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:

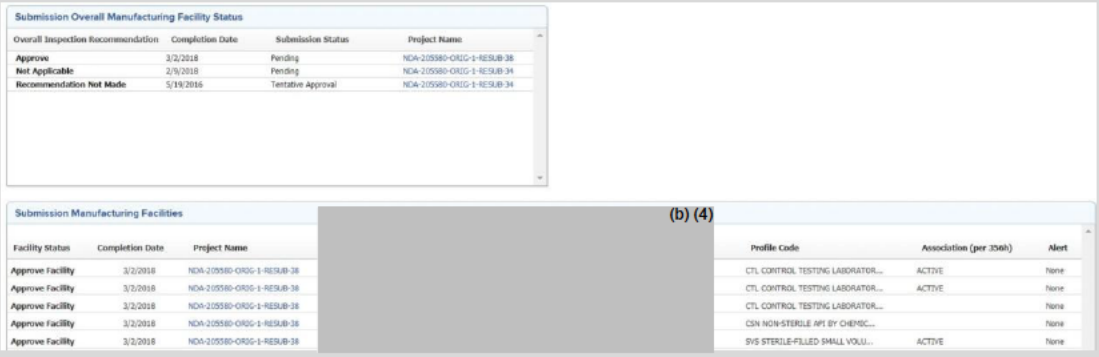
In the resubmission, there were modifications noted in the proposed drug product specifications based on approved post-marketing CMC submissions for BENDEKA (bendamustine hydrochloride) injection 100mg/4mL (25 mg/mL) for infusion under Eagle's NDA 208194 which was approved in December 2015. Of note, 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

Sherita McLamore

Digitally signed by Sherita McLamore
Date: 3/15/2018 01:15:49PM
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Memorandum

To: NDA 205-580

CC:

From: A. K. Mitra, Ph.D. through A. Banerjee, Ph.D.

Date: 3/5/2018

Re: Resubmission, dated 31-JAN-2018

The original NDA 205-580 was tentatively approved on 02-JUL-2014, pending patent expiry of the listed drug. The resubmission application cover memo states the following: "It should be noted that certain modifications have been proposed for the drug product specifications, based on the following approved post-marketing CMC submissions for BENDEKA (bendamustine hydrochloride) injection 100mg/4mL (25 mg/mL) for infusion in a 50 mL admixture under the Eagle NDA 208194 (approved on December 7, 2015- Table 1). BENDEKA is the same formulation and uses the same container/closure system as Bendamustine Hydrochloride Injection.

Table 1 Postmarketing Submissions Approved Under NDA 208194

Postmarketing Submission	Submission Type	Submission Date	Approval Date	Approved Change
Supplement S-004 (SN0055)	PAS	11/14/2016	02/16/2017	To increase the long-term stability for the impurity of (b) (4) (b) (4) (b) (4)
Supplement S-007 (SN0066)	PAS	05/10/2017	08/25/2017	To provide specifications for (b) (4) (b) (4) with limits of (b) (4) respectively.

As noted above, a Reviewer's Guide is provided that lists the summaries of the proposed changes, including the information provided for approval of the supplements listed in Table 1, under NDA 208194. All documentation submitted under NDA 208194 to support these changes is included herein. Please note that, since the establishment of these specifications and limits was after testing of the registration batches was completed, batch analysis data and stability data provided for the registration batches ZBM011, ZBM012, and ZBM013, in Section 3.2.P.5.4 and Section 3.2.P.8.3 of this submission will not reflect these updates".

Therefore, the review of the entire CMC submission was not conducted thoroughly again because of two month PDUFA goal date on the resubmission. However, 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. The current specification for the drug product including the supplemental changes for NDA 205-580 is recorded below.

Summary of Bendamustine HCl Injection, 25mg/mL
Specifications for Release and Shelf-Life Testing

Test	Acceptance Criteria		
Description	Release: Clear colorless to slight yellow solution, essentially free from visible particulates		
	Shelf: Clear colorless to yellow solution, essentially free from visible particulates		
Identification: HPLC	By HPLC: The retention time of the major peak in the sample solution corresponds to that in the standard solution as obtained in the Assay.		
Identification: HPLC/UV	By HPLC: In the HPLC assay, the UV spectrum of the analyte peak in the sample solution exhibits the same maxima as those in the UV spectrum of the standard.		
Bendamustine HCl Assay (By HPLC)	Release: (b) (4)% to (b) (4)0%		
	Shelf: (b) (4)% to (b) (4)%		
Related Substances:	Release:	Shelf:	In-Use Stability*:
(b) (4)	NMT (b) (4)% NMT % NMT % NMT % NMT % NMT %	NMT (b) (4)% NMT % NMT % NMT % NMT % NMT %	NMT (b) (4)% NMT % NMT % NMT % NMT % NMT %
Single Unknown impurity:	NMT %	NMT %	NMT (b) (4)
Total impurities:	NMT %	NMT %	NMT %
(b) (4)			
Particulate Matter	≥ 10 µm: NMT (b) (4) particles ≥ 25 µm: NMT (b) (4) particles		
Volume in Container	Release only: NLT (b) (4) mL		
Sterility	Sterile		
Bacterial Endotoxin	NMT (b) (4) EU/mg		

