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RESEARCH**

APPLICATION NUMBER:

209191Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	9 July 2018
From	Nicole Gormley, MD; Acting Deputy Division Director
Subject	Division Director Summary Review
NDA/BLA #	NDA 209191
Applicant	Hospira, Inc.
Date of Submission	16 May 2018
PDUFA Goal Date	16 July 2018
Proprietary Name	Bortezomib for Injection
Dosage forms / Strength	For Injection: 2.5 mg vial of bortezomib as a lyophilized powder
Proposed Indication(s)	For treatment of patients with multiple myeloma
Recommended Action:	Approval

Material Reviewed/Consulted	Reviewer
Clinical Review, Division of Hematology Products	Bindu Kanapuru, MD
Clinical Pharmacology Review, Office of Clinical Pharmacology	Guoxiang Shen, PhD; Olanrewaju Okusanya, PharmD, MS.
Division of Hematology and Oncology Toxicology	Emily Place, PhD, MPH; Christopher Sheth, PhD
Division of Medication Error Prevention and Analysis (DMEPA) Consult	Nicole Garrison, Pharm.D, BCPS; Hina Mehta, PharmD
Cross-Discipline Team Leader (CDTL) Review	Sherita McLamore, PhD

1. Introduction

On May 16, 2018, Hospira (Applicant) re-submitted NDA 209191 for Bortezomib for Injection. NDA 209191 was submitted for the purpose of licensure of Bortezomib for Injection under section 505(b) of the Federal Food, Drug and Cosmetic Act. The proposed indication for Bortezomib for Injection is the treatment of patients with multiple myeloma. Hospira developed Bortezomib for Injection, as a 2.5 mg per vial, which was intended to have the same dosage form, route of administration, inactive ingredients and dosing regimen as the Reference Listed Drug (RLD), Velcade ®. The RLD has a vial strength of 3.5 mg/vial. The Applicant states that their 2.5 mg/vial strength was developed as a means to reduce drug waste. The Applicant relied on the Agency's previous determination of the safety and effectiveness for the RLD, Velcade ®.

2. Summary

Source: Derived in part from the reviews by Drs. Kanapuru and McLamore.

NDA 209191 was initially submitted on June 30, 2016. It received a tentative approval on April 26, 2017 as it was determined that the RLD upon which the application relied 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 (hereforth designated as the 446 patent) in the United States District Court For The District Of Delaware (Case 1:16-cv-00998-UNA).

On April 19, 2017, the final judgement from the district court was rendered, which stated that the 446 patent was invalid, and dismissed with prejudice any other claim that Hospira infringes on the 446 patent. The Applicant resubmitted the NDA on September 7, 2017. A CR letter was issued on November 3, 2017 due to unresolved deficiencies (b) (4)

On December 22, 2017 the Applicant resubmitted the application. At that time all facilities were acceptable; however, an elemental impurity issue was identified and OPQ recommended a CR action. A CR letter was issued on February 22, 2018. On May 16, 2018, the Applicant resubmitted the application. The Applicant provided 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). The drug product review team recommends approval of NDA 209191 with no additional corrective actions or control measures.

There was no new clinical pharmacology, non-clinical, clinical/statistics or product quality information apart from the elemental impurities risk assessment information in this resubmission. The Applicant did not seek an indication for the treatment of patients with mantle cell lymphoma or for the retreatment of patients with multiple myeloma as these indications were protected under exclusivity at the time of the initial application submission. The Applicant requested both subcutaneous and intravenous routes of administration.

3. Other Relevant Regulatory Issues

Source: Derived in part from the reviews by Drs. Kanapuru and McLamore.

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. This was revised by the Applicant.

Facilities

All facilities remain acceptable. OPF recommends approval.

4. Recommendations/Risk Benefit Assessment

All review disciplines and the CDTL recommend approval of NDA 209191. There are no outstanding issues that would preclude approval of this application.

Recommended Regulatory Action: Approval

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICOLE J GORMLEY
07/12/2018

Summary Review for Regulatory Action

Date	04/26/17
From	Albert Deisseroth MD, PhD, Associate Division Director
Subject	Division Director Summary Review
NDA #/Supplement#	NDA 209191
Applicant	Hospira, Inc.
Date of Submission	June 30, 2016
PDUFA Goal Date	April 30, 2017
Proprietary Name/Proper Name	Bortezomib for Injection
Dosage Forms/Strength	2.5 mg/vial for reconstitution (b) (4) for IV or SC administration
Recommendation	Approval
Recommended Indication	For the treatment of patients with multiple myeloma

Material Reviewed/Consulted	
Medical Officer Review	Bindu Kanapuru, MD, and Nicole Gormley, MD
Labeling Review	Gini Kwitkowski, RN
Non-Clinical	Emily Place, PhD and Chris Sheth, PhD
Clinical Pharmacology	Yuhong Chen, PhD, and Stacy Shord, PhD
Product Quality Microbiology (OGD/DM/MT1)	Yuansha Chen, PhD
OPQ CMC	Sherita McLamore, PhD and Animitro Banerjee, PhD
DEMPA	Nicole Garrison, PharmD
RPM	Kris Kolibab, PhD

Signatory Authority Review Template

1. Introduction/Executive Summary:

(This section is derived in part from the reviews for NDA 209191 of Dr. Bindu Kanapuru, and Dr. Sherita McLamore.)

