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RESEARCH**

APPLICATION NUMBER:

209191Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	2-Jul-2018
From	Sherita McLamore, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA	209191
Type of Application	505(b)(2)
Applicant	Hospira Inc.
Date of Receipt	16-May-18
PDUFA Goal Date	16-Jul-18
Proposed Proprietary Name	None
Dosage forms / Strength	Injection/2.5 mg/vial
Route of Administration	Intravenous or Subcutaneous
Proposed Indication(s)	Indicated for the treatment of multiple myeloma
Recommended:	APPROVAL

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Clinical (Bindu Kanapuru, M.D.)
- Pharmacology/Toxicology (Emily Place, Ph.D.)
- DEMPA (Nicole Garrison, Pharm. D.)
- Drug Product (Rajiv Agarwal, Ph.D.)
- Drug Substance (Hari Sarker, Ph.D.)
- Microbiology (Yuansha Chen, Ph.D.)
- Manufacturing Facilities (Rose Xu, Ph.D.)
- Manufacturing Process (Sung Kim, Ph.D.)
- Quality Biopharmaceutics (Om Anand, Ph.D.)

1. Introduction

NDA 209191 was submitted for Bortezomib for Injection, 2.5 mg/vial in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act. Bortezomib is therapeutic proteasome inhibitor that was originally approved under the brand name VELCADE® for the treatment of multiple myeloma. VELCADE® was approved under NDA 021602 in 2003 and is the listed drug (LD) for this NDA. VELCADE® is a sterile, lyophilized product supplied in a single-use vial containing 3.5 mg of the active. The major difference between the Hospira product and the LD is strength of vial (2.5mg/vial vs.3.5mg/vial). Hospira’s proposed Bortezomib for Injection is presented as a 2.5 mg/vial sterile, lyophilized powder. The applicant proposed the 2.5 mg/vial strength in an effort to reduce drug waste. Like the listed drug, Hospira’s Bortezomib for Injection formulation contains only the active ingredient bortezomib, mannitol (b) (4)

The concentration per mL of active ingredient on reconstitution for the Hospira product is the same as the listed drug. The proposed indication, dose, route, and duration of administration for the Hospira, Inc. product are the same as those of Velcade®. No clinical studies were performed with the proposed drug product, Bortezomib for Injection as this submission relies on the Velcade® (NDA 021602) for safety and efficacy. Accordingly, approval of NDA 209191 from clinical, non-clinical and clinical pharmacology perspectives will be primarily based on publicly available information for Velcade

2. Background

Bortezomib is the first therapeutic proteasome inhibitor to be used in humans. Bortezomib is currently approved for initial treatment of patients with multiple myeloma, the retreatment of adult patients with multiple myeloma and the treatment of mantle cell lymphoma. The current application contains no clinical data but instead relies on the Agency's determination of safety and efficacy for the listed drug, Velcade® which was previously approved for marketing under NDA 021602. Unlike the listed drug, the applicant did not request indication for the treatment of patients with mantle cell lymphoma nor for the retreatment of patients with multiple myeloma.

NDA 209191 was originally submitted to the agency in December of 2016. At the conclusion of that review cycle, all disciplines recommended approval; however, the application was issued a tentative approval (TA) as the listed drug, Velcade®, was potentially subject to a period of patent protection based on the outcome of the patent infringement suit against the applicant with respect to patent 6,713,446 in the United States District Court For The District of Delaware. On September 17, 2017, NDA 209191 was resubmitted to the agency with a request for final approval. At that time the application received a complete response (CR) due to deficiencies (b) (4)

The applicant responded to the CR in December of 2017. At that time all facilities were acceptable; however, an elemental impurity issue was identified and in February 2018 the OPQ recommended a CR action for this submission. The applicant responded to the February 2018 CR in May of 2018 and provided a risk assessment for elemental impurities in the proposed drug product in accordance with ICH Q3D and USP<232/233>. This submission is the basis of this review. There was no new clinical pharmacology, non-clinical pharmacology/toxicology, clinical/statistics or product quality information apart from the elemental impurities risk assessment information in this resubmission.