Summary of Bendamustine HCl Injection, 25mg/mL Specifications for Release and Shelf-Life Testing (cont.)

Test	Acceptance Criteria
Elemental Impurities: [redacted] (b) (4)	Release only: [redacted] (b) (4) NMT NMT NMT NMT NMT NMT NMT NMT NMT NMT NMT NMT NMT

*Not intended for every batch at release. In-Use stability studies performed on the 3 registration batches at the end of expiry.

Reviewer's comment: Since the applicant chose the option of drug product analysis based on the maximum daily dose compared to the PDE, the applicant included elemental impurities in the drug product specification. The acceptance criteria of the elements are all below PDE for individual elements for a parenteral drug product.

The established name and the strength expression do not meet the USP salt policy of expression of strength based on the active moiety and not the salt. However, this non-compliance is widespread and several approved generics and 505(b)2 bendamustine drug products are already in the market with the expression of strength based on salt and not the active moiety. Therefore, this issue was discussed at the interdisciplinary labeling meeting. The clinical team wanted to keep the current expression with the view that the implementation of salt policy may have medical error implication. In addition, there are historical reasons for keeping the strength expression based on salt. Therefore, the strength expression on the label and on the submission, is not changed.

Since rest of the resubmission is based on the approved supplemental information above, no further review of the resubmission is conducted. The drug product reviewer recommends approval.

Amit Mitra

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Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 3/05/2018 10:55:05AM
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 03/14/2018

TO: Rabiya Halder
Regulatory Project Manager
CDER/OPQ/OPRO

FROM: Jonathan Burgos, Ph.D.
Review Microbiologist
CDER/OPQ/OPF/DMA/Branch 1

THROUGH: Elizabeth Bearr, Ph.D.
Review Microbiologist
CDER/OPQ/OPF/DMA/Branch 1

SUBJECT: NDA: 205580
Submission Date: 01/31/2018
Drug Product: Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL)
Applicant: Eagle Pharmaceuticals, Inc.

Conclusion: The submission **is recommended** for approval on the basis of sterility assurance.

In 31 January 2018, Eagle Pharmaceuticals, Inc. submitted an amendment to support the final approval of NDA 205580. The application was originally received in 01 July 2013 and it was recommended for approval in 02 July 2014 pending acceptable overall recommendation from the Office of Compliance. A review of the product quality microbiological data can be accessed in the NDA 205580 CMC and Microbiology Review document, dated 05 May 2014. Below is a review of the microbiological-relevant changes proposed in the current submission. The proposed changes, detailed in Reviewer's Guide (Section 1.2), have been organized according to their respective common technical document sections.

Section 3.2.P.3.1 (Manufacturers, [Page 1/3]) and *3.2.P.5.3, Validation of Analytical Procedures,* [Page 1/2]*)*

An additional drug product stability testing facility was proposed. In the 2013 submission, stability testing was only performed at the manufacturing facility.

Proposed Testing Facility: (b) (4)

M E M O R A N D U M

(b) (4)

Responsible for: Performing HPLC identification and related substances studies. Microbiological-relevant stability studies will continue to be performed at the manufacturing facility, (b) (4) , and will not be performed at the new testing facility.

The information provided by the applicant was adequate.

Acceptable

(b) (4)

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Jonathan Burgos

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Date: 3/14/2018 01:21:14PM
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Elizabeth Bearr

Digitally signed by Elizabeth Bearr
Date: 3/14/2018 01:22:52PM
GUID: 55370d1e00cfd67fc04d8bfbedbf3096

Sherita McLamore

Digitally signed by Sherita McLamore
Date: 3/15/2018 01:22:01PM
GUID: 503257950000415755492db5bb8b1a5c

NDA 205580

Bendamustine Hydrochloride

Eagle Pharmaceuticals Inc.

