CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206927Orig1s000

CLINICAL REVIEW(S)

File Memorandum

NDA: 206927

Applicant: Dr. Reddy's Laboratories Inc.

Product: Bortezomib for Injection (3.5 mg/ml) vial

Submission date: May 3, 2019

Clinical reviewer: Bindu Kanapuru, MD

Clinical team leader: Nicole Gormley, MD

Regarding: 505(b) (2) NDA

Summary and Recommendation on Regulatory Action

NDA 206927 for Bortezomib for Injection is a 505(b)(2) application referencing Velcade® as approved for treatment of patients with multiple myeloma and for treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy. Bortezomib for injection is a new formulation and contains tromethamine and citric acid in place of mannitol present in the reference listed drug (RLD) Velcade. This submission was submitted to address the Complete Response letter issued 05/04/2016. The Applicant is seeking the intravenous route only. There were no clinical deficiencies listed in the Complete Response letter, and there is no new clinical information in this supplement.

The clinical information for the reference listed drug supports a finding of efficacy and clinical safety of Bortezomib for Injection by intravenous route for the proposed indications.

Application background

Proposed Indication:

- Treatment of patients with multiple myeloma
- Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy

Route: Intravenous administration Only

Pharmaceutical Information

Drug Established Name: Bortezomib
Proposed Trade Name: Bortezomib For Injection
Dosage Forms: Injection, lyophilized (3.5 mg)
Therapeutic Class: Antineoplastic
Chemical Class: Heterocyclic boronic acid

Mechanism of Action: Bortezomib is a reversible inhibitor of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway regulates the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Disruption of these normal homeostatic mechanisms by bortezomib leads to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types in vitro.

Pharmaceutical differences with the RLD Velcade

The Dr. Reddy's drug product Bortezomib for Injection 3.5 mg/vial is qualitatively and quantitatively similar to Reference Listed Drug (RLD) Velcade® with respect to drug substance. However, it is different with respect to excipients as it contains tromethamine and citric acid (instead of mannitol) (b) (4)

Summary of Presubmission Regulatory Activity Related to Submission

Presubmission communications were conducted under pre-IND 118389. A written response in lieu of a Type B meeting was issued 6/21/2013. In this letter, the Division agreed that a 505(b)(2) application would be appropriate for the applicant's product, and that the NDA should include adequate scientific information/data supporting the bridging of the applicant's product to the listed drug to support a waiver of the bioequivalence study.

NDA 206927 was received 3/4/2014 (b) (4) . A CR was issued 12/17/2014 (b) (4) due to deficiencies in the DMF (b) (4) NDA206927 was resubmitted on 11/23/2015 as a Class 2 resubmission. A CR was issued on 05/04/2016 due to issues with product quality.

Reviewer comment: Dr. Reddy's laboratories does not intend to seek indication for treatment of patients with newly diagnosed mantle cell lymphoma as this indication is protected under exclusivity. The Applicant has requested the intravenous routes of administration only. (b) (4)

Labelling Recommendations: The Applicant submitted a draft PI (b) (4) Specific instructions for reconstitution and administration for the proposed 3.5 mg/ml intravenous route is included in the label.

At the time of this review labelling negotiations were still ongoing. Please see final NDA 206927 USPI for approved labelling recommendations.

Conclusion: There is no clinical data submitted in this 505 (b) (2) application for NDA 206927 Bortezomib for Injection. The Applicant has referenced the FDAs findings of clinical safety and

effectiveness of the RLD Velcade (NDA021602). (b) (4)

Based on my review, I recommend granting approval for NDA 209191 Bortezomib for Injection for treatment of patients with multiple myeloma and treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

The Application is pending assessment by the 505(b)2 review committee.

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/s/

BINDU N KANAPURU
09/10/2019 10:50:25 AM

NICOLE J GORMLEY
09/10/2019 11:37:44 AM

Secondary (Team Leader) Review

Date	April 8, 2016
From	Albert Deisseroth, MD, PhD
Subject	Secondary Review
NDA Number	206927
Applicant	Dr. Reddy's Laboratories Ltd
Date of Submission	November 23, 2015
PDUFA Goal Date	May 23, 2016
Established Name/Proprietary Name (Proposed)	Bortezomib/Bortezomib for Injection
Dosage Regimen	1.3 mg/m^2 intravenously twice weekly
Approved Indication	Treatment of patients with multiple myeloma Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy
Recommendation:	Approval

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Donna Przepiorka, MD, PhD
Project Manager	Alycia Anderson

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1. EXECUTIVE SUMMARY: (This section was excerpted from the review of Dr. Donna Przepiorka. Please see her review for details.).

