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APPLICATION NUMBER:

209191Orig1s000

CLINICAL REVIEW(S)

File Memorandum

NDA: 209191

Applicant: Hospira

Product: Bortezomib for Injection (2.5 mg/ml)

Submission date: May 16, 2018

Clinical reviewer: Bindu Kanapuru, MD

Clinical team leader: Vishal Bhatnagar, MD

Regarding: 505(b) (2) NDA Class I resubmission

This is a brief review of the class I resubmission for this 505 (b)2 NDA 209191 Bortezomib for Injection. The reference listed drug (RLD) is Velcade.

Please refer to the clinical review for the original submission (DAARTS 03/27/2017) and first resubmission (DAARTS, 11/01/107) for additional details.

No clinical data was submitted in the original submission dated 30 June,2016, resubmission #1 dated 7 September 2017, resubmission #2 dated 12/22/2017 or this resubmission #4.

NDA 209191 received a recommendation for tentative approval on 4/26/2017, as the listed drug, Velcade®, was thought to 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.

Refer to submission eCTD0018/18 regarding the decision on the Class Action Suit and reason for first resubmission on 7 September 2017. A CR was issued on 11/3/2017 following review of the 7 September, 2017 Class I resubmission due to unresolved deficiencies associated with the drug substance manufacturing facility (b) (4)

The Class I resubmission dated 12/22/2017 resulted in a CR action on February 22, 2018 due to unresolved product quality issues. Hospira is resubmitting this 505(b)2 Application for Bortezomib for Injection for approval consideration.

At the time of the last resubmission (12/22/2017), DPMH consult was requested to review the proposed language from the applicant in section 8.4 of the PI and determine if this language needed revision under FDARA. The language below was included in the label based on DPMH's recommendation.

USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
Additional information describing a clinical study in which efficacy was not demonstrated in pediatric patients is approved for Millennium Pharmaceuticals, Inc. VELCADE (bortezomib) Injection. However, due to Millennium Pharmaceuticals, Inc.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

Table 1 Pending Exclusivities for RLD Velcade

Exclusivity Code	*Expiration Date (w/peds ext)*	*Velcade approval - basis*
M-165 - PROVIDES FOR UPDATES TO THE PEDIATRIC USE SECTION BASED ON THE PEDIATRIC STUDY REPORT ENTITLED, 'A PHASE II PILOT TRIAL OF BORTEZOMIB IN COMBINATION WITH INTENSIVE RE-INDUCTION THERAPY IN CHILDREN WITH RELAPSED ACUTE LYMPHOBLASTIC LYMPHOMA (LL)'	9/14/2018 (3/14/2019)	21-602/S-042, approved 9/14/2015 Updates to the Pediatric Use section of the United States Prescribing Information based on the pediatric study report for Study AALL07P1, entitled "A Phase II Pilot Trial of Bortezomib in Combination with Intensive Re-Induction Therapy for Children with Relapsed Acute Lymphoblastic Leukemia (ALL) and Lymphoblastic Lymphoma (LL)."
ODE - ORPHAN DRUG EXCLUSIVITY	10/8/2021 (4/8/2022)	21-602/S-040, approved 10/8/2014 See above

M-139 exclusivity code that provides exclusivity for dosing and administration section of the package insert regarding retreatment with Velcade for patients with multiple myeloma expired (including pediatric extension) on 2/8/2018.

D-141, D-142, and I-695 exclusivities related to dosing and indication for mantle cell lymphoma (including pediatric extension) have expired.

Reviewer comment: Hospira did not seek an indication for treatment of patients with mantle cell lymphoma at the time of filing of the original Application. The applicant did not seek the retreatment indication at the time of the original submission (30 June, 2016) and carved out this information from the PI.

Labelling Recommendations: The applicant submitted a draft PI with this resubmission. The Applicant did not include any changes to the PI with the most recent resubmission. The expired exclusivity indications for retreatment of patients with multiple myeloma and (b) (4) mantle cell lymphoma indications were not requested by the Applicant in the initial submission or in this resubmission. The label will not be revised to include these indications in this resubmission.

At the time of this review the application was still under review by the 505(b)(2) committee.
Please see final NDA 209191 USPI for approved labelling recommendations.

Conclusion: No clinical data was submitted in this 505 (b) 2 Class I resubmission application for NDA 209191 bortezomib for injection. Based on my clinical review, NDA 209191 bortezomib for injection for "treatment of patients with multiple myeloma" can be granted approval.

