to 1884 L/m² following single-or (b) (4)-dose administration of 1 mg/m² or 1.3 mg/m² (b) (4)</p> <p>The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100 to 1000 ng/mL.</p> <p>Metabolism: (b) (4)</p> <p>(b) (4)</p> <p>Elimination: (b) (4)</p>	<p>mg/m².</p> <p>The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100 to 1000 ng/mL.</p> <p>Elimination</p> <p>The mean elimination half-life of bortezomib after multiple-dose administration ranged from 40 hours to 193 hours after the 1 mg/m² dose and 76 hours to 108 hours after the 1.3 mg/m² dose. The mean total body clearance was 102 L/h and 112 L/h following the first dose for doses of 1 mg/m² and 1.3 mg/m², respectively, and ranged from 15 L/h to 32 L/h following subsequent doses for doses of 1 mg/m² and 1.3 mg/m², respectively.</p> <p>Metabolism: 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 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to bortezomib.</p> <p>In vitro studies indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 (CYP) enzymes 3A4, 2C19, and 1A2. Bortezomib metabolism by CYP2D6 and 2C9 enzymes is minor.</p> <p>Excretion: The pathways of elimination of bortezomib have not been characterized.</p> <p>Specific Populations</p> <p>Age: Analyses of data after the first dose of Cycle 1 (Day 1) in patients who had received intravenous doses of 1 mg/m² or 1.3 mg/m² showed</p>
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(b) (4)

that both dose-normalized AUC and C_{max} tend to be less in younger patients. Patients less than 65 years of age had about 25% lower mean dose-normalized AUC and C_{max} than those greater than or equal to 65 years of age.

Sex: Sex has no clinically important effect on bortezomib exposure.

Hepatic Impairment: Mild hepatic impairment had no clinically important effect on dose-normalized AUC or C_{max} . The dose-normalized mean AUC was increased by approximately 60% in patients with moderate hepatic impairment (defined as total bilirubin greater than 1.5 to 3 times the upper limit of normal and any AST) or severe hepatic impairment (defined as total bilirubin greater than 3 times the upper limit of normal and any AST) [see *Dosage and Administration (2.6) and Use in Specific Populations (8.7)*].

Hepatic Impairment:

(b) (4)

(b) (4)

Renal Impairment: Dose-normalized AUC and C_{max} was comparable for patients with creatinine clearance (CLcr) from 59 mL/min/1.73 m² to less than 20 mL/min/1.73 m² compared to patients with CLcr greater than or equal to 60 mL/min/1.73 m² [see *Use in Specific Populations (8.6)*].

Drug Interaction Studies

Effect of Other Drugs on Bortezomib: The coadministration of omeprazole, a strong inhibitor of CYP2C19, had no effect on the exposure of bortezomib.

The coadministration of ketoconazole, a strong CYP3A4 inhibitor, increased the exposure of bortezomib by 35%.

Renal Impairment:

(b) (4)

The coadministration of rifampin, a strong CYP3A4 inducer, is expected to decrease the exposure of bortezomib by at least 45%. Decreases greater

(b) (4)

than 45% may occur, as the drug interaction trial was not designed to evaluate the maximum effect of rifampin on bortezomib exposure.

Effect of Bortezomib on Other Drugs: Bortezomib inhibits CYP2C19 activity in vitro and the coadministration of Bortezomib for Injection with sensitive or narrow therapeutic CYP2C19 substrates may increase their exposure. Bortezomib did not inhibit CYP1A2, 2C9, 2D6, or 3A4 in vitro.

Bortezomib did not induce CYP3A4 or 1A2 activity in vitro.

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/s/

YUHONG CHEN
03/24/2017

STACY S SHORD
03/24/2017
I concur.