On March 4, 2014, Dr. Reddy's laboratory, Ltd. submitted NDA 206927 which requested approval of their "Bortezomib for Injection" for the indications of 1. Treatment of patients with multiple myeloma, and 2. Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy. There were no new clinical data submitted. The benefit and risk of Bortezomib for Injection from a clinical point of view is expected to be the same as that of the listed drug Velcade®.

The finding of the clinical review team was that this application was approvable from a clinical point of view. However, the CMC review team reported that the characterization of the drug substance was incomplete and recommended a complete response until the issue of the structure of "Bortezomib for Injection" was resolved.

A complete response letter was sent on December 17, 2014. The Complete Response letter listed the following product quality issues (b) (4)

1. Your application referenced the Drug Master File (DMF) 23996. This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on December 4, 2014. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.

2. The waiver request for the CFR requirement to provide data from an *in vivo* bioequivalence study for the intravenous route of administration cannot be granted at this time due to outstanding issues with the identity of the drug substance (refer to DMF) and the identity of the structures in the drug product and reconstituted solution. You may resubmit the biowaiver request or alternatively you may conduct a bioequivalence study between the proposed drug product and the listed drug product for the intravenous route of administration. (b) (4)

(b) (4)

On November 23, 2015, Dr. Reddy's Laboratories Ltd submitted a supplement to NDA 206927 to address the Complete Response letter which was issued on December 17, 2014. There were no clinical deficiencies listed in the Complete Response letter, and there is no new clinical information in this supplement. The clinical information for the reference listed drug adequately supports a finding of efficacy and clinical safety of Bortezomib for Injection for the proposed indications.

Risk Benefit Assessment: There are no new clinical data submitted. The benefit and risk of Bortezomib For Injection is expected to be the same as that of the listed drug Velcade®.

Regulatory Recommendation: This secondary reviewer recommends approval.

2. BACKGROUND: (This section was excerpted in part from the review of Dr. Donna Przepiorka. Please see her review for details).

Presubmission communications were conducted under pre-IND 118389. A written response in lieu of a Type B meeting was issued 6/21/2013. In this letter, the Division agreed that a 505(b)(2) application would be appropriate for the applicant's product, and that the NDA should include adequate scientific information/data supporting the bridging of the applicant's product to the listed drug to support a waiver of the bioequivalence study. NDA 206927 was received 3/4/2014 (b) (4) A
(b) (4)
CR was issued 12/17/2014 due to deficiencies in the DMF

3. SIGNIFICANT ISSUES RELATED TO OTHER REVIEW DISCIPLINES: (This section was excerpted in part from the review of Dr. Donna Przepiorka. Please see her review for details).

At the time of completion of this review, the assessments of all other review disciplines were pending.

4. REVIEW OF EFFICACY: (This section was excerpted in part from the review of Dr. Donna Przepiorka. Please see her review for details).

No clinical study data were submitted. Efficacy is based on the data presented in the Prescribing Information for Velcade.®

5. REVIEW OF EFFICACY: (This section was excerpted in part from the review of Dr. Donna Przepiorka. Please see her review for details).

Safety is based on the data presented in the Prescribing Information for Velcade.®

6. POSTMARKET EXPERIENCE: (This section was excerpted in part from the review of Dr. Donna Przepiorka. Please see her review for details).

There is no postmarketing experience reported by the applicant.

7. ADVISORY COMMITTEE MEETING: (This section was excerpted in part from the review of Dr. Donna Przepiorka. Please see her review for details).

This application was not discussed with an advisory committee.

8. LABELLING: (This section was excerpted in part from the review of Dr. Donna Przepiorka. Please see her review for details).

No deviations from the current prescribing information for Velcade® are recommended except those specific to the chemistry of Bortezomib for Injection.

9. RECOMMENDATIONS FOR POSTMARKET RISK EVALUATION AND MITIGATION STRATEGIES: None

10. RECOMMENDATIONS FOR POSTMARKET REQUIREMENTS AND COMMITMENTS: None

11. REGULATORY RECOMMENDATION: This secondary reviewer recommends approval.

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/s/

ALBERT B DEISSEROTH
04/11/2016

CLINICAL REVIEW

Application Number(s)	NDA 206927
Application Type	Type 5
Priority or Standard	Class 2 Resubmission
Submit Date(s)	11/23/2015
Received Date(s)	11/23/2015
PDUFA Goal Date	5/23/2016
Review Completed	4/6/2016
Office / Division	Office of Hematology and Oncology Products / Division of Hematology Products
Primary Reviewer	Donna Przepiorka, MD, PhD
Team Leader	Albert Deisseroth, MD, PhD
Established Name	Bortezomib
(Proposed) Trade Name	Bortezomib for Injection
Therapeutic Class	Antineoplastic
Applicant	Dr. Reddy's Laboratories Limited
Formulation(s)	Injection, lyophilized (3.5 mg)
Dosage	1.3 mg/m^2 intravenously (b) (4)
Indication(s)	• Treatment of patients with multiple myeloma. • Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