Drug Product Team Review:

Erika Pfeiler, Ph.D. (Microbiology)
Gaetan Ladouceur, Ph.D. (CMC)

New Drug Microbiology Staff
and
Office of New Drug Quality Assessment
(Division I Branch II)

for
The Division of Oncology Products

Table of Contents

CMC & Microbiology Review Data Sheet

1. NDA 205580

2. REVIEW #: 1

3. REVIEW DATE: 05-May-2014

4. REVIEWERS: Erika A. Pfeiler, Ph.D., Microbiologist
   Gaetan Ladouceur, Ph.D., Chemist

5. PREVIOUS DOCUMENTS:

Previous Documents	**Document Date**
IND 109789	
Pre-IND Meeting comments	04-Nov-2010
Type B teleconference	12-Nov-2010
Review Microbiology (Jessica G. Cole)	16-Nov-2010
EOP2 Meeting Comments	06-Dec-2012
EOP2 Meeting Minutes	13-Dec-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	**DARRTS SD Number**	**Document Date**
Original NDA Submission	SD 000	01-Jul-2013
Amendment (SR 001)	SD 002	17-Jul-2013
Amendment (SR 004)	SD 005	19-Jul-2013
Amendment (SR 005)	SD 006	19-Jul-2013
Amendment (SR 008)	SD 009	15-Oct-2013
Amendment (SR 010)	SD 011	26-Nov-2013
Amendment (SR 011)	SD 012	27-Dec-2013
Amendment (SR 012)	SD 013	08-Jan-2014
Amendment (SR 015)	SD 016	30-Jan-2014
Amendment (SR 016)	SD 017	06-Feb-2014
Amendment (SR 018)	SD 019	07-Mar-2014
Amendment (SR 019)	SD 021	01-Apr-2014
Amendment (SR 020)	SD 020	31-Mar-2014
Amendment (SR 021)	SD 022	07-Apr-2014
Amendment (SR 022)	SD 023	11-Apr-2014
Amendment (SR 023)	SD 024	25-Apr-2014
Amendment (SR 027)	SD 028	13-May-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Eagle Pharmaceuticals Inc.
Address:	50 Tice Blvd Ste 315 Woodcliff Lake, New Jersey 07677
Representative:	Foma Rashkovsky, Senior Director Regulatory Affairs
Telephone:	201-326-5300
email:	frashkovsky@eagleus.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	NA
b) Non-Proprietary Name:	Bendamustine Hydrochloride
c) Code Name/# (ONDQA only):	NA
d) Chem. Type/Submission Priority (ONDQA only):	
• Chem. Type:	3
• Submission Priority:	S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Alkylating agent

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 100 mg/4 mL (25 mg/mL)

13. ROUTE OF ADMINISTRATION: IV Infusion

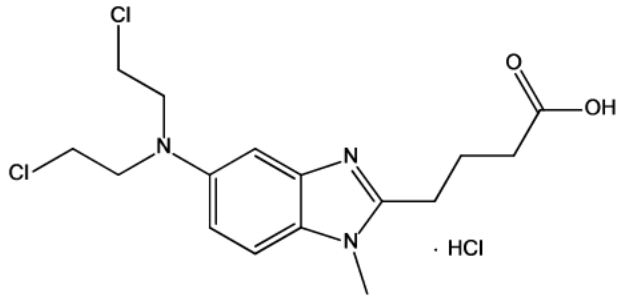
14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__√___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s)	
- United States Adopted Name [USAN]: Bendamustine Hydrochloride - Chemical Name: 1H-benzimidazole-2-butanoic acid, 5- [bis(2-chloroethyl)amino]-methyl-, monohydrochloride, or 4-{ 5-[Bis(2-chloroethyl)amino]-1-methyl-1 H- benzimidazol-2-yl} butanoic acid hydrochloride	
Empirical Formula	$C_{16}H_{21}Cl_2N_3O_2 \cdot HCl$
Molecular Weight	394.72 g
CAS Registry Number	3543-75-7
Structural Formula	

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED/ LOA DATE	CODE	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	--	--	Adequate information in the submission
	III			4	--	--	Adequate information in the submission
	III			4	--	--	Information was found to be adequate in Microbiology Review #25, DARRTS Date 08/20/2013

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	109789	Original IND

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
Facility Reviewer	Pending	--	Erika Pfeiler
Pharm/Tox	Acceptable	12/20/13	Christopher Sheth
Biopharm	Acceptable	05/13/14	Elsbeth G Chikhale
LNC	Established name satisfactory	05/02/14	Gaetan Ladouceur
Methods Validation	N/A	N/A	DPA
DMEPA	Pending	--	Tingting Gao
EA	Categorical exclusion granted.	05/02/14	Gaetan Ladouceur

DMEPA: Division of Medication Error Prevention and Analysis; DPA: Division of Pharmaceutical Analysis in St. Louis

The Chemistry and Microbiology Review for NDA 205580

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of Chemistry, Manufacturing and Controls (CMC) and Microbiology, this NDA is recommended for 'approval' pending acceptable overall recommendation from the Office of Compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry and Microbiology Assessments

A. Description of the Drug Substance and Drug Product

(1) Drug Substance

Refer to Dr. Joyce Crich's review of NDA 205580 drug substance.