On June 30, 2016, Hospira submitted a 505(b)(2) application for “Bortezomib for Injection”. The reference drug is Velcade (bortezomib), manufactured by Millennium Pharmaceuticals, Inc. (NDA 21602). Bortezomib for Injection is intended to have the same dosage form, route of administration and dosing regimen as the reference listed drug: Velcade (bortezomib). In 2003, VELCADE® (bortezomib) was approved for the treatment of patients with multiple myeloma (NDA 021602). In 2006, Velcade was approved for patients with mantle cell lymphoma who have received at least one prior therapy.

The indication proposed for Bortezomib for Injection by Hospira is treatment of patients with multiple myeloma. Hospira does not intend to seek the indication for the retreatment of patients with multiple myeloma nor the treatment of patients with mantle cell lymphoma which is still protected by exclusivity.

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 Reference Listed Drug, Velcade®. 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 Reference Listed Drug, Hospira’s Bortezomib for Injection formulation contains only the active ingredient bortezomib and mannitol (b) (4)

No new clinical or nonclinical data were provided with this submission, as no such studies were conducted for this 505(b)(2) application. The benefit risk assessment is the same as the listed drug.

While all disciplines recommended approval of this NDA, the cross disciplinary team lead recommendation was 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.

Regulatory Recommendation of Supervisory Associate Division Director: Tentative Approval

2. Background:

(This section is derived in part from the review of Dr. Sherita McLamore.)

Velcade is the first therapeutic proteasome inhibitor to be used in humans. Velcade is currently approved for the 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 Reference Listed Drug. Unlike the listed drug, the applicant did not request an indication for the retreatment of patients with multiple myeloma nor the treatment of patients with mantle cell lymphoma as these indications are both currently protected under exclusivity.

3. CMC/Device:

(This section was derived in part from the review of Dr. Sherita McLamore.)

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.

Regulatory Recommendation: The recommendation of the CMC review was Tentative Approval with which the Supervisory Associate Division Director agrees.

4. Product Quality Microbiology:

(This section is derived in part from the reviews of Dr. Yuansha Chen and Dr. Sherita McLamore.)

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.

Regulatory Recommendation: The recommendation of the Microbiology review was Tentative Approval with which the Supervisory Associate Division Director agrees.

5. Nonclinical Pharmacology/Toxicology:

(This section is derived in part from the review of Dr. Emily Place.)

This application contains no new pharmacology/toxicology information. 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.

Regulatory Recommendation: The conclusion of the Pharmacology/Toxicology review is that there are no pharmacology/toxicology issues for NDA 209191 to preclude Tentative Approval of the drug with which the Supervisory Associate Division Director agrees.

6. Clinical Pharmacology/Biopharmaceutics:

(This section is derived in part from the review of Dr. Yuhong Chen.)

No new clinical pharmacology information was included in this application. 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[®].

Regulatory Recommendation: The conclusion of the Clinical Pharmacology review is that there are no issues for NDA 209191 to preclude Tentative Approval of the drug with which the Supervisory Associate Division Director agrees.

7. Clinical/Statistical-Efficacy:

(This section has been derived in part from the review of Dr. Bindu Kanapuru.)

There is no clinical data submitted by Hospira in this 505 (b) (2) application for NDA 209191 Bortezomib for Injection. The Applicant has referenced the FDAs findings of clinical safety and effectiveness of the Reference Listed Drug, Velcade (NDA021602), and the Velcade clinical efficacy and safety sections in the USPI. The Applicant has carved out the mantle cell lymphoma indication and the multiple myeloma retreatment indication from the label. The Applicant has requested both subcutaneous and intravenous routes of administration. These are not protected under patent or exclusivity and the request for both routes is acceptable to the Agency.

Regulatory Recommendation: The conclusion of the Clinical/Stats efficacy review is that there are no issues for NDA 209191 to preclude Tentative Approval of the drug with which the Supervisory Associate Division Director agrees.

8. Safety:

(This section has been derived in part from the review of Dr. Bindu Kanapuru.)

No new safety data was submitted or reviewed.

Regulatory Recommendation: The conclusion of the Safety review is that there are no issues for NDA 209191 to preclude Tentative Approval of the drug with which the Supervisory Associate Division Director agrees.

9. Advisory Committee Meeting: This product was not taken to an Oncologic Drugs Advisory Committee because there were no issues requiring discussion.

10. Pediatrics: This application does not trigger PREA since the proposed product does not involve any new active ingredients, indications, dosage forms, dosing regimens or routes of administration. There is no requirement for a pediatric assessment.

11. Other Relevant Regulatory Issues: The sponsor reported that depending on the outcome of the patent infringement suit brought by Millenium against the applicant with respect to patent 6,713,446 in the United States District Court For The District of Delaware, that Velcade may be subject to an period of patent protection.

There will be no Postmarketing Commitments or Requirements. There will be no Postmarketing Risk Management Activities.

12. Labeling: A label has been negotiated between the FDA and the Applicant. For details, please see the labeling review of Gini Kwitkowski, RN.

13. Decision/Action/Risk Benefit Assessment:

(This section is derived in part from the review of Dr. Sherita McLamore.)

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. The risk benefit assessment is the same as for the listed drug.

While all disciplines recommended approval of this NDA, the cross disciplinary team lead recommendation was 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.

14. Regulatory Recommendation of Supervisory Associate Division Director: Tentative Approval.

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/s/

ALBERT B DEISSEROTH
04/26/2017