Reference ID: 4504436

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 206927 for Bortezomib for Injection is a 505(b)(2) application referencing Velcade® as approved for treatment of patients with multiple myeloma and for treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy. This supplement was submitted to address the Complete Response letter issued 12/17/2014. There were no clinical deficiencies listed in the Complete Response letter, and there is no new clinical information in this supplement. The clinical information for the reference listed drug adequately supports a finding of efficacy and clinical safety of Bortezomib for Injection for the proposed indications.

1.2 Risk Benefit Assessment

There are no new clinical data submitted. The benefit and risk of Bortezomib For Injection is expected to be the same as that of the listed drug Velcade®.

1.3 Recommendations for Labeling

No deviations from the current prescribing information for Velcade® are recommended except those specific to the chemistry of Bortezomib for Injection.

1.4 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.5 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Drug Established Name:	Bortezomib
Proposed Trade Name:	Bortezomib For Injection
Dosage Forms:	Injection, lyophilized (3.5 mg)
Therapeutic Class:	Antineoplastic
Chemical Class:	Heterocyclic boronic acid

Mechanism of Action: Bortezomib is a reversible inhibitor of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway regulates the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Disruption of these normal homeostatic mechanisms by bortezomib leads to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types in vitro.

Proposed Indication:
- Treatment of patients with multiple myeloma.
- Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

Proposed Dose-Schedule:

- The recommended starting dose of bortezomib for injection is 1.3 mg/m^2. The starting dose is reduced to 0.7 mg/m^2 in patients with moderate or severe hepatic impairment.
- Bortezomib is administered intravenously.
- In previously untreated multiple myeloma. bortezomib is given twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32) in Cycles 1-4 and once weekly (days 1, 8, 22 and 29) in Cycles 5-9.
- For relapsed multiple myeloma and mantle cell lymphoma, bortezomib is given twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12-21). For extended therapy of more than 8 cycles, bortezomib for injection may be administered on the schedule described or once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35).
- Bortezomib should be withheld for severe or life-threatening neuropathic pain or neuropathy. The dose should be reduced for mild to moderate pain or for moderate neuropathy.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Presubmission communications were conducted under pre-IND 118389. A written response in lieu of a Type B meeting was issued 6/21/2013. In this letter, the Division agreed that a 505(b)(2) application would be appropriate for the applicant's product, and that the NDA should include adequate scientific information/data supporting the bridging of the applicant's product to the listed drug to support a waiver of the bioequivalence study. NDA 206927 was received 3/4/2014 (b) (4). A CR was issued 12/17/2014 due to deficiencies in the DMF (b) (4)

2.7 Compliance with the Pediatric Research Equity Act

A waiver of study in all pediatric age groups is recommended due to the lack of occurrence of myeloma and mantle cell lymphoma in the pediatric population. This recommendation was agreed to by the PeRC PREA Subcommittee on 11/12/2014.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This supplement was received 11/23/2015 in eCTD format. There was no new clinical information in Module 2 or Module 5.

4 Significant Issues Related to Other Review Disciplines

At the time of completion of this review, the assessments of all other review disciplines were pending.

5 Sources of Clinical Data

No clinical study data were submitted.

6 Review of Efficacy

Efficacy is based on the data presented in the Prescribing Information for Velcade.®

7 Review of Safety

Safety is based on the data presented in the Prescribing Information for Velcade.®

8 Postmarket Experience

There is no postmarketing experience reported by the applicant.

9 Appendices

9.1 Advisory Committee Meeting

This application was not discussed with an advisory committee.