(2) Drug Product

The drug product is a stable ready-to-dilute (b) (4) solution formulation of bendamustine hydrochloride. It contains 25 mg/mL of bendamustine hydrochloride, 5 mg/mL of monothioglycerol as an (b) (4), and 0.1 mL/mL of propylene glycol as a (b) (4) in polyethylene glycol 400. The container closure system consists of a 5 mL glass vial with 20 mm rubber stopper and 20 mm aluminum flip-off seal. The target filling volume is (b) (4) mL.

The drug product is intended for multiple uses. It does not contain an antimicrobial preservative, but it demonstrates self-preserving characteristics. The applicant presented appropriate preservative effectiveness studies to demonstrate that the drug product in its undiluted form is microbiologically stable for a 28 day in-use period.

The drug product is sterilized by (b) (4) (b) (4) (b) (4). The (b) (4) (b) (4) properties of the (b) (4) were appropriately validated. The equipment used for equipment and container closure (b) (4) is appropriately qualified and operated using validated loading patterns. Data from media fills performed in 2009 (initial qualification) and 2013 (periodic requalification) indicate that the (b) (4) process at this facility is in a state of microbiological control.

Bendamustine is susceptible to hydrolysis and undergoes rapid degradation in the presence of water to form mainly one degradant. This degradant (HP1), which is also a metabolite, is significantly observed when the admixture is prepared for IV administration.

A repeat of the in-use stability study was requested due to a significant discrepancy observed in the levels of HP1 degradant between two concentrations of the admixture. It was later found by the applicant that an error was made in the calculation of HP1 levels for that study. Nevertheless, the repeat of the in-use stability study was still performed because of the applicant's original commitment. In the repeat in-use stability study, the results showed that the drug product produced proportional levels of the HP1 impurity when compared side by side to the RLD (Treanda®). The data support a post-dilution hold times of 3 hours at room temperature and 24 hours under refrigeration. No microbiological in-use stability data are necessary to support these hold times.

No significant changes were observed in the long-term stability studies up to 18 months, but a single unknown impurity was out of specification at the end of the stability studies conducted under accelerated conditions. According to ICHQ1A (R2), if a significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long-term storage condition. Therefore, an expiration date of 18 months, under the recommended controlled room temperature storage conditions, is granted. Also, storage precautions are required as the drug product is light sensitive. The primary container must be kept in the secondary packaging in order to protect the drug product from light.

B. Description of How the Drug Product is Intended to be Used

Bendamustine hydrochloride is an alkylating agent indicated for the treatment of cancer. It is a (b) (4) 100 mg (25 mg/mL) bendamustine hydrochloride solution which is ready for further dilution in an IV solution.

C. Basis for Approvability or Not-Approval Recommendation

Approval:

- The applicant provided satisfactory information on the manufacturing, control and stability of the drug substance (see CMC review by Dr. Joyce Crich).
- The applicant provided satisfactory information on the manufacturing, controls and stability of the drug product.
- The applicant provided satisfactory information on the microbiological quality of the drug product and manufacturing process.
- The drug product and drug substance manufacturing sites recommendations are still pending.

III. Administrative

A. Reviewer's Signature *{see electronic signature page}*

B. Endorsement Block *{see electronic signature page}*

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section

Item	Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	Bendamustine HCl ((b) (4)). *Inadequate, "Bendamustine hydrochloride" should be used instead as per the RLD and the statement " (b) (4) " should be removed as it is not an acceptable dosage form.*
Dosage form, route of administration	For intravenous infusion
Dosage Forms and Strengths (201.57(a)(8))	Injection: 100 mg/4 mL

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths

Item	Information Provided in NDA
Available dosage forms	Injection
Strengths: in metric system	100 mg/4 mL
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	A clear and colorless to yellow solution

#11: Description

Item	Information Provided in NDA
Proprietary name and established name	Bendamustine HCl Injection [redacted (b) (4)]. *Inadequate, "Bendamustine hydrochloride" should be used instead, as per the RLD, and the statement "([redacted (b) (4)])" should be removed as it is not an acceptable dosage form.*
Dosage form and route of administration	Intravenous infusion
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable. The salt form is used to maintain consistency with the currently marketed drug.
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	0.1 mL of propylene glycol, USP, 5 mg of monothioglycerol, NF, and q.s. to 1 mL polyethylene glycol 400, NF. [redacted (b) (4)]
Statement of being sterile (if applicable)	Included, acceptable.
Pharmacological/ therapeutic class	Alkylating drug.
Chemical name, structural formula, molecular weight	Provided, *but the structural formula should show subscript numbers for each atom.*
Other important chemical or physical properties (such as pKa or pH)	Not included. *Inadequate, "clear, colorless to yellow" should be added.*

#16 & 17: How Supplied/Storage and Handling

Item	Information Provided in NDA
Strength of dosage form	100 mg/4 mL
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	*The description in section 16.2 was found inadequate, see the tracked changes below.*
Special handling (e.g., protect from light)	Retain in original package until time of use to protest from light.
Storage conditions	Between 2° and 8° C (36° to 46° F)
Manufacturer/distributor name (21 CFR 201.1(h)(5))	(b) (4) Eagle Pharmaceuticals, Inc. Woodcliff Lake, NJ

Product Reviewer Comment:

- Section 16.2 was revised and is shown below:

(b) (4)

Process Reviewer Comment: Drug product is intended for dilution in 0.9% sodium chloride for injection USP or 2.5% dextrose/0.45% sodium chloride for injection USP. Dosage and administration instructions state that the product should be used within 24 hours when held under refrigeration or 3 hours when stored at room temperature (these times include administration time). Package insert states that in-use vials should be discarded after 28 days. Patient endotoxin exposure from the drug product is shown below.

Endotoxin exposure from the maximum drug product doses. Compiled from Proposed Package Insert.

Indication	Route of Administration	Maximum Product Dose	Endotoxin Specification	EU/maximum dose[1]	EU/maximum dose when diluted in 0.9% Sodium Chloride for Injection USP[2]	EU/dose when diluted in 2.5% Dextrose/0.45% Sodium Chloride Injection, USP[3]
Chronic Lymphocytic Leukemia	Intravenous – to be diluted in 500 mL of 0.9% Sodium Chloride Injection, USP or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP	100 mg/m^2, resulting in 180 mg in a 1.8 m^2 adult (Administered over a 30 minute period)	NMT (b) (4) EU/mg	(b) (4) EU	(b) (4) EU	(b) (4) EU
Indolent B-cell non-Hodgkin Lymphoma		120 mg/m^2, resulting in 216 mg in a 1.8 m^2 adult (Administered over a (b) (4) minute period)		(b) (4) EU	(b) (4) EU	(b) (4) EU

[1]Parenteral injection endotoxin limit: 350 EU/hour for a 70 kg or 1.8 m^2 adult
[2]USP Monograph for Sodium Chloride Injection - NMT 0.5 EU/mL (250 EU/500 mL)
[3]USP Monograph for 2.5% Dextrose/0.45% Sodium Chloride – NMT 10 EU/gram dextrose (125 EU/500 mL)

Process Reviewer Comment: The proposed in-use holding periods are acceptable from the standpoint of product quality microbiology. Endotoxin exposure from the drug product does not exceed limits set forth in USP <85>. (b) (4)

2. **Immediate container labels (latest revision is shown):**

Item	Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Bendamustine HCl Injection ((b) (4)). *Inadequate, "Bendamustine hydrochloride" should be used instead, as per the RLD, and the statement "((b) (4))" should be removed as it is not an acceptable dosage form.*
Dosage strength	*25 mg/mL is provided. However, "(25 mg/mL)" should go underneath the net content "100 mg/4 mL".*
Net contents	100 mg/4 mL
"Rx only" displayed prominently on the main panel	Provided, adequate.
NDC number (21 CFR 207.35(b)(3)(i))	NDC 42367-520-25
Lot number and expiration date (21 CFR 201.17)	Provided, adequate.

Storage conditions	2° and 8° C (36° to 46° F)
Bar code (21CFR 201.25)	*Not provided. A bar code must be added.*
Name of manufacturer/distributor	Manufactured by: (b) (4)
Must be diluted prior to administration.	Adequate.

