CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209191Orig1s000

OTHER ACTION LETTERS

NDA 209191

TENTATIVE APPROVAL

Hospira, Inc.
Attention: Craig Hernandez
Associate, Global Regulatory Affairs
275 North Field Drive
Department 0389
Lake Forest, IL 60045

Dear Mr. Hernandez:

Please refer to your new drug application (NDA) dated and received on March 11, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bortezomib for Injection 2.5 mg/vial and 1 mg/vial.

We acknowledge receipt of your amendment dated June 30, 2021, which constituted a complete response resubmission to our April 14, 2021, action letter.

This NDA provides for the use of Bortezomib for Injection for the treatment of adult patients with multiple myeloma and for the treatment of adult patients with mantle cell lymphoma who have received at least 1 prior therapy.

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed-upon enclosed labeling (text for the Prescribing Information and carton and container labeling). This determination is based upon information available to the Agency at this time, [i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product]. This determination is subject to change on the basis of any new information that may come to our attention.

Final approval of your application is subject to expiration of a period of patent protection and exclusivity. Therefore, final approval of your application may not be granted before the period has expired.

The Orphan Drug provisions of the FD&C Act, 21 U.S.C. §§ 360aa-360dd, provide for a grant of seven years of market exclusivity to which a period of pediatric exclusivity may attach. Orphan drug exclusivity blocks approval of any other application for the same drug for the same indication or use. Due to the orphan exclusivity granted to Millennium Pharmaceuticals product, Velcade, your application for Bortezomib may not be finally approved for marketing under section 505 of the FD&C Act until the period has expired.

To obtain final approval of this application, submit an amendment two or six months prior to the: (1) expiration of the patent(s) and/or exclusivity protection or (2) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as **"REQUEST FOR FINAL APPROVAL"**. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

Until we issue a final approval letter, this NDA is not approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labeling must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. (See the guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names*[1] and *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022*.)

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call Laura Wall, Senior Regulatory Project Manager, at 301-796-2237.

Sincerely,

{See appended electronic signature page}

Nicole Gormley, MD
Director
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

41 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

NICOLE J GORMLEY
12/17/2021 01:04:15 PM

NDA 209191

CONVERSION TO NDA TENTATIVE APPROVAL

Hospira, Inc., A Pfizer Company
Attention: Pamela Cabrera, PharmD
Senior Associate, Global Regulatory Affairs
275 North Field Drive
Department 0389
Lake Forest, IL 60045

Dear Dr. Cabrera:

We refer to your new drug application (NDA) 209191 for bortezomib for injection, received on March 11, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and approved on July 12, 2018. We are writing to inform you that, consistent with the Final Judgment issued on October 10, 2019, the Agency hereby converts the final approval of NDA 209191 to a tentative approval, and considers that this conversion occurred on the date of that decision. This action conforms the NDA's status to the court's final judgment, as described in detail below.

The listed drug relied upon for approval of your 505(b)(2) application, Velcade injection NDA 021602, of Millennium Pharmaceuticals, Inc. (Millennium), is subject to periods of patent protection. The following patents and expiration dates are listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
6,713,446 (the '446 patent)	January 25, 2022 (July 25, 2022 with pediatric extension)
6,958,319 (the '319 patent)	January 25, 2022 (July 25, 2022 with pediatric extension)

Your NDA contained paragraph IV certifications to the '446 and '319 patents under section 505(b)(2)(A)(iv) of the FD&C Act stating that the patents were invalid, unenforceable, or would not be infringed by your manufacture, use, or sale of bortezomib injection under this NDA. You had notified the agency that Hospira complied with the requirements of section 505(b)(3) of the FD&C Act, and that litigation was initiated for infringement of the '446 patent and was brought against Hospira within the statutory 45-day period in the United States District Court for the District of Delaware [Millennium Pharmaceuticals, Inc. v. Hospira, Inc, Civil Action No. 1:16-cv-00998-GMS] triggering a 30-month stay of approval of your NDA. On April 19, 2017, the District Court entered a consent judgment finding that the four asserted claims of the '446 patent were invalid due to obviousness. The 30-month stay was terminated by the April 19, 2017, district court judgment. Although patent litigation with respect to the '446 patent was ongoing, Hospira's NDA was resubmitted on May 16, 2018. FDA approved Hospira's NDA on

July 12, 2018, as there were no barriers to approval at that time.

Millennium filed a notice of appeal in the U.S. Court of Appeals for the Federal Circuit (Federal Circuit). On June 27, 2017, the appeal was stayed pending the final resolution of *Millennium Pharmaceuticals, Inc. v. Sandoz Inc.*, No. 2015-2066. In the *Sandoz* case, the district court had entered judgment that the asserted claims of the '446 patent were invalid as obvious. On appeal, the Federal Circuit reversed those validity determinations. The mandate in the *Sandoz* case issued on October 27, 2017.

On November 22, 2017, the Federal Circuit vacated the district court's judgment in *Millennium Pharmaceuticals v. Hospira* and the appeal was remanded to the district court for further proceedings. On October 10, 2019, the district court entered Final Judgment in favor of Millennium, finding that the asserted claims of the '446 patent are not invalid and Hospira's NDA would infringe the asserted claims of the '446 patent. The district court also found that pursuant to 35 U.S.C. § 271(e)(4) the effective date of any FDA approval of Hospira's NDA shall not be earlier than May 1, 2022.