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/s/

DONNA PRZEPIORKA
04/06/2016

ALBERT B DEISSEROTH
04/06/2016

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	206927 Original 1 (b) (4)
Applicant Name	Dr. Reddy's Laboratory Limited
Date of Submission	March 4, 2014
PDUFA Goal Date	January 4, 2015
Proprietary Name / **Established (USAN) Name**	Bortezomib
Dosage Forms / Strength	Lyophilized powder
Proposed Indication(s)	Same indications as Velcade (RLD)
Action/Recommended Action for NME:	**Complete Response**

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Donna Przepiorka, M.D./Albert Deisseroth, M.D., Ph.D.
Statistical Review	N/A
Pharmacology Toxicology Review	Christopher Sheth, Ph.D./Brenda Gehhrke, Ph.D.
CMC Review/OBP Review	Jean Tang, M.S./Janice Brown, M.S./Ali Al-Hakim, Ph.D./Elsbeth Chikdale, Ph.D./Angelica Dorantes, Ph.D.
Microbiology Review	Erika Pfeiler, Ph.D./Stephen Langille, Ph.D.
Clinical Pharmacology Review	No review- NAI
DDMAC	Nisha Patel/Kathleen Davis
OSI	N/A
CDTL Review	Janice Brown, M.S.
OSE/DMEPA	
OSE/DDRE	
OSE/DSRCS	
Other -MHT	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
OSI=Office of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

This application for NDA 206927 (bortezomib) is a 505 b2 application.

2. Background

The reference listed drug is NDA 21602 Velcade (bortezomib).

3. CMC/Device

The NDA cannot be approved due to the following identified deficiencies from the CDTL review:

Deficiencies - Original 1 (intravenous route of administration):

1. Your application reference Drug Master File (DMF) 23996. This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on December 4, 2014. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.

2. The waiver request for the CFR requirement to provide data from an in vivo bioequivalence study for the intravenous route of administration cannot be granted at this time due to outstanding issues with the identity of the drug substance (refer to DMF) and the identity of the structures in the drug product and reconstituted solution. You may resubmit the biowaiver request or alternatively you may conduct a bioequivalence study between the proposed drug product and the listed drug product for the intravenous route of administration.

(b) (4)

I concur with the CDTL that these issues preclude approval.

4. Nonclinical Pharmacology/Toxicology

No issues that would preclude approval were identified.

5. Clinical Pharmacology/Biopharmaceutics

Review is NAI or no action indicated.

6. Microbiology

No issues that would preclude approval were identified.

7. Clinical/Statistical-Efficacy

No new clinical data was submitted. The clinical review team reviewed the proposed labeling and compared it with the RLD labeling.

From the review:
This reviewer recommends tentative approval of Bortezomib for Injection for use by the intravenous route for the proposed indications pending expiration of exclusivity.

8. Safety

No new safety issues have been identified. The clinical review team reviewed the proposed labeling and compared it with the RLD labeling.

9. Advisory Committee Meeting

This product is not a NME.

10. Pediatrics

N/A

11. Other Relevant Regulatory Issues

None other than those identified by CMC

12. Labeling

All disciplines made recommendations for labeling.

13. Decision/Action/Risk Benefit Assessment

-
- Recommended regulatory action

  Complete Response letter will include the CMC/Bioequivalence deficiencies noted above
- Risk Benefit Assessment

  N/A
- Recommendation for Post marketing Risk Management Activities

  None

- Recommendation for other Post marketing Study Requirements/ Commitments

  None

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/s/

ANN T FARRELL
12/15/2014

Cross-Discipline Team Leader Review

Date	See electronic date stamp
From	Janice Brown
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 206927 – Original 1 (intravenous route of administration) (b) (4)
Applicant	Dr. Reddy's Laboratories Limited
Date of Submission	March 04, 2014 (received March 04, 2014)
PDUFA Goal Date	January 04, 2015
Proprietary Name / Established (USAN) names	bortezomib
Dosage forms / Strength	Injection, Powder, Lyophilized, For Solution/3.5 mg per vial
Proposed Indication(s)	1. Treatment of patients with multiple myeloma. 2. Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.
Recommended:	Original 1: Complete Response (b) (4)

Deficiencies - Original 1 (intravenous route of administration):

1. Your application reference Drug Master File (DMF) 23996. This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on December 4, 2014. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.

2. The waiver request for the CFR requirement to provide data from an *in vivo* bioequivalence study for the intravenous route of administration cannot be granted at this time due to outstanding issues with the identity of the drug substance (refer to DMF) and the identity of the structures in the drug product and reconstituted solution. You may resubmit the biowaiver request or alternatively you may conduct a bioequivalence study between the proposed drug product and the listed drug product for the intravenous route of administration.

(b) (4)

(b) (4)

1. Introduction

Bortezomib is a small molecule, proteasome inhibitor approved for intravenous or subcutaneous administration for the treatment of patients with multiple myeloma or with mantle cell lymphoma who have received at least one prior therapy. The current 505(b)(2) NDA is a new formulation of Bortezomib for Injection 3.5 mg lyophilized powder. The innovator product, Velcade (bortezomib) for Injection from Millennium Pharmaceuticals, Inc. (NDA 21602) is a single-use vial containing 3.5 mg of bortezomib as a lyophilized powder.

2. Background

The applicant for this NDA is relying upon information in the public domain (labeling for approved bortezomib product and published studies and information about bortezomib) to support the safety and efficacy of the new product. The subject of the current NDA application is a new formulation of bortezomib for injection. This NDA was submitted on March 04, 2014 (received March 04, 2014). The proposed drug product is a single dose sterile lyophilized powder containing 3.5 mg of bortezomib, tromethamine, citric acid, (b) (4) in a 10 mL vial. No clinical or clinical pharmacology primary data are submitted to support the application.

(b) (4)

3. CMC

Product Quality Review

Drug Substance: Bortezomib is a dipeptide prepared by synthesis from a boronate and two amino acids, L-leucine, and L-phenylalanine. The CMC information for the drug substance was provided in DMF No. 23996 from Dr. Reddy's Laboratories, Ltd. The applicant provided adequate reference to their Type II DMF No. 23996 for information pertaining to the drug substance. DMF 23996 was previously reviewed and the DMF holder received a six item deficiency list in a DMF Complete Response letter on July 29, 2014. The DMF holder responded to the deficiencies on October 16, 2014 and November 5, 2014. The DMF holder's response was found not adequate and the review concluded that the DMF is inadequate to support the NDA (see DMF reviews by Erin M Skoda, final signatures on July 29, 2014 and November 19, 2014). The deficiencies include (1) the structure of the drug substance is not adequately supported, (2) revise the drug substance specification to include a test for (b) (4) and (3) tighten the limit for (b) (4)

Drug Product: Bortezomib for injection is supplied as a single use vial containing 3.5 mg of bortezomib, anhydrous citric acid and tromethamine as a sterile lyophilized powder. The manufacturing process for Bortezomib for injection consists of (b) (4) The product is packed in 10 mL USP (b) (4) tubular glass vial stoppered with 13 mm (b) (4) rubber stoppers and sealed with 13 mm flip-off seal. The proposed shelf life of Bortezomib for Injection stored at 20°-25°C (68°-77°F); [USP Controlled Room Temperature) was found acceptable.

The CMC product review (Zhe J. Tang, Ph.D., final signature December 1, 2014) did not have any outstanding deficiencies and recommends a Complete Response for this NDA due to the outstanding deficiencies identified in the drug substance and biopharmaceutics reviews.

Microbiology

(b) (4) The product quality microbiology review completed by Erika Pfeiler, Ph.D., (final signature September 10, 2014) found the microbiological information acceptable and recommended approval of the NDA from a quality microbiology standpoint.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review (Christopher Sheth, Ph.D., final signature June 03, 2014) stated, "From the Pharmacology/Toxicology perspective, Dr. Reddy's bortezomib may be approved for the proposed indications." Pharmacology/Toxicology has no concerns with the nonclinical findings and the excipients used for the Bortezomib for Injection at the defined levels and the review recommends approval of the NDA.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology

There is no Clinical Pharmacology review for this NDA.

Biopharmaceutics

The Applicant requested a waiver of *in vivo* bioavailability/bioequivalence (BA/BE) requirements for Bortezomib for Injection based on 21 CFR § 320.22 (b)(i).

Biowaiver for Intravenous Route of Administration: The Biopharmaceutics review stated, "The biowaiver for the i.v. route of administration cannot be granted until the CMC Reviewer can confirm the identity of the drug substance and the identity of the structures which the Applicant claims are present upon reconstitution of the lyophilized powder. Therefore, the biowaiver request for the i.v. route of administration cannot be granted by the Biopharmaceutics team at this time." The Biopharmaceutics review recommended a Complete Response for NDA 206927-Original 1 for Bortezomib for Injection – i.v., 3.5 mg/vial.

(b) (4)

6. Clinical Microbiology

There was no Clinical Microbiology review for this NDA.

7. Clinical/Statistical-Efficacy

There was no Statistical Review was done for this NDA. The applicant did not conduct any human clinical studies and therefore no efficacy information is included in the NDA. Efficacy is based on the data presented in the Prescribing Information for Velcade.

8. Safety

There was no Safety Review for this NDA. Safety is based on the data presented in the Prescribing Information for Velcade.

9. Advisory Committee Meeting

There was no Advisory Committee meeting held for this application.

10. Pediatrics

There is no Pediatric and Maternal Health Staff (PMHS) review for this NDA.