3. Product Quality

The following comment was included in the agency's February 22, 2018 Complete Response (CR) Letter:

Establish a validated test method for elemental impurities as part of the drug product specification consistent with ICH Q3D and USP <232/233>. Update the drug product specifications accordingly with controls for elemental impurities, if necessary.

The applicant provided a response to the agency's CR letter on May 16, 2018. This response included a risk assessment for elemental impurities in the proposed drug product in accordance with ICH Q3D and USP<232/233>. The data shows that the total elemental impurities in the final drug product from all potential sources are present at levels significantly lower than the 30% of permitted

daily exposure (PDE) (see attached elemental impurities risk memo). Based on the applicant's evaluation of the Risk Assessment of Elemental Impurities the drug product review team recommends approval of this NDA 209191 with no additional corrective actions or control measures to be implemented.

Facilities:

All facilities remain acceptable for the responsibilities listed. Accordingly, NDA 209191 is recommended for approval by the OPF.

Overall CMC Recommendation: The Office of Pharmaceutical Quality recommends **APPROVAL** for NDA 209191.

6. Clinical Pharmacology

No clinical/pharmacology information provide in the resubmission.

7. Non-Clinical Pharmacology/Toxicology

No non-clinical pharmacokinetic or toxicology information provided in the resubmission.

8. Clinical/Statistical-Efficacy

No clinical or statistical information provided in the resubmission.

9. Safety N/A

10. Advisory Committee Meeting N/A

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling

The labeling review was completed and determined to be acceptable by DMEPA, DDMAC, Clinical, Non-Clinical and CMC during the previous review cycles. DMEPA noted the use of a trailing zero in the Prescribing Information in Section 10 Overdosage. The following recommendation was provided and the applicant was advised that it was to be implemented prior to approval:

Remove the trailing zero (e.g. 3.0 mg/m2) to avoid a ten-fold misinterpretation.

The b2 committee noted that there are two unexpired exclusivities listed in the Orange Book: M-165 exclusivity that expires 3/14/19 inclusive of pediatric exclusivity and orphan exclusivity for the mantle cell indication and which expires 4/8/22 inclusive of pediatric exclusivity. All other exclusivities have expired. No other labeling recommendations were noted during this review cycle.

Overall Labeling Recommendation:

The applicant accepted the change recommended by the agency. The labeling for Hospira's Bortezomib for Injection, 2.5 mg/vial is acceptable.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product relies on the safety and efficacy of the listed product, Velcade®. The Hospira product is nearly identical to the listed product, as the Hospira product has the same active ingredient and inactive ingredient, is the same dosage form and has the same routes of administration and concentration of bortezomib following reconstitution as the Listed Drug, Velcade®. No new clinical or nonclinical data were provided with this submission, as no such studies were conducted for this 505(b)(2) application.

As there are no outstanding issues precluding the approval of this application and all disciplines recommended approval of this NDA the CDTL recommends **APPROVAL** of NDA 209191.

- **Risk Benefit Assessment**

Please refer to NDA 021602.

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Cross-Discipline Team Leader Review

Date	12-Apr-17
From	Sherita McLamore, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	209191
Type of Application	505(b)(2)
Applicant	Hospira, Inc.
Date of Receipt	30-Jun-16
PDUFA Goal Date	2-Apr-2017
Proposed Proprietary Name	Bortezomib for Powder for Injection
Dosage forms / Strength	Lyophilized powder for Injection 2.5 mg/vial
Route of Administration	Intravenous or Subcutaneous
Proposed Indication(s)	Bortezomib for Injection is indicated for the treatment of patients with multiple myeloma
Recommended:	TENATIVE APPROVAL