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/s/

BINDU N KANAPURU
07/02/2018

VISHAL BHATNAGAR
07/02/2018

File Memorandum

NDA: 209191

Applicant: Hospira

Product: Bortezomib for Injection (2.5 mg/ml)

Submission date: 12/22/2017

Clinical reviewer: Bindu Kanapuru, MD

Clinical team leader: Nicole Gormley, MD

Regarding: 505(b) (2) NDA Class I resubmission

This is a brief review of the class I resubmission for this 505 (b)2 NDA 209191 Bortezomib for Injection. The reference listed drug (RLD) is Velcade. Please refer to the clinical review for original submission (DAARTS 03/27/2017) and first resubmission (DAARTS, 11/01/107) for additional details. No clinical data was submitted in the original submission dated 30 June,2016, resubmission 1 dated 7 September 2017 or this resubmission.

NDA 209191 received recommendation for tentative approval on 4/26/2017 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.

Refer to submission eCTD0018/18 regarding decision on Class Action Suit and reason for first resubmission on 7 September 2017. A CR was issued on 11/3/2017 following review of the 7 September, 2017 Class I resubmission due to unresolved deficiencies associated with the drug substance manufacturing facility (b) (4)

The CMC and facilities reviewer reported that the facility issues were resolved prior to the most recent 12/22/2017 resubmission and this was deemed a class I resubmission pending labelling recommendations.

Table 1 Pending Exclusivities for RLD Velcade

Exclusivity Code	***Expiration Date (w/peds ext)***	***Velcade approval - basis***
D-141- DOSING INFORMATION IN PREVIOUSLY UNTREATED MANTLE CELL LYMPHOMA	10/8/2017 (4/8/2018)	21-602/S-040, approved 10/8/2014 Revised indication for VELCADE® for the treatment of patients with mantle cell lymphoma. The United States prescribing information (USPI) has been updated with additional information regarding the dosing, administration, safety, and efficacy of VELCADE® for mantle cell lymphoma. (*Orphan Indication*)

D-142 - DOSE MODIFICATION GUIDELINES FOR BORTEZOMIB WHEN GIVEN IN COMBINATION WITH RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, AND PREDNISONE	10/8/2017 (4/8/2018)	21-602/S-040, approved 10/8/2014 See above
I-695 - REVISED INDICATION FOR BORTEZOMIB IN THE TREATMENT OF PATIENTS WITH MANTLE CELL LYMPHOMA	10/8/2017 (4/8/2018)	21-602/S-040, approved 10/8/2014 See above
M-165 - PROVIDES FOR UPDATES TO THE PEDIATRIC USE SECTION BASED ON THE PEDIATRIC STUDY REPORT ENTITLED, 'A PHASE II PILOT TRIAL OF BORTEZOMIB IN COMBINATION WITH INTENSIVE RE-INDUCTION THERAPY IN CHILDREN WITH RELAPSED ACUTE LYMPHOBLASTIC LYMPHOMA (LL)'	9/14/2018 (3/14/2019)	21-602/S-042, approved 9/14/2015 Updates to the Pediatric Use section of the United States Prescribing Information based on the pediatric study report for Study AALL07P1, entitled "A Phase II Pilot Trial of Bortezomib in Combination with Intensive Re-Induction Therapy for Children with Relapsed Acute Lymphoblastic Leukemia (ALL) and Lymphoblastic Lymphoma (LL)."
ODE - ORPHAN DRUG EXCLUSIVITY	10/8/2021 (4/8/2022)	21-602/S-040, approved 10/8/2014 See above

M-139 exclusivity code that provides exclusivity for dosing and administration section of the package insert regarding retreatment with Velcade for patients with multiple myeloma expired (including pediatric extension) on 2/8/2018.

Reviewer comment: Hospira did not seek an indication for treatment of patients with mantle cell lymphoma at the time of filing of the original Application. The exclusivity period for the retreatment indication expires on February 8, 2018 prior to the goal date for approval of this resubmission. The applicant did not seek the retreatment indication at the time of the original submission (30 June, 2016) and carved out this information from the PI.

Labelling Recommendations: The applicant submitted a draft PI with this resubmission. The Applicant did not include any changes to the PI with the most recent resubmission. DPMH consult was requested to review the proposed language from the applicant in section 8.4 of the PI and determine if this language needs revision under FDARA [redacted] (b) (4) The DPMH recommendation is shown below.

USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
The safety and effectiveness of bortezomib in children have not been established.
Additional information describing a clinical study in which efficacy was not demonstrated in pediatric patients is approved for Millennium Pharmaceuticals, Inc. VELCADE (bortezomib) Injection. However, due to Millennium Pharmaceuticals, Inc.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

At the time of this review the application was still under review by the 505(b)(2) committee.
Please see final NDA 209191 USPI for approved labelling recommendations.

Conclusion: There is no clinical data submitted in this 505 (b) 2 Class I resubmission application for NDA 209191 bortezomib for injection. Based on my clinical review, NDA 209191 bortezomib for injection for "treatment of patients with multiple myeloma" can be granted approval.

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/s/

BINDU N KANAPURU
02/15/2018

NICOLE J GORMLEY
02/16/2018

File Memorandum

NDA: 209191

Applicant: Hospira

Product: Bortezomib for Injection (2.5 mg/ml)

Submission date: September 7, 2017

Clinical reviewer: Bindu Kanapuru, MD

Clinical team leader: Nicole Gormley, MD

Regarding: 505(b) (2) NDA Class I resubmission

This is a brief review of a class I resubmission for NDA 209191 Bortezomib for Injection. Please refer to the review for original submission (DAARTS 03/27/2017) for additional details. No clinical data was submitted in the original submission or this resubmission.

NDA 209191 received recommendation for tentative approval on 4/26/2017 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.

Refer to submission 18/0018 regarding decision on Class Action Suit and reason for resubmission.

U.S. Patent No. 5,780,454 expires on May 3, 2017 and is subject to a period of pediatric exclusivity that expires on November 3, 2017.

Table 1 Pending Exclusivities for RLD Velcade

Exclusivity Code	***Expiration Date (w/peds ext)***	***Velcade approval - basis***
D-141- DOSING INFORMATION IN PREVIOUSLY UNTREATED MANTLE CELL LYMPHOMA	10/8/2017 (4/8/2018)	21-602/S-040, approved 10/8/2014 Revised indication for VELCADE® for the treatment of patients with mantle cell lymphoma. The United States prescribing information (USPI) has been updated with additional information regarding the dosing, administration, safety, and efficacy of VELCADE® for mantle cell lymphoma. (*Orphan Indication*)
D-142 - DOSE MODIFICATION GUIDELINES FOR BORTEZOMIB WHEN GIVEN IN COMBINATION WITH RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, AND PREDNISONE	10/8/2017 (4/8/2018)	21-602/S-040, approved 10/8/2014 See above
I-695 - REVISED INDICATION FOR BORTEZOMIB IN THE TREATMENT OF PATIENTS WITH MANTLE CELL LYMPHOMA	10/8/2017 (4/8/2018)	21-602/S-040, approved 10/8/2014 See above
M-139 - INFORMATION ADDED TO THE DOSING AND ADMINISTRATION SECTION OF	8/8/2017 (2/8/2018)	21-602/S-038, approved 8/8/2014 Updates to the package insert with

Exclusivity Code	*Expiration Date (w/peds ext)*	*Velcade approval - basis*
D-141- DOSING INFORMATION IN PREVIOUSLY UNTREATED MANTLE CELL LYMPHOMA	10/8/2017 (4/8/2018)	21-602/S-040, approved 10/8/2014 Revised indication for VELCADE® for the treatment of patients with mantle cell lymphoma. The United States prescribing information (USPI) has been updated with additional information regarding the dosing, administration, safety, and efficacy of VELCADE® for mantle cell lymphoma. (*Orphan Indication*)
D-142 - DOSE MODIFICATION GUIDELINES FOR BORTEZOMIB WHEN GIVEN IN COMBINATION WITH RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, AND PREDNISONE	10/8/2017 (4/8/2018)	21-602/S-040, approved 10/8/2014 See above
I-695 - REVISED INDICATION FOR BORTEZOMIB IN THE TREATMENT OF PATIENTS WITH MANTLE CELL LYMPHOMA	10/8/2017 (4/8/2018)	21-602/S-040, approved 10/8/2014 See above
THE PACKAGE INSERT REGARDING RETREATMENT WITH VELCADE FOR PATIENTS WITH MULTIPLE MYELOMA		information regarding the dosing, administration, safety, and efficacy of retreatment with Velcade for relapsed multiple myeloma.
M-165 - PROVIDES FOR UPDATES TO THE PEDIATRIC USE SECTION BASED ON THE PEDIATRIC STUDY REPORT ENTITLED, 'A PHASE II PILOT TRIAL OF BORTEZOMIB IN COMBINATION WITH INTENSIVE RE-INDUCTION THERAPY IN CHILDREN WITH RELAPSED ACUTE LYMPHOBLASTIC LYMPHOMA (LL)'	9/14/2018 (3/14/2019)	21-602/S-042, approved 9/14/2015 Updates to the Pediatric Use section of the United States Prescribing Information based on the pediatric study report for Study AALL07P1, entitled "A Phase II Pilot Trial of Bortezomib in Combination with Intensive Re-Induction Therapy for Children with Relapsed Acute Lymphoblastic Leukemia (ALL) and Lymphoblastic Lymphoma (LL)."
ODE - ORPHAN DRUG EXCLUSIVITY	10/8/2021 (4/8/2022)	21-602/S-040, approved 10/8/2014 See above

