

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205004Orig1s000

OTHER ACTION LETTERS



NDA 205004

TENTATIVE APPROVAL

Fresenius Kabi USA, LLC
Attention: Bridget Walsh
Regulatory Specialist
Three Corporate Drive
Lake Zurich, IL 60047

Dear Ms. Walsh:

Please refer to your New Drug Application (NDA) dated November 30, 2012, received December 3, 2012, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bortezomib for Injection, 3.5 mg/vial.

We acknowledge receipt of your amendment dated May 22, 2015, which constituted a complete response to our April 2, 2015, action letter.

This NDA provides for the use of Bortezomib for Injection, 3.5 mg/vial for the treatment of patients with multiple myeloma and for the treatment of patients with mantle cell lymphoma who have received at least one 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 submitted labeling (text for the package insert submitted November 13, 2015, carton and immediate container labels submitted October 30, 2015). 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 and exclusivity 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.

The Orphan Drug provisions of the Federal Food, Drug, and Cosmetic 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. Due to the orphan exclusivity granted to Millennium Pharmaceuticals Inc.'s product, Velcade® (bortezomib) for Injection, your application for Bortezomib for Injection lyophilized powder, 3.5 mg/vial may not be finally approved for marketing under Section 505 of the 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 patents and 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 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 Janet G. Higgins, Regulatory Project Manager, at (240) 402-0330.

Sincerely,

{See appended electronic signature page}

Edvardas Kaminskas, M.D.
Deputy Division Director
Division of Hematology Products
Office of Hematology Oncology Products
Center for Drug Evaluation and Research

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/s/

EDVARDAS KAMINSKAS
11/17/2015



NDA 205004

COMPLETE RESPONSE

Fresenius Kabi USA, LLC
Attention: Bridget Walsh
Regulatory Specialist
Three Corporate Drive
Lake Zurich, IL 60047

Dear Ms. Walsh:

Please refer to your New Drug Application (NDA) dated November 30, 2012, received December 3, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bortezomib for Injection.

We acknowledge receipt of your amendments dated December 28, 2012; January 18 and 29; February 5 and 18, March 21 and 22, April 11 and 26, and September 9, 2013; October 3, 2014; and March 6, and 12, 2015.

The October 3, 2014, submission constituted a complete response to our October 3, 2013, action letter.

FDA's district office also acknowledged receipt of a response on March 27, 2015, to the deficiencies conveyed by FDA's field investigator, which was not reviewed for this action.

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 Fresenius Kabi USA LLC manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved. Your resubmission should include a statement that all the deficiencies have been addressed.

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](#) website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the PI 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>.

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 the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA 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 NDA 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. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference 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 FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.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 Toni-Ann Cox, Regulatory Project Manager, at (240) 402-4775.

Sincerely,

{See appended electronic signature page}

Edvardas Kaminskas, MD
Deputy Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

EDVARDAS KAMINSKAS
04/02/2015



NDA 205004

COMPLETE RESPONSE

Fresenius Kabi USA, LLC
Attention: Aditi Dron
Manager, Regulatory Affairs
Three Corporate Drive
Lake Zurich, IL 60047

Dear Ms. Dron:

Please refer to your New Drug Application (NDA) dated November 30, 2012, received December 3, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bortezomib for Injection.

We acknowledge receipt of your amendments dated December 28, 2012, January 18, 29, 2013, February 5, 18, 2013, March 21, 22, 29, 2013, April 11, 26, 2013 and September 9, 2013.

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.

QUALITY – SPECIFICATION, PROCESS, and FACILITIES

1. During a recent inspection of APP Pharmaceuticals, LLC, Grand Island NY, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.
2. You have not provided sufficient data to show that you have adequately developed your product lyophilization cycle. Your March 29, 2013 response to item 19 of our March 15, 2013 letter was incomplete and, therefore, is insufficient. Furthermore, you stated in your response to item 17 of the same letter that you have been unable to produce a batch with moisture content below (b) (4)%. Provide evidence that you have fully developed each stage of the lyophilization cycle that you intend to validate in commercial-scale batches. State explicitly your criteria for determining advancement through each stage of the lyophilization cycle and provide data showing that the criteria have been met. Include temperature mapping (b) (4) the lyophilizer.
3. You have not appropriately set your finished product moisture content limit (b) (4)%. Specifically, you have added a (b) (4) for water content without demonstrating that (b) (4). In addition, it is unknown if the water content between (b) (4)% impacts product stability; you have not justified the approach you use to calculate your moisture limit. Specifically, you have not provided justification for

calculating the limit based on [REDACTED] (b) (4)
Either revise your moisture content and remove the [REDACTED] (b) (4) or redevelop your lyophilization process.

4. Your March 29, 2013 response to item 11 of our March 15, 2013 letter is inadequate because you did not revise your [REDACTED] (b) (4)
5. Your March 29, 2013 response to item 22 of our March 15, 2013 letter is insufficient. Because you have not stated that these additional reconstitution time data points are results from [REDACTED] (b) (4)
[REDACTED] (b) (4)
response.

LABELING

6. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, 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>.

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.

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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.
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Under 21 CFR 314.102(d), you may request a meeting or telephone conference 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 FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.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 Ebla Ali Ibrahim, M.S., Lead Regulatory Project Manager, at (301) 796-3691.

Sincerely,

{See appended electronic signature page}

Edvardas Kaminskas, M.D.
Deputy Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

EDVARDAS KAMINSKAS
10/03/2013