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Drug Product (Rajiv Agarwal, Ph.D.); in Panorama, dated 20-Mar-2017
- Drug Substance (Hari Sarker, Ph.D.); in Panorama, dated 17-Mar-2017
- Microbiology (Yuansha Chen, Ph.D.); in Panorama, dated 24-Oct-2016
- Manufacturing Facilities (Ruo Xu, Ph.D.); in Panorama, dated 28-Mar-2017
- Manufacturing Process (Sung Kim, Ph.D.); in Panorama, dated 23-Feb-2017
- Quality Biopharmaceutics (Om Anand, Ph.D.); in Panorama, dated 22-Dec-2016
- Clinical (Bindu Kanapuru, M.D.); in DARRTS, dated 27-Mar-2017
- Clinical Pharmacology (Yuhong Chen, Ph.D.); in DARRTS, dated 24-Mar-2017
- Pharmacology/Toxicology (Emily Place, Ph.D.); in DARRTS, dated 23-Mar-2017
- DEMPA (Nicole Garrison, Pharm. D., BCPS); in DARRTS, dated 05-Jan-2017

1. Introduction

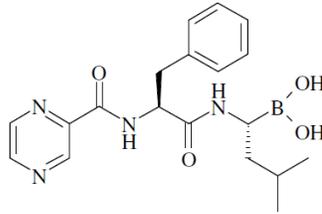
Hospira, Inc. has submitted NDA 209191 in support of a 2.5 mg/vial lyophilized formulation for bortezomib. The application is a 505(b)(2) application, referencing the lyophilized powder formulation of Millennium Pharmaceutical's, VELCADE®. VELCADE® was approved under NDA 021602 in 2003 for the treatment of patients with multiple myeloma. VELCADE is a sterile, lyophilized product contained in a single-dose vial containing 3.5 mg of the active manufactured by Millennium Pharmaceuticals, Inc. The major difference between the Hospira drug product and the listed product is strength of vial (2.5mg/vial vs. 3.5mg/vial). Hospira's proposed Bortezomib for Injection is presented as a single-dose vial containing 2.5 mg of the sterile, lyophilized powder. The applicant proposed the 2.5 mg/vial strength in an effort to reduce drug waste. Like the listed drug, Hospira's Bortezomib for Injection formulation contains only the active ingredient bortezomib and mannitol (b) (4)

2. Background

Bortezomib is the first therapeutic proteasome inhibitor to be used in humans. Bortezomib is currently approved for initial treatment of patients with multiple myeloma, the retreatment of adult patients with multiple myeloma and the treatment of mantle cell lymphoma. The current application contains no clinical data but instead relies on the Agency's determination of safety and efficacy for the listed drug, Velcade® which was previously approved for marketing under NDA 021602. The active ingredient, route of administration, dosage form, unit of use, and concentration of bortezomib following reconstitution are the same as those of the listed drug. Unlike the listed drug, the applicant did not request indication for the treatment of patients with mantle cell lymphoma nor for the retreatment of patients with multiple myeloma as these indications are both protected under exclusivity.

3. Chemistry, Manufacturing and Controls (CMC)

The drug substance for this NDA is bortezomib. The drug substance is a white to off-white slightly hygroscopic powder with two chiral centers that has four possible stereoisomers. Bortezomib drug substance is manufactured and supplied by (b) (4). The applicant referenced DMF (b) (4) for all aspects pertaining to the manufacture and control of Bortezomib. As such, there was minimal information included in the NDA. For additional detail pertaining to the manufacturing and control of the drug substance, refer to the DMF (b) (4) reviews. DMF (b) (4) was last reviewed in October 2016 and is considered adequate to support the approval of this NDA.



[(1*R*)-3-Methyl-1-({2*S*)-3-phenyl-2[(pyrazin-2-yl carbonyl) amino] propanoyl} amino)butyl]boronic acid
 $C_{19}H_{25}BN_4O_4 \cdot H_2O$
MW = 402.24

Hospira's proposed presentation is a 2.5 mg/vial white to off white lyophilized powder for IV injection or for subcutaneous route of administration. The product is designed to be reconstituted with 0.9% NaCl for injection. Like the innovator product, Hospira's bortezomib formulation contains only the active ingredient bortezomib and mannitol. (b) (4)

(b) (4) All excipients are compendial grade. There are no overages in the formulation.

The packaging for the Hospira product is consistent with the listed drug. The drug product is stored in a 10 mL, 13 mm clear glass vial with a 13 mm (b) (4) stopper and aluminum flip off seal. Extractable and leachable studies demonstrate that there are no leachable substances that require monitoring on stability. Stability studies demonstrate that the Hospira product (b) (4) will remain within the proposed specification through the proposed 24 month shelf-life.

The proposed commercial batch size is (b) (4) The manufacturing process for the drug product (b) (4)

The method of sterilization for the drug product (b) (4)

Eighteen months of long-term and intermediate stability data together with 6 months of accelerated stability data were included to support a 24 month shelf-life for the drug product. At the time tested, data for all attributed remained within the proposed acceptance criteria with no

significant changes or noteworthy trends. In addition to the long-term, intermediate and accelerated data, the applicant included forced degradation studies and freezer stability. The forced degradation studies revealed that the product is only susceptible to degradation under harsh oxidative conditions and the freezer stability results demonstrate that the product is not adversely affected by the freezer conditions (i.e. 2 days frozen at $-20\pm 5^{\circ}\text{C}$ and 2 days at $40^{\circ}\text{C}/75\%\text{RH}$ and 6 days at $-20\pm 5^{\circ}\text{C}$ and 6 days at $40^{\circ}\text{C}/75\%\text{RH}$). The results of the stability studies indicate that the Hospira product (b)(4) is expected to remain within the proposed specification for the proposed shelf life. Accordingly, a 24 month shelf life will be granted for the product when stored at (b)(4) excursions between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature] based on the real time stability data. The drug substance and the drug product reviewers recommended approval of the NDA 209191.

Facilities: The facility reviewer found no significant manufacturing risks that would impede the approval of this NDA. The risk associated with their manufacture of this product are Medium and there was no PAI needed. All facilities were found acceptable based on its manufacturing capability and inspectional history as noted in the facilities review; however, on 4/5/17 it was noted that the Facility Compliance Status Changed to Potential Official Action Indicated for Hospira Australia Ltd (FEI 3001174929). While a 483 was issued, the facilities reviewer indicated that role of this Hospira facility is limited to conducting the tech transfer for this submission and that the 483 issued is not related to the tech transfer. Accordingly, the facilities reviewer determined that the Hospira Australia facility is acceptable for this NDA (email from Dr. Rose Xu dated April 11, 2017, 10:19 am). The application is therefore recommended for approval from a facilities perspective.

4. Product Quality Microbiology

This product is (b)(4) sterilized and contains no antimicrobial preservatives (single-dose). During the manufacturing process (b)(4)

The microbiological study supports proposed bulk hold time. The drug product specification includes bacterial endotoxins testing and sterility testing as per USP <85> and USP <71>, respectively. There pending microbiological concerns remain for the NDA and this application is recommended for approval on the basis of sterility assurance.

5. Biopharmaceutics

The proposed drug product has the same active ingredient (bortezomib) and inactive ingredient, and is the same dosage form, route of administration and concentration of bortezomib following reconstitution as the Listed Drug, Velcade®. The pH and osmolality of the proposed drug product and the listed drug, after reconstitution with 0.9 % sodium chloride injection, 1 mg/ml, are similar. The Division of Biopharmaceutics has concluded that the disposition kinetics of Bortezomib should therefore be similar for Hospira's bortezomib and Velcade®. Accordingly, Hospira's request for a waiver of the in vivo study for their proposed product was granted. The Biopharmaceutics reviewer recommended approval of the NDA 209191 from the Biopharmaceutics perspective.

Overall CMC Recommendation: The Office of Pharmaceutical Quality recommends APPROVAL for NDA 209191 from a CMC perspective.