Section 505(b) of the FD&C Act does not expressly provide for a change in approval status when the patent litigation results in a finding that one or more listed patents is infringed; however, pursuant to 21 CFR 314.107(g), if a court enters an order requiring, in the case of an already approved 505(b)(2) application, that the date of approval be delayed, FDA will convert the approval to a tentative approval, if appropriate.[1] Therefore, after consideration of the district court's October 10, 2019 Final Judgment, FDA is converting the July 12, 2018, final approval of Hospira's NDA 209191 for bortezomib for injection to a tentative approval.

In addition, pursuant to 21 CFR 314.50(i)(6)(i), an applicant who has submitted a paragraph IV certification and is sued for patent infringement must submit an amendment to change its certification if a court enters a final decision from which no appeal has been or can be taken, or signs and enters a settlement order[2] or consent decree in the action that includes a finding that the patent is infringed, unless the final decision, settlement order, or consent decree also finds the patent to be invalid. In its amendment, the applicant must certify under 21 CFR 314.50(i)(1)(i)(A)(*3*) that the patent will expire on a specific date (i.e., paragraph III certification). Once an amendment for the change has been submitted, the NDA will no longer be considered to contain a paragraph IV certification to the patent. If you believe that your NDA

[1] As explained in the preamble to the proposed rule that included 21 CFR 314.107(g), FDA explained:

> An approved application may be converted to tentatively approved status if a court determines that a listed patent has been infringed by a 505(b)(2) or ANDA applicant and issues an order pursuant to 35 U.S.C. 271(e)(4) requiring that the effective date of approval shall not be earlier than the date on which the infringed patent will expire, including any pediatric exclusivity that may attach to that patent (see, ***e.g.,*** ***Mylan Labs., Inc.*** v. ***Thompson,*** 389 F.3d 1272 (D.C. Cir. 2004)).

Abbreviated New Drug Applications and 505(b)(2) Applications, 80 FR 6802, 6869 (Feb. 6, 2015).

[2] We note that that if a settlement order permits approval of a 505(b)(2) application before the expiration of the relevant patent, then an applicant should maintain its paragraph IV certification. See 21 CFR 314.50(i)(3).

is eligible for approval prior to the expiration of the '446 patent, as extended by pediatric exclusivity,[3] please submit documentation that the exclusivity period has been waived.

Please be aware that any approved supplemental NDAs (i.e., supplement 001 approved on December 28, 2018) filed to this NDA since July 12, 2018, are considered tentatively approved because the underlying NDA is considered tentatively approved. We also note that supplement 001 to NDA 209191 for a new 1mg/vial strength included a paragraph III patent certification with respect to Velcade's '446 and '319 patents, both of which expire July 25, 2022, inclusive of a pediatric extension. Consistent with this patent certification, supplement 001 was not eligible for approval on December 28, 2018.[4] This supplement should be re-submitted in full as a MAJOR amendment to the original NDA or as a new supplemental NDA once final approval of your NDA has been obtained.

(b) (4)

Any annual report changes submitted to the NDA should be resubmitted in full as either an amendment to the original NDA or consistent with 21 CFR 314.70 after final approval of the NDA has been obtained.

RESUBMISSION

To request final approval, please submit an amendment titled "FINAL APPROVAL REQUESTED" with enough time to permit FDA review prior to the date you believe that your NDA will be eligible for final approval. A request for final approval that contains no new data, information, or other changes to the NDA generally requires a period of 2 months for Agency review. Accordingly, such a request for final approval should be submitted no later than 2 months prior to the date on which you seek approval. A request for final approval that contains substantive changes to this NDA or changes in the status of the manufacturing and testing facilities' compliance with cGMPs will be classified and reviewed according to OND policy.

The amendment requesting final approval should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, settlement or licensing agreement, or other information described in 21 CFR 314.107, as appropriate. It should also identify changes, if any, in the conditions under which the NDA was tentatively approved, e.g., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a "FINAL APPROVAL REQUESTED."

In addition to the amendment requested above, the Agency may request, at any time prior to the date of final approval, that you submit an additional amendment containing information as

[3] See section 505A(c)(1)(B) of the FD&C Act.
[4] See section 505(c)(3)(B) of the FD&C Act and 21 CFR 314.107(b)(1)(iii).

specified by the Agency. Failure to submit either or, if requested, both types of amendments described above may result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final Agency approval under section 505(c) of the FD&C Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the FD&C Act. Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under section 505(c) of the FD&C Act, and will not be listed in the Orange Book. Should you believe that there are grounds for issuing the final approval letter prior to the date of the court order and/or the date of the pediatric extension, you should amend your NDA accordingly.

For further information on the status of this NDA, or prior to submitting additional amendments, please contact Theresa Carioti, Chief Project Management Staff, at 301-796-2848.