Product Reviewer Comment: CMC and DMEPA groups issued the following IR (sent to the applicant on 03/18/2014):

1. Container Label:

a. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore it is an important safety feature that should be part of the label whenever possible. Your product has not been provided an exception, therefore we request you add the product barcode to each individual vial as required per 21 CFR 201.25(b)(1)(ii).

b. There is a possibility that the peel-back labels may become detached from the product container under normal use. Therefore, we recommend that the peel-back label should be resealable, able to withstand repeated openings and closings without detaching itself from the product container, and able to withstand moisture without detaching from the product container.

c. Remove the statement "((b) (4))" since it is not an acceptable dosage form.
d. Replace the name "Bendamustine HCl" by "Bendamustine Hydrochloride" as per the RLD.

e. "(25 mg/mL)" should go underneath "100 mg/4 mL".

f. Add names of all inactive ingredients. (The immediate container label should have names of all inactive ingredients: 21CFR 201.100(b)(5) and quantity if for injectables unless the label is too small)

2. Ferrule and cap overseal label:
Our review of the Failure Mode Effect Analysis conducted by Drug Safety Institute indicates that the proposed bendamustine ferrule and cap overseal label contains the statement (b) (4). This statement may not prevent medication error if the healthcare practitioner does not know that 25 mg/mL is a concentrated strength of bendamustine. We recommend revising the statement (b) (4) to "Dilute Before Using" as suggested by the United States Pharmacopeia (USP) General Chapter <1> Injections labeling standard.

Product Reviewer Comment: CMC and DMEPA groups issued the following IR (sent to the applicant on 04/11/2014):

a. The "Hydrochloride" part of the established name is in a different font size and does not appear to be part of the drug name. Revise the drug name so that the entire drug name, "Bendamustine hydrochloride" is presented in the same font size and boldness.

3. Carton labeling (latest revision is shown):

Item	Information Provided in NDA
Proprietary name, established name (font size, prominence)	Bendamustine HCl Injection [redacted (b) (4)]. *Inadequate, "Bendamustine hydrochloride" should be used instead, as per the RLD, and the statement* [redacted (b) (4)] *should be removed as it is not an acceptable dosage form.*
Dosage strength	25 mg/mL
Net quantity of dosage form	100 mg/4 mL
"Rx only" displayed prominently on the main panel	Provided, adequate.
Lot number and expiration date	Provided, adequate.
Storage conditions	2° and 8° C (36° to 46° F)
Bar code (21CFR 201.25)	Provided, adequate.
NDC number (21 CFR 207.35(b)(3)(i))	NDC 42367-520-25
Manufacturer/distributor's name	Manufactured by: [redacted (b) (4)]
Statement of being sterile (if applicable)	Provided, adequate.
"See package insert for dosage information"	Provided, adequate.

Product Reviewer Comment: CMC and DMEPA groups issued the following IR (sent to the applicant on 03/18/2014):

a. *Remove the statement* [redacted (b) (4)] *since it is not an acceptable dosage form.*

b. *Replace the name "Bendamustine HCl" by "Bendamustine Hydrochloride" as per the RLD.*

Product Reviewer Comment: CMC and DMEPA groups issued the following IR (sent to the applicant on 04/11/2014):

a. *The "Hydrochloride" part of the established name is in a different font size and does not appear to be part of the drug name. Revise the drug name so that the entire drug name, "Bendamustine hydrochloride" is presented in the same font size and boldness.*

b. *The barcode on the vial label appears to be a* [redacted (b) (4)] *barcode instead of a linear barcode. Revise this barcode to a linear barcode that contains, at a minimum, the appropriate National Drug Code (NDC) number in accordance with 21 CFR 201.25(c).*

B. Environmental Assessment or Claim of Categorical Exclusion

A categorical exclusion from the preparation of an environmental assessment (EA) was requested under 21 CFR 25.31(a). The basis of this exclusion is the fact that this application, a 505(b)(2), for marketing approval does not increase the use of the active moiety.

Evaluation: Adequate.

III. List of Deficiencies Communicated

(b) (4)

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Attachment I:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 205580/000	**Sponsor:**	EAGLE PHARMS
Org. Code:	161		50 TICE BLVD STE 315
Priority:	5		WOODCLIFF LAKE, NJ 07677
Stamp Date:	01-JUL-2013	**Brand Name:**	BENDAMUSTINE HYDROCHLORIDE CONCENTRATE F
PDUFA Date:	06-JUL-2014	**Estab. Name:**	
Action Goal:		**Generic Name:**	BENDAMUSTINE HYDROCHLORIDE CONCENTRATE F
District Goal:	07-MAY-2014	**Product Number; Dosage Form; Ingredient; Strengths**	001; INJECTION; BENDAMUSTINE HYDROCHLORIDE; 100MG/4MG (25MG/ML)

FDA Contacts:	J. CRICH	Prod Qual Reviewer		3017963882
	J. MARTIN	Product Quality PM	(HFV-530)	3017962072
	M. FAGBAMI	Regulatory Project Mgr	(HFD-150)	3017961348
	J. BROWN	Team Leader		3017961652

Overall Recommendation: PENDING on 06-MAR-2014 by EES_PROD
PENDING on 28-OCT-2013 by EES_PROD

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)
DMF No: **AADA:**
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** POTENTIAL OAI
Last Milestone: INSPECTION PERFORMED
Milestone Date: 28-FEB-2014

(b) (4)
Establishment: **CFN:** **FEI:**
(b) (4)
DMF No: **AADA:**
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER
Profile: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** NONE
Last Milestone: INSPECTION PERFORMED
Milestone Date: 31-JAN-2014

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/s/

ERIKA A PFEILER
05/14/2014

JOHN W METCALFE
05/14/2014
I concur with the assessment of the information pertaining to product quality microbiology.