6. Clinical Pharmacology

Hospira, Inc. submitted this NDA for Bortezomib for Injection under Section 505(b)(2). Velcade® is the listed Drug (NDA 021602; approved in 2003 for 3.5 mg/vial). The major difference between the Hospira drug product and the listed product is strength of vial (2.5mg/vial vs.3.5mg/vial). The concentration per millimeter of active ingredient on reconstitution for the Hospira product is the same at the listed drug. The proposed indication, dose, route, and duration of administration for the Hospira, Inc. product are the same as those of Velcade® and the approval will be primarily based on publicly available information for Velcade®.

Labeling was modified in accordance with current labeling practices and this application is recommended for APPROVAL from a clinical pharmacology perspective.

7. Non-Clinical Pharmacology/Toxicology

The proposed indication, route, and duration of administration of Hospira Inc. Bortezomib for Injection 2.5 mg/vial will be the same as those of the listed drug, Velcade®. No new non-clinical pharmacokinetic or toxicology information is included in this submission. Therefore, reliance on the pharmacology/toxicology information required for the approval of this product is based on previous FDA findings for the safety of the listed drug. A pharmacology/toxicology review was not performed as no pharmacology/toxicology issues that could impact the acceptability of this application or the approval of this NDA were identified.

8. Clinical/Statistical-Efficacy

No clinical studies were performed with the proposed drug product, Bortezomib for Injection as this submission relies on the Velcade® (NDA 021602) for safety and efficacy. The clinical reviewer has recommended approval NDA 209191 for the treatment of patients with multiple myeloma.

9. Safety N/A

10. Advisory Committee Meeting N/A

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling

The labeling review was performed by DMEPA, Clinical, Non-Clinical, Clinical Pharmacology and CMC.

Clinical Recommendations:

- Provide justification for carving out the relapsed multiple myeloma indication.
- Clinical reviewer noted that at the completion of the clinical review labeling negotiations were ongoing and defers to the final USPI for approved labeling recommendations.

DMEPA Recommendations:

- Delete all instances of trailing zeros. DMEPA recommend this revision to avoid use of a trailing zero, an error prone dose designation, which may be misinterpreted if the decimal point is not seen. This comment was sent for the prescribing information, the carton labeling and the sticker label).
- Made several recommendations to increase the readability and prominence of important information and promote the safe use of the product in the carton container labels and USPI.
- it was noted that labels and labeling contains the term, [REDACTED] (b) (4) which is inconsistent with the draft guidance

Clinical Pharmacology Recommendations:

- 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).

Non-Clinical Recommendations:

- Based on labeling negotiations, the applicant inquired about the basis for the recommendation regarding male contraception. The agency proposed the duration of contraception based on current thinking which is 3 months plus 5 half-lives which is approximately 4 months based on genotoxic drugs.

CMC Recommendations:

No comments noted

Overall Labeling Recommendation:

The comments were conveyed to the applicant (see labeling review dated 3/12/17 by Virginia E. Kwitkowski). The applicant accepted the changes recommended by the agency. The labeling for the Hospira's Bortezomib product is acceptable.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product relies on the safety and efficacy of the listed product, Velcade®. The Hospira product is nearly identical to the listed product, as the Hospira product has the same active ingredient and inactive ingredient, is the same dosage form and has the same routes of administration and concentration of bortezomib following reconstitution as the Listed Drug, Velcade®. No new clinical or nonclinical data were provided with this submission, as no such studies were conducted for this 505(b)(2) application.

While all disciplines recommended approval of this NDA, the cross disciplinary team lead recommendation is for a **TENTATIVE APPROVAL** as the listed drug, Velcade[®], may be subject to a period of patent protection based on the outcome of the patent infringement suit against the applicant with respect to patent 6,713,446 in the United States District Court For The District of Delaware.

- **Risk Benefit Assessment**

Please refer to NDA 021602.



Sherita
McLamore

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