11. Other Relevant Regulatory Issues

Facilities review and inspection

An Establishment Evaluation Request (EER) was submitted to the Office of Compliance, and an overall acceptable recommendation was issued for the application April 16, 2014.

- Application Integrity Policy (AIP): Not applicable
- Exclusivity or patent issues of concern: Not applicable
- Financial disclosures: Not applicable
- Other GCP issues: None
- DSI audits: Not applicable
- Other discipline consults: None

12. Labeling

(b) (4)

The proposed labeling for Dr. Reddy's Bortezomib for Injection has been reviewed and comments from all disciplines were conveyed to the applicant. The applicant submitted revised labeling incorporating the Division's recommendations for Original 1.

(b) (4)

Proprietary name: There was no proprietary name proposed for this product.

Patient labeling/Medication guide: This is not required for this product.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Complete Response

- Risk Benefit Assessment

According to the clinical reviewer the benefit and risk of Bortezomib for Injection is expected to be the same as that of the listed drug Velcade®.

There are substantial drug substance and biopharmaceutics review deficiencies associated with this application. Therefore, this product is currently unsuitable for commercial production and marketing.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Commitments

None

- Recommended Comments to Applicant

None

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/s/

JANICE T BROWN
12/05/2014

ALI H AL HAKIM
12/05/2014

Secondary (Team Leader) Review

Date	December 2, 2014
From	Albert Deisseroth, MD, PhD
Subject	Secondary Review
NDA Number	206927
Applicant	Dr. Reddy's Laboratories Ltd
Date of Submission	March 4, 2014
PDUFA Goal Date	January 2, 2015
Established Name/Proprietary Name (Proposed)	Bortezomib/Bortezomib for Injection
Dosage Regimen	1.3 mg/m^2 intravenously twice weekly
Approved Indication	Treatment of patients with multiple myeloma Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy
Recommendation:	Complete Response

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Donna Przepiorka, MD, PhD
Biopharmaceutics Review	Elsbeth Chikhale, PhD, Angelica Dorantes, PhD, and Paul Seo, PhD
ONDQA, Branch II	Janice Brown, MS, and Ali Al-Hakim, PhD
Product Quality Microbiology Review	Erika Pfeiler, PhD.
DMEPA	Michelle Rutledge, PharmD, and Yelena Maslov, PharmD
Project Manager	Alycia Anderson

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY: (This section was excerpted from the review of Dr. Donna Przepiorka).

On March 4, 2014, Dr. Reddy's laboratory, Ltd. submitted NDA 206927 which requested approval of their "Bortezomib for Injection" for the indications of 1. Treatment of patients with multiple myeloma, and 2. Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy. There were no new clinical data submitted. The benefit and risk of Bortezomib for Injection from a clinical point of view is expected to be the same as that of the listed drug Velcade®. The finding of the clinical review team is that this application is approvable from a clinical point of view. However, the CMC review team reports that the characterization of the drug substance is incomplete and is recommending a complete response until the issue of the structure of "Bortezomib for Injection" is resolved.

Regulatory Recommendation: This secondary reviewer recommends approval once the problems identified with the structural characterization identified by CMC are resolved.

2. BACKGROUND: (This section was derived in part from the review of Dr. Donna Przepiorka).

Bortezomib is available only as Velcade. Velcade received accelerated approval in the United States in 2003 for treatment of patients with multiple myeloma progressing after 2 prior therapies. Regular approval was granted in 2005 for patients with multiple myeloma progressing after 1 prior therapy, and the broad indication treatment of multiple myeloma was approved in 2008 based on a study of first-line treatment of multiple myeloma. Velcade also received regular approval in 2006 for treatment of patients with mantle cell lymphoma failing at least 1 prior therapy.

Mechanism of Action: Bortezomib is a reversible inhibitor of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Disruption of these normal homeostatic mechanisms by bortezomib leads to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types in vitro. Bortezomib causes a delay in tumor growth in vivo in nonclinical tumor models, including multiple myeloma

Proposed Indication:

- Treatment of patients with multiple myeloma.
- Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

Proposed Dose-Schedule:

- The recommended starting dose of bortezomib for injection is 1.3 mg/m^2. The starting dose is reduced to 0.7 mg/m^2 in patients with moderate or severe hepatic impairment.

- Bortezomib is administered intravenously.
- In previously untreated multiple myeloma. bortezomib is given twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32) in Cycles 1-4 and once weekly (days 1, 8, 22 and 29) in Cycles 5-9.
- For relapsed multiple myeloma and mantle cell lymphoma, bortezomib is given twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12-21). For extended therapy of more than 8 cycles, bortezomib for injection may be administered on the schedule described or once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35).
- Bortezomib should be withheld for severe or life-threatening neuropathic pain or neuropathy. The dose should be reduced for mild to moderate pain or for moderate neuropathy.