GAETAN LADOUCEUR
05/14/2014

ALI H AL HAKIM
05/14/2014

NDA 205580

Bendamustine Hydrochloride (b) (4) for Injection

Eagle
Pharmaceuticals, Inc.

Drug Substance Section of Team Review

Joyce Z Crich

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II
Chemistry, Manufacturing, and Controls (CMC)
For the Division of Hematology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 205580

2. REVIEW #: 1

3. REVIEW DATE: 14-MAY-2014

4. REVIEWER: Joyce Crich, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Pre-IND 109789 Meeting Package submission	30-Sep-2010
Pre-IND 109789 Type B Teleconference Meeting Minutes	12-Nov-2010
Pre-IND 109789 Correspondence Meeting Minutes	13-Dec-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date
Original Submission (SN 000)	SDN 1	01-JUL-2013
Amendment (SN 024)	SDN 25	05-MAY-2014
Amendment (SN 025)	SDN 26	07-MAY-2014
Amendment (SN 026)	SDN 27	09-MAY-2014

Refer to DMF [redacted] (b) (4) reviewed by Dr. Joyce Crich dated 06-May-2014 in DARRTS

7. NAME & ADDRESS OF APPLICANT:

Name:	Eagle Pharmaceuticals Inc.
Address:	50 Tice Blvd Ste 315 Woodcliff Lake, New Jersey 07677
Representative:	Foma Rashkovsky, Senior Director Regulatory Affairs
Telephone:	201-326-5300
email:	frashkovsky@eagleus.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Bendamustine Hydrochloride

c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Alkylating Agent

11. DOSAGE FORM: Parenteral, Sterile solution, injection

12. STRENGTH/POTENCY: 100 mg/4 mL (25 mg/ml)

13. ROUTE OF ADMINISTRATION: Intravenous

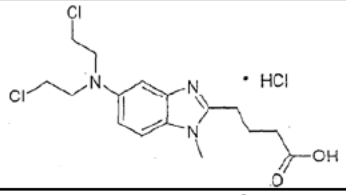
14. Rx/OTC DISPENSED: _x __Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__x____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Structure	
Molecular Formula	$C_{16}H_{21}C1_2N_3O_2.HCl$
Molecular Weight	394.72 g/mol
United States Adopted Name (USAN)	Bendamustine Hydrochloride
Chemical Name (CA Index Name)	1H-Benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-methyl-, hydrochloride (1:1)
IUPUI Name	4-{ 5-[Bis(2-chloroethyl)amino]-1-methyl-1 H-benzimidazol-2-yl} butanoic acid hydrochloride
Chemical Abstracts Service (CAS) Registry Number	3543-75-7

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
DMF (b) (4)	II	(b) (4)	Bendamustine Hydrochloride Drug Substance	1	Adequate	05-MAY-2014	Reviewed by Joyce Crich

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	109789	Pre-IND for 505(b)(2)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		Dr. Erika Pfeiler
Pharm/Tox	Acceptable	20-DEC-2013	Dr. Christopher Sheth
Biopharm	Acceptable	13-May-2014	Dr. Elsbeth G Chikhale
LNC	Established name satisfactory	02-MAY-2014	Dr. Gaetan Ladouceur
Methods Validation	Not required		
DMETS	Pending		Tingting Gao
EA	Categorical exclusion granted	02-MAY-2014	Dr. Gaetan Ladouceur
Microbiology	Acceptable	05-MAY-2014	Dr. Erika Pfeiler

The Chemistry Review for 205580

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of Chemistry, Manufacturing and Controls (CMC), this NDA is recommended for 'approval' pending overall acceptable recommendation from the Office of Compliance.

For drug product review section of the NDA, refer to the quality review of NDA 205580 drug product by Drs. Erika Pfeiler and Gaetan Ladouceur.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The drug substance Bendamustine Hydrochloride is known active pharmaceutical ingredient as a nitrogen mustard for the treatment of chronic lymphocytic leukemias (CLL) and lymphomas.

