

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212209Orig1s000

OTHER ACTION LETTERS



NDA 212209

TENTATIVE APPROVAL

Slayback Pharma, LLC
Attention: Praveen Subbappa
Senior Director
301 Carnegie Center, Suite 303
Princeton, NJ 08540

Dear Mr. Subbappa:

Please refer to your new drug application (NDA) dated and received August 31, 2018, and your amendments submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Vivimusta (bendamustine hydrochloride) injection.

We acknowledge receipt of your amendment dated June 27, 2022, following our March 16, 2022, tentative approval letter.

This NDA provides for the use of Vivimusta (bendamustine hydrochloride) injection for:

- Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.
- Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

We have completed our review of this application. 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 submitted labeling (carton and container labeling submitted June 27, 2022). 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 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 Eagle Pharmaceutical Inc.'s product, Bendeka, your application for bendamustine hydrochloride injection 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 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.

If you have any questions, call Wanda Nguyen, PharmD, Regulatory Project Manager, at 301-796-2808.

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 (CDER)

ENCLOSURE:

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

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/s/

NICOLE J GORMLEY
08/26/2022 04:16:13 PM



NDA 212209

TENTATIVE APPROVAL

Slayback Pharma, LLC
Attention: Praveen Subbappa
Senior Director
301 Carnegie Center, Suite 303
Princeton, NJ 08540

Dear Mr. Subbappa:

Please refer to your new drug application (NDA) dated and received June 16, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Vivimusta (bendamustine hydrochloride injection).

We acknowledge receipt of your major amendment dated November 17, 2021, which extended the goal date by three months.

This NDA provides for the use of Vivimusta (bendamustine hydrochloride injection) for:

- Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.
- Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

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 submitted labeling (carton and container labeling submitted March 14, 2022). 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/or 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 Eagle Pharmaceutical Inc.'s product, Bendeka, your application for bendamustine

hydrochloride injection may not be finally approved for marketing under section 505 of the FD&C Act until the period has expired.

A listed drug(s) upon which your application relies is subject to a period of patent protection and your application contains a certification(s) to one or more patents under section 505(b)(2)(A)(iv) of the FD&C Act stating that the patent(s) is/are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of, this drug product under this application ("paragraph IV certification").

Section 505(c)(3)(C) of the FD&C Act provides that approval of a new drug application submitted pursuant to section 505(b)(2) of the FD&C 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 45 days from the date the notice provided under section 505(b)(3) of the FD&C Act is received by the patent owner/approved application holder. You notified us that you complied with the requirements of section 505(b)(3). However, because the 45-day period described in section 505(c)(3)(C) of the FD&C Act has not yet expired, final approval cannot be granted.

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.

If you have any questions, call Wanda Nguyen, PharmD, Regulatory Project Manager, at 301-796-2808.

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 (CDER)

ENCLOSURE:

- Content of Labeling
 - o Prescribing Information
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/s/

NICOLE J GORMLEY
03/16/2022 04:46:12 PM



NDA 212209

TENTATIVE APPROVAL

Slayback Pharma, LLC
Attention: Praveen Subbappa
Senior Director
301 Carnegie Center, Suite 303
Princeton, NJ 08540

Dear Mr. Subbappa:

Please refer to your new drug application (NDA) dated February 14, 2020, received February 14, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bendamustine Hydrochloride injection.

We acknowledge receipt of your amendment dated February 14, 2020, which constituted a complete response to our September 16, 2019, action letter.

This NDA provides for the use of Bendamustine Hydrochloride injection for:

- Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.
- Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

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 submitted labeling (carton and container labeling submitted June 19 2020.) 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 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 Eagle Pharmaceuticals Incorporation's product, Bendeka, your application for Bendamustine Hydrochloride 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 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.

Please note that this drug product may not be marketed in the United States without final agency approval under section 505 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 501 of the FD&C 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 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 Wanda Nguyen, PharmD, Regulatory Project Manager, at 301-796-2808.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):

- Content of Labeling
 - o Prescribing Information

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/s/

NICOLE J GORMLEY
07/02/2020 12:09:02 PM



NDA 212209

COMPLETE RESPONSE

Slayback Pharma, LLC
Attention: Praveen Subbappa
Senior Director
301 Carnegie Center, Suite 303
Princeton, NJ 08540

Dear Mr. Subbappa:

Please refer to your new drug application (NDA) dated July 1, 2019, received July 1, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bendamustine Hydrochloride injection.

We acknowledge receipt of your amendment dated July 1, 2019, which constituted a complete response to our June 17, 2019, 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

The drug substance manufacturing site, (b) (4) was found deficient. Refer to the comment in the Facility Inspections section below.

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 Information¹ and Pregnancy and Lactation Labeling Final Rule² 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.

¹ <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

² <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>

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 FDA.gov.³

FACILITY INSPECTIONS

During a recent inspection of the (b) (4) drug substance manufacturing facility for this application, our field investigator observed objectionable conditions at the facility and conveyed deficiencies to the representative of the facility at the close of the inspection. Satisfactory resolution of these deficiencies is required before this application may be approved.

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 guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

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

³ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

If you have any questions, call Wanda Nguyen, Regulatory Project Manager, at (301) 796-2808.

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

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/s/

ALBERT B DEISSEROTH
09/16/2019 11:41:56 AM



NDA 212209

COMPLETE RESPONSE

Slayback Pharma, LLC
Attention: Praveen Subbappa
Senior Director
301 Carnegie Center, Suite 303
Princeton, NJ 08540

Dear Mr. Subbappa:

Please refer to your new drug application (NDA) dated August 31, 2018, received August 31, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bendamustine Hydrochloride Injection. We also acknowledge receipt of your amendment dated June 5, 2019, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this 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

The drug substance manufacturing site, (b) (4) was found deficient. Refer to the comment in the Facility Inspections section below.

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 Information¹ and Pregnancy and Lactation Labeling Final Rule² 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.

¹ <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

² <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>

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 FDA.gov.³

FACILITY INSPECTIONS

During a recent inspection of the [REDACTED] (b) (4) drug substance manufacturing facility for this application, our field investigator observed objectionable conditions at the facility and conveyed deficiencies to the representative of the facility at the close of the inspection. Satisfactory resolution of these deficiencies is required before this application may be approved.

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.

³ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

- (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.

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 Wanda Nguyen, Regulatory Project Manager, at (301) 796-2808.

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

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/

ALBERT B DEISSEROTH
06/17/2019 09:29:11 AM