According to the current prescribing information for Velcade, bortezomib is contraindicated in patients with a known hypersensitivity to bortezomib, boron or any component of the formulation. It is also contraindicated by the intrathecal route. Warnings address the risks of peripheral neuropathy, hypotension, cardiac failure, acute respiratory syndrome, posterior reversible encephalopathy, gastrointestinal toxicity, thrombocytopenia, neutropenia, tumor lysis syndrome, hepatic toxicity and embryo-fetal effects. Nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, and anorexia were the most frequent ($\geq$20%) adverse reactions reported. Frequent monitoring for toxicity is recommended when bortezomib is used in combination with CYP3A4 inhibitors, and concomitant use of strong CYP3A4 inducers is to be avoided. Additional glucose monitoring is recommended for patients with diabetes taking oral hypoglycemic agents.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC):

3.A. New Drug Quality Assessment Division II: The finding of the CMC review team is that the structural characterization of Bortezomib for Injection is incomplete. For details, please see the CMC review.

Regulatory Recommendation of the CMC Team: Complete Response

3.B. Product Quality Microbiology Review: (This section has been excerpted from the review of Dr. Erika Pfeiler). The finding of the Microbiology review team is that the application is approvable. For details, see the review of Dr. Erika Pfeiler.

Regulatory Recommendation of Microbiology: Approval

4. PHARMACOLOGY/TOXICOLOGY: (This section was derived from the review of Dr. Donna Przepiorka). No approvability issues were identified with this application by the Pharmacology/Toxicology Team.

5. CLINICAL PHARMACOLOGY: (This section was derived from the review of Dr. Donna Przepiorka). Biopharmaceutics Reviewer determined that (b) (4) that there were no issues regarding the proposed use by the intravenous route.

6. CLINICAL EFFICACY: (This section was derived from the review of Dr. Donna Przepiorka). No new clinical data was submitted but the recommendation of the Clinical Review Team is approval.

7. SAFETY (This section is excerpted from the review of Dr. Donna Przepiorka). No new clinical data was submitted but the recommendation of the Clinical Review Team is approval.

8. ADVISORY COMMITTEE MEETING: No Advisory Committee meeting.

9. OTHER RELEVANT REGULATORY ISSUES: None

10. LABELING: Not applicable.

11. RECOMMENDATIONS FOR POSTMARKET REQUIREMENTS AND COMMITMENTS: Not applicable.

12. REGULATORY RECOMMENDATION: This secondary reviewer recommends approval once the CMC Review Team finds that the problems with the characterization with the structure of the drug substance have been resolved.

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/s/

ALBERT B DEISSEROTH
12/02/2014

CLINICAL REVIEW

Application Type	Original 505(b)(2)
Application Number(s)	NDA 206927
Priority or Standard	Standard
Submit Date(s)	3/4/2014
Received Date(s)	3/4/2014
PDUFA Goal Date	1/2/2015
Review Completed	8/18/2014
Office / Division	Office of Hematology and Oncology Products / Division of Hematology Products
Primary Reviewer	Donna Przepiorka, MD, PhD
Team Leader	Albert Deisseroth, MD, PhD
Established Name	Bortezomib
(Proposed) Trade Name	Bortezomib for Injection
Therapeutic Class	Antineoplastic
Applicant	Dr. Reddy's Laboratories Limited
Formulation(s)	Injection, lyophilized (3.5 mg)
Dosing Regimen	1.3 mg/m^2 intravenously twice weekly
Indication(s)	• Treatment of patients with multiple myeloma. • Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

Reference ID: 4504436

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This NDA for Bortezomib for Injection is a 505(b)(2) application referencing Velcade® as approved for treatment of patients with multiple myeloma and for treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy. This reviewer recommends tentative approval of Bortezomib for Injection for use by the intravenous route for the proposed indications pending expiration of exclusivity.

1.2 Risk Benefit Assessment

There are no new clinical data submitted. The benefit and risk of Bortezomib For Injection is expected to be the same as that of the listed drug Velcade®.

1.3 Recommendations for Labeling

No deviations from the current prescribing information for Velcade® are recommended except to limit the route of administration to intravenous.