Chemistry, manufacturing, and controls information for the drug substance is cross-referenced to a DMF. A Letter of Authorization dated 25-MAR-2013 for Bendamustine Hydrochloride, Type II DMF # (b) (4) from the DMF holder (b) (4) is provided in support of this application. This DMF was found to be adequate (see Dr. Joyce Crich's review dated 06-MAY-2014 in DARRTS).

The manufacturing process for Bendamustine Hydrochloride provided in DMF (b) (4) The complete CMC information is provided for the proposed manufacturing process for bendamustine hydrochloride. Detailed information

regarding designation of the proposed starting material, the commercial sources, acceptance criteria, and associated methods of analysis are provided.

Bendamustine Hydrochloride is a white crystalline powder and slightly soluble in water. Though the DMF holder claims the Bendamustine Hydrochloride produced by (b) (4) (b) (4) (b) (4) Bendamustine Hydrochloride has no impact on its use in the drug product "Bendamustine Hydrochloride (b) (4) for Injection" by Eagel Pharmceuticals Inc. (refer to NDA 205580 which the DMF is referenced for). Since the drug product is in injection solution dosage form, the API, Bendamustine Hydrochloride will be dissolved in the drug product vehicle completely, (b) (4) n addition, the assay measurement of Bendamustine Hydrochloride is on anhydrous basis; drug product strength will not be affected by (b) (4) in the API, Bendamustine Hydrochloride. Therefore, the current (b) (4) Bendamustine Hydrochloride drug substance supports the drug product in solution dosage form.

The stability data shows no trend for impurities up to 6 months under accelerated conditions (b) (4)). The long-term drug substance stability data support a (b) (4) month retest period under storage conditions of (b) (4) Based on the stability data, the retest period should be no longer than (b) (4) months when the drug substance is stored in (b) (4)

During the review cycle, the DMF holder revised the specification for Bendamustine Hydrochloride in S.4.1, the related Analytical Procedures in S.4.2, and the Validation of Analytical Procedures in S.4.3, as the results of addressing the deficiencies identified in the DMF. Accordingly, the applicant of NDA 205580 revised the regulatory specification for drug substance Bendamustine Hydrochloride in the Amendment (SN 026, corresponding SDN 27 in DARRTS dated 09-May-2014.

(2) Drug Product

Refer to the quality review of NDA 205580 drug product by Drs. Erika Pfeiler and Gaetan Ladouceur.

B. Description of How the Drug Product is Intended to be Used

Refer to the quality review of NDA 205580 drug product by Drs. Erika Pfeiler and Gaetan Ladouceur.

C. Basis for Approvability or Not-Approval Recommendation

Approval:

- The applicant provided satisfactory information on the manufacturing, control and stability of the drug substance

- The applicant provided satisfactory information on the manufacturing, controls and stability of the drug product. Refer to the quality review of NDA 205580 drug product by Drs. Erika Pfeiler and Gaetan Ladouceur.

- The applicant provided satisfactory information on the microbiological quality of the drug product and manufacturing process. Refer to the quality review of NDA 205580 drug product by Drs. Erika Pfeiler and Gaetan Ladouceur.

- **However, the recommendations of the drug product and drug substance manufacturing sites recommendations are still pending.**

III. Administrative

A. Reviewer's Signature

Joyce Z Crich, Ph.D.,
Review Chemist
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

B. Endorsement Block

Ali H Al Hakim, Ph.D.
Branch Chief, Branch II,
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

C. CC Block

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/s/

JOYCE Z CRICH
05/14/2014

ALI H AL HAKIM
05/14/2014

Chemistry, Manufacturing and Control Memorandum
NDA 205580
(Bendamustine Hydrochloride)

Subject:	Refuse To File
To:	NDA 205580 Bendamustine Hydrochloride [redacted] for Injection
From:	Ali Al-Hakim, Branch Chief, ONDQA
Division:	DHP/OHOP
Date:	August 23, 2013

The DMF holder did not submit sufficient drug substance stability data to justify a re-test period in their DMF in support of the above NDA. The holder submitted 6 months of long term [redacted] and six month data at the accelerated conditions of [redacted] for three batches of bendamustine hydrochloride drug substance. Results met the proposed limits; however, at both accelerated and long term conditions, some batches were at the maximum moisture content limit of [redacted]%. For more details, see Quality Filing Review in DARRTS dated August 07, 2013. The lack of 12 months long term stability data is a refuse to file issue. This is based on the *Guidance for Review Staff and Industry Good Review Management Principles and Practices for PDUFA Products* (GRMPs), which indicates that all NDAs are to be complete in the original submission.

In conclusion, CMC recommends refuse to file action for this NDA because the application does not contain sufficient stability data at the time of submission.

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/s/

ALI H AL HAKIM
08/23/2013