Reviewer comment: Hospira did not seek an indication for treatment of patients with mantle cell lymphoma at the time of filing of the original Application. The Applicant has carved out the information protected by exclusivity. The Applicant has requested both subcutaneous and intravenous routes of administration.

Labelling Recommendations: The applicant submitted a draft PI with this resubmission. Changes were made to be consistent with the RLD which underwent PLLR conversion and included new post marketing safety data since the Original NDA 209191 tentative approval.

The PLLR updates were reviewed by the pharmacology toxicology reviewer. The changes to the post marketing safety section were consistent with the RLD and are acceptable.Please see final NDA 209191 USPI for approved labelling recommendations.

Conclusion: There is no clinical data submitted in this 505 (b) 2 Class I resubmission application for NDA 209191 bortezomib for injection. Based on my clinical review, NDA 209191 bortezomib for injection for "treatment of patients with multiple myeloma" can be granted approval.

The CMC reviewer has recommended CR based on unresolved deficiencies associated with the drug substance manufacturing facility (b) (4)

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/s/

BINDU N KANAPURU
11/01/2017

NICOLE J GORMLEY
11/01/2017

Addendum

Financial Disclosure Information Assessment

NDA: 209191
Applicant: Hospira
Product: Bortezomib for Injection (2.5 mg/ml)
Submission date: June 30, 2016
Clinical reviewer: Bindu Kanapuru, MD
Clinical team leader: Nicole Gormley, MD
Regarding: 505(b) (2) NDA

This addendum is to provide information regarding Financial Disclosure information for NDA2019191.

No clinical studies were submitted in support of this NDA.

There is no financial disclosure information with this application because there was no clinical trial data provided with the NDA. Therefore, the financial disclosure assessment is not applicable.

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BINDU N KANAPURU
04/06/2017

File Memorandum

NDA: 209191

Applicant: Hospira

Product: Bortezomib for Injection (2.5 mg/ml)

Submission date: June 30, 2016

Clinical reviewer: Bindu Kanapuru, MD

Clinical team leader: Nicole Gormley, MD

Regarding: 505(b) (2) NDA

Application background

The Applicant has submitted a 505(b) (2) application for Bortezomib for Injection. Bortezomib for Injection is a 2.5 mg/vial, which is intended to have the same dosage form, route of administration, inactive ingredients (mannitol) and dosing regimen as the Reference Listed Drug (RLD), VELCADE®.

Indication: Treatment of patients with multiple myeloma (MM).

No clinical data has been submitted for review.

The Application relies on;

- Previous findings of effectiveness NDA 021602 for "treatment of patients with MM.
- Product Information Velcade® 1, 12, and 14.
- Previous findings of safety NDA 021602 Velcade® injection
- Product Information Velcade® Sections 4,5,6,8, and 10

Table 1 Pharmaceutical Information for Hospira Bortezomib for Injection and Velcade

	Millenium Pharmaceuticals Velcade	**Hospira Bortezomib for Injection**
Active Ingredient(s)	Bortezomib	Bortezomib
Inactive Ingredient(s)	Mannitol, USP (35 mg)	Mannitol, USP (25 mg)
Route of Administration	Powder IV, SC	Powder IV, SC
Dosage Form	Injectable	Injectable
Strength	3.5 mg/vial	2.5 mg/vial

Table 2 Patent Data for Velcade Powder for Injection

Patent Number	Patent Expiration	Drug Substance Claim	Drug Product Claim
5,780,454	May 3, 2017	Y	Y
5,780,454*PED	Nov 3, 2017		
6,713,446	Jan 25, 2022	Y	Y
6,713,446*PED	Jul 25, 2022		
6,958,319	Jan 25, 2022	Y	Y
6,958,319*PED	Jul 25, 2022		

Hospira certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 5,780,454 expires on May 3, 2017 and is subject to a period of pediatric exclusivity that expires on November 3, 2017.