1.4 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Drug Established Name:	Bortezomib
Proposed Trade Name:	Bortezomib For Injection
Dosage Forms:	Injection, lyophilized (3.5 mg)
Therapeutic Class:	Antineoplastic
Chemical Class:	Heterocyclic boronic acid
Mechanism of Action:	Bortezomib is a reversible inhibitor of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome

pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Disruption of these normal homeostatic mechanisms by bortezomib leads to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types in vitro. Bortezomib causes a delay in tumor growth in vivo in nonclinical tumor models, including multiple myeloma

Proposed Indication:

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Proposed Dose-Schedule:

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- Bortezomib is administered intravenously.
- In previously untreated multiple myeloma. bortezomib is given twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32) in Cycles 1-4 and once weekly (days 1, 8, 22 and 29) in Cycles 5-9.
- For relapsed multiple myeloma and mantle cell lymphoma, bortezomib is given twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12-21). For extended therapy of more than 8 cycles, bortezomib for injection may be administered on the schedule described or once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35).
- Bortezomib should be withheld for severe or life-threatening neuropathic pain or neuropathy. The dose should be reduced for mild to moderate pain or for moderate neuropathy.

2.2 Currently Available Treatments for Proposed Indication

The drugs approved for treatment of multiple myeloma include cyclophosphamide, melphalan, carmustine, bortezomib, thalidomide, lenalidomide, liposomal doxorubicin, carfilzomib, and pomalidomide.

The drugs approved for treatment of mantle cell lymphoma include bortezomib, lenalidomide and ibrutinib.

2.3 Availability of Proposed Active Ingredient in the United States

Bortezomib is available only as Velcade. Velcade received accelerated approval in the United States in 2003 for treatment of patients with multiple myeloma progressing after 2 prior therapies. Regular approval was granted in 2005 for patients with multiple myeloma progressing after 1 prior therapy, and the broad indication treatment of multiple myeloma was approved in 2008 based on a study of first-line treatment of multiple myeloma. Velcade also received regular

approval in 2006 for treatment of patients with mantle cell lymphoma failing at least 1 prior therapy.

2.4 Important Issues with Consideration to Related Drugs

According to the current prescribing information for Velcade, bortezomib is contraindicated in patients with a known hypersensitivity to bortezomib, boron or any component of the formulation. It is also contraindicated by the intrathecal route. Warnings address the risks of peripheral neuropathy, hypotension, cardiac failure, acute respiratory syndrome, posterior reversible encephalopathy, gastrointestinal toxicity, thrombocytopenia, neutropenia, tumor lysis syndrome, hepatic toxicity and embryo-fetal effects. Nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, and anorexia were the most frequent ($\geq$20%) adverse reactions reported. Frequent monitoring for toxicity is recommended when bortezomib is used in combination with CYP3A4 inhibitors, and concomitant use of strong CYP3A4 inducers is to be avoided. Additional glucose monitoring is recommended for patients with diabetes taking oral hypoglycemic agents.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A written response in lieu of a Type B meeting was issued 6/21/2013. In this letter, the Division agreed that a 505(b)(2) application would be appropriate for the applicant's product, and that the NDA should include adequate scientific information/data supporting the bridging of the applicant's product to the listed drug to support a waiver of the bioequivalence study.

2.6 Other Relevant Background Information

Velcade was approved for use by the subcutaneous route 1/23/2012. Exclusivity for the new route extends through 1/23/2015, and orphan exclusivity extends through 6/20/2015.

2.7 Compliance with the Pediatric Research Equity Act

A waiver of study in all pediatric age groups was recommended.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

NDA was received 3/4/2014. The application was in eCTD format. No clinical items were missing, and the NDA was filed 5/3/2014. (b) (4)

Note: Since no clinical studies were submitted, subsections 3.2 and 3.3 are omitted from this Section.

4 Significant Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There were no approvability issues identified by the Chemistry Manufacturing and Controls review team.

4.2 Preclinical Pharmacology/Toxicology

The Preclinical Pharmacology/Toxicology Reviewer identified no deficiencies and recommended approval for the proposed indications.

4.3 Clinical Pharmacology

The Biopharmaceutics Reviewer determined (b) (4) that there were no issues regarding the proposed use by the intravenous route.

5 Sources of Clinical Data

No clinical study data were submitted.

6 Review of Efficacy

Efficacy is based on the data presented in the Prescribing Information for Velcade.®

7 Review of Safety

Safety is based on the data presented in the Prescribing Information for Velcade.®

8 Postmarket Experience

There is no postmarketing experience reported by the applicant.

9 Appendices

9.1 Advisory Committee Meeting

This application was not discussed with an advisory committee.

9.2 Literature Reviewed/ References

None

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/s/

DONNA PRZEPIORKA
08/19/2014

ALBERT B DEISSEROTH
08/19/2014