Sincerely,

{See appended electronic signature page}

Nicole Gormley, MD
Director
Division of Hematologic Malignancies II
Office of Oncologic Drugs
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling

34 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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
04/14/2021 07:09:06 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209191

NDA APPROVAL

Hospira, Inc., A Pfizer Company
Attention: Pamela Cabrera, PharmD
Senior Associate, Global Regulatory Affairs
275 North Field Drive
Department 0389
Lake Forest, IL 60045

Dear Dr. Cabrera:

Please refer to your New Drug Application (NDA) dated June 30, 2016, received June 30, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bortezomib for Injection, 2.5 mg/vial.

We acknowledge receipt of your amendment dated May 16, 2018, which constituted a complete response to our February 22, 2018, action letter.

This new drug application provides for the use of Bortezomib for Injection, 2.5 mg/vial for the treatment of patients with multiple myeloma.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on May 16, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 209191**." Approval of this submission by FDA is not required before the labeling is used.

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. (See the guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Nicole Gormley, MD
Acting Deputy Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Content of Labeling

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/s/

NICOLE J GORMLEY
07/12/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209191

COMPLETE RESPONSE

Hospira, Inc.
Attention: Pamela Cabrera, PharmD
Senior Associate, Global Regulatory Affairs
275 N Field Drive
Building H2-2, Department 0389
Lake Forest, IL 60045

Dear Dr. Cabrera:

Please refer to your New Drug Application (NDA) dated June 30, 2016, received June 30, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bortezomib for Injection, 2.5 mg/vial.

We acknowledge receipt of your amendment dated December 22, 2017, which constituted a complete response to our November 3, 2017, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

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.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling that are identical to the carton and immediate container labels submitted on December 22, 2017.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
    - Present tabulations of the new safety data combined with the original application data.
    - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
02/22/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209191

COMPLETE RESPONSE

Hospira, Inc.
Attention: Pamela Cabrera, PharmD
Senior Associate Global Regulatory Affairs
275 North Field Drive, Dept. 0389
Lake Forest, IL 60045

Dear Dr. Cabrera:

Please refer to your New Drug Application (NDA) dated June 30, 2016, received June 30, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bortezomib for Injection, 2.5 mg/vial.

We acknowledge receipt of your amendment dated September 7, 2017, which constituted a complete response to our April 26, 2017, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

During a recent inspection of the (b) (4) manufacturing facility for this NDA, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this NDA may be approved.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling that are identical to the carton and immediate container labels submitted on October 18, 2017.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
    - Present tabulations of the new safety data combined with the original application data.
    - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
11/03/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209191

TENTATIVE APPROVAL

Hospira, Inc.
Attention: Pamela Cabrera, PharmD
Senior Associate Global Regulatory Affairs
275 N Field Drive, Dept. 0389
Lake Forest, IL 60045

Dear Dr. Cabrera:

Please refer to your New Drug Application (NDA) dated June 30, 2016, received June 30, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bortezomib for Injection, 2.5 mg/vial.

This NDA provides for the use of Bortezomib for Injection, 2.5 mg/vial for the treatment of patients with multiple myeloma.

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed-upon enclosed labeling (text for the package insert, submitted carton and immediate container labels submitted April 14, 2017). This determination is based upon information available to the Agency at this time, [i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product]. This determination is subject to change on the basis of any new information that may come to our attention.

The listed drug upon which your application relies is subject to a period of patent protection and therefore final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the period has expired.

Your application contains certifications to each of the patents under section 505(b)(2)(A)(iv) of the Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of, this drug product under this application ("Paragraph IV certifications").

Section 505(c)(3)(C) of the Act provides that approval of a new drug application submitted pursuant to section 505(b)(2) of the Act shall be made effective immediately, unless an action is brought for infringement of one or more of the patents that were the subject of the paragraph IV certifications. This action must be taken prior to the expiration of forty-five days from the date the notice provided under section 505(b)(3) is received by the patent owner/approved application holder. You notified us that you complied with the requirements of section 505(b)(3) of the Act.

In addition, you have notified the Agency that the patent owner and/or approved application holder has initiated a patent infringement suit against you with respect to patent 6,713,446 in the United States District Court For The District Of Delaware (Case 1:16-cv-00998-UNA). Therefore, final approval cannot be granted until:

1. a. expiration of the 30-month period provided for in Section 505(c)(3)(C) beginning on the date of receipt of the 45-day notice required under Section 505(b)(3), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or
   b. the date the court decides that the patent is invalid or not infringed as described in section 505(c)(3)(C)(i), (ii), (iii,) or (iv) of the Act, or,
   c. the listed patent has expired, and
2. we are assured there is no new information that would affect whether final approval should be granted.

To obtain final approval of this application, submit an amendment two or six months prior to the: 1.) expiration of the patent or 2.) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as **"REQUEST FOR FINAL APPROVAL"**. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

Until we issue a final approval letter, this NDA is not deemed approved.

Please note that this drug product may not be marketed in the United States without final agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d).

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. See the guidance for industry titled, "Contents of a Complete Submission for the Evaluation of Proprietary Names", at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that if this application is ultimately approved, you will need to meet these requirements.

If you have any questions, call Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling

33 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALBERT B DEISSEROTH
04/26/2017