Hospira provided paragraph IV certification for Patent Nos. 6,713,446 and 6,958,319 and that, in its opinion and to the best of its knowledge, U.S. Patent Nos. 6,713,446 and 6,958,319 is either invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Hospira' s Bortezomib for Injection for which this application is submitted.

Table 3 Exclusivity Data for Velcade Powder for Injection

Exclusivity Code	Exclusivity Definition	Exclusivity Expiration
I-695	Revised indication for bortezomib in the treatment of patients with mantle cell lymphoma	08 Oct 2017
D- 142	Dose modification guidelines for bortezomib when given in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone	08 Oct 2017
D - 141	Dosing information in previously Untreated mantle cell lymphoma	08 Oct 2017
ODE	Orphan drug exclusivity	08 Oct2021
M -139	Information added to the dosing and administration section of the package insert regarding retreatment with velcade for patients with multiple myeloma	08 Aug 2017
M-165	Provides for updates to the pediatric use section based on the pediatric study report entitled, 'a phase ii pilot trial of Bortezomib in combination with intensive re-induction therapy in children with relapsed acute lymphoblastic lymphoma (ALL)'	14 Sep 2018
PED	Pediatric Exclusivity	08 Apr2018
PED	Pediatric Exclusivity	08 Apr 2018
PED	Pediatric Exclusivity	08 Apr 2018
PED	Pediatric Exclusivity	08 Apr2022
PED	Pediatric Exclusivity	08 Feb 2018
PED	Pediatric Exclusivity	14 Mar2019

Reviewer comment: Hospira does not intend to seek indication for treatment of patients with mantle cell lymphoma and for the retreatment of patients with multiple myeloma as these indications are protected under exclusivity. The Applicant has requested both subcutaneous and intravenous routes of administration.

Labelling Recommendations: The Applicant submitted a draft PI with the mantle cell lymphoma, retreatment for multiple myeloma and relapsed multiple myeloma indications carved out. Specific instructions for reconstitution and administration for the proposed new dose 2.5 mg/ml is also included in the label.

An information request was sent to the application requesting justification for carving out the relapsed multiple myeloma indication.

The Applicant responded to the IR by amending the PI to include the relapsed multiple myeloma indication.

At the time of this review labelling negotiations were still ongoing. Please see final NDA 209191 USPI for approved labelling recommendations.

Conclusion: There is no clinical data submitted 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 RLD Velcade (NDA021602) and the RLD 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.

Based on my review, I recommend granting approval for NDA 209191 Bortezomib for Injection for “treatment of patients with multiple myeloma”.

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/s/

BINDU N KANAPURU
03/23/2017

NICOLE J GORMLEY
03/27/2017

Division of Hematology Products (DHP) Labeling Review

Application Number	NDA 209191
Application Type	505(b)(2)
Proprietary Name **(nonproprietary name)**	Bortezomib for Injection (bortezomib)
Receipt Date	06/30/2016
PDUFA Goal Date	04/30/2017
Review Classification	Standard
Proposed Indication (or current indication if unchanged)	Bortezomib for Injection is a proteasome inhibitor indicated for treatment of patients with multiple myeloma.
Dosing Regimen	The recommended starting dose of Bortezomib for Injection is 1.3 mg/m2 administered either as a 3 to 5 second bolus intravenous injection or subcutaneous injection.
From	Virginia Kwitkowski, MS, ACNP-BC Associate Director for Labeling, DHP

Background of Application:

In this review, I propose labeling recommendations and edits in the Bortezomib for Injection labeling to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of Bortezomib for Injection.

The following pages contain the working version of the Bortezomib for Injection labeling with recommended edits and comments identified as 'VK1' through 'VK35'. This labeling version also includes comments from other members of the review team. Given that the scientific review of the labeling is ongoing, my labeling recommendations in this review should be considered preliminary and may not represent DHP's final recommendations for the Bortezomib for Injection labeling.

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/s/

VIRGINIA E KWITKOWSKI
03/13/2017