

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205580Orig1s000

SUMMARY REVIEW

Deputy Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	R. Angelo de Claro, MD
Subject	Deputy Division Director Summary Review
NDA/BLA # and Supplement #	NDA 205580 Resubmission/Class 1
Applicant	Eagle Pharmaceuticals, Inc.
Date of Submission	4 April 2018
PDUFA Goal Date	4 June 2018
Proprietary Name	Not applicable
Established or Proper Name	Bendamustine Hydrochloride
Dosage Form(s)	Injection: 100mg/4mL (25mg/mL)
Applicant Proposed Indication(s)/Population(s)	<ul style="list-style-type: none">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.
Action or Recommended Action:	<i>Approval</i>
Approved/Recommended Indication(s)/Population(s) (if applicable)	<ul style="list-style-type: none">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.

1. Regulatory Action

Recommended Regulatory Action: Approval

All review team members recommend approval. The outstanding patent-related issue described in the March 30, 2018, tentative approval letter has been resolved, and there are no barriers to final approval.

2. Background

On September 6, 2013, Eagle Pharmaceuticals, Inc. (Applicant) