CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205580Orig1s000

PRODUCT QUALITY REVIEW(S)

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 205580 for Bendamustine Hydrochloride Injection, 100 mg/4 mL (25 mg/mL). As part of this action, OPQ grants a (b) (4)-month re-test period for the drug substance when stored in (b) (4) There are no outstanding issues and no post-approval agreements to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

Bendamustine is a small molecule alkylating agent that was originally approved by the FDA in 2009 (NDA 22249) for treatment of patients with chronic lymphocytic leukemia (CLL) and indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab containing regimen. NDA 205580 was submitted as a 505(b)(2) NDA with Treanda® (bendamustine) as the Listed Drug (LD). The proposed drug product, Bendamustine Hydrochloride Injection, 100 mg/4 mL (25 mg/mL, is a ready-to-dilute solution, whereas the LD is a lyophilized powder that requires reconstitution. The drug product is intended for IV infusion.

Bendamustine Hydrochloride is manufactured by (b) (4) (b) (4) (b) (4). Information pertaining to the manufacture and control of the drug substance was incorporated into the application by way of reference to DMF (b) (4) DMF (b) (4) was reviewed in conjunction with the review of NDA 205580 and was deemed adequate to support the approval of NDA 205580. The drug product, bendamustine hydrochloride, 25 mg/mL is a ready-to-dilute, (b) (4), self-preserving solution formulation intended for multiple doses. The drug product formulation includes 25 mg/mL of bendamustine hydrochloride (100 mg/vial), 5 mg/mL of monothioglycerol as an (b) (4) (20 mg/vial), and 0.1 mL/mL of propylene glycol as a (b) (4) (0.4 mg/vial) in polyethylene glycol 400 (QS to 4 mL). The drug product is sterilized by (b) (4) (b) (4) (b) (4)

The dosing regimen for Bendamustine Hydrochloride Injection, 100 mg/4 mL (25 mg/mL) for patients with chronic lymphocytic leukemia (CLL) is 100 mg/m^2 administered intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles. The dosing regimen for Bendamustine Hydrochloride Injection, 100 mg/4 mL (25 mg/mL) for patients with indolent B-cell non-Hodgkin lymphoma (NHL) is 120 mg/m^2 administered intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles.
Based on the information provided in this application (original submission, resubmission, amendments and responses to information requests), OPQ considers all review issues

adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 205580 and grants a (b) (4)-month re-test period for the drug substance and a 24 month expiration period for the drug product when stored between 2 -8 C (36 to 46 F) in the commercial packaging. The drug product should be used within 24 hours when held under refrigeration or 3 hours when stored at room temperature (these times include administration time). Each vial is not recommended for more than a total of six dose withdrawals and should be discarded after 28 days.

Proposed Indication(s) including Intended Patient Population	• 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.
Duration of Treatment	The recommended dose for CLL is 100 mg/m^2 administered intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles. The recommended dose for NHL is 120 mg/m^2 administered intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles.
Maximum Daily Dose	(b) (4) mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

NDA 205580 was originally submitted in February 2013 and tentatively approved (TA) in July 2014. The application could not be granted final approval until all exclusivities expired. There were no outstanding CMC issues at this time. NDA 205580 was resubmitted to the agency in January 2018. At which time it was concluded that this application would be a Class 1.

Drug Product:

In the resubmission, there were modifications noted in the proposed drug product specifications based on approved post-marketing CMC submissions for BENDEKA (bendamustine hydrochloride) injection 100mg/4mL (25 mg/mL) for infusion under Eagle's NDA 208194 which was approved in December 2015. Of note, the DP reviewer states that due to the current OPQ policy on resubmissions for implementation of USP<232> and USP<233>, the elemental impurities specification in the drug product was verified (see appended drug product memo).

In the original submission, the applicant requested a 24 month expiry for the drug product. At that time the drug product reviewer recommended an (b) (4) month expiry for the drug product. In support of the proposed 24 month drug product expiry, the

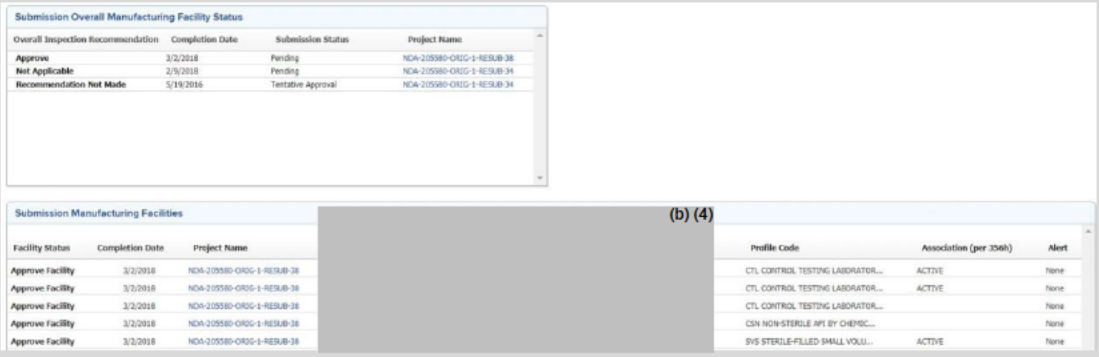
applicant has provided 24 months of long term and 6 month of accelerated stability data. All data was acceptable. Accordingly, Eagle Pharmaceuticals proposed and the FDA accepts the expiration dating period of **24 months** for the drug product when stored at stored between 2 -8 C (36 to 46 F) in the commercial packaging based on real time data.

Microbiology:

The resubmission included updated details pertaining to process and micro validation. The micro team reviewed the submission and it was concluded that all information provided by the applicant was adequate and as such the application is recommended for approval on the basis of sterility assurance (see appended microbiology memo).

Facilities:

All facilities_are ACCEPTABLE and recommended for approval for the functions listed in the application.



Submission Overall Manufacturing Facility Status

Overall Inspection Recommendation	Completion Date	Submission Status	Project Name
Approve	3/2/2018	Pending	NDA-205580-ORIG-1-RESUB-38
Not Applicable	2/9/2018	Pending	NDA-205580-ORIG-1-RESUB-34
Recommendation Not Made	5/19/2016	Tentative Approval	NDA-205580-ORIG-1-RESUB-34

Submission Manufacturing Facilities

Facility Status	Completion Date	Project Name	(b) (4)	Profile Code	Association (per 356h)	Alert
Approve Facility	3/2/2018	NDA-205580-ORIG-1-RESUB-38		CTL CONTROL TESTING LABORATOR...	ACTIVE	None
Approve Facility	3/2/2018	NDA-205580-ORIG-1-RESUB-38		CTL CONTROL TESTING LABORATOR...	ACTIVE	None
Approve Facility	3/2/2018	NDA-205580-ORIG-1-RESUB-38		CTL CONTROL TESTING LABORATOR...		None
Approve Facility	3/2/2018	NDA-205580-ORIG-1-RESUB-38		CSN NON-STERILE API BY CHEMIC...		None
Approve Facility	3/2/2018	NDA-205580-ORIG-1-RESUB-38		SVS STERILE-FILLED SMALL VOLU...	ACTIVE	None

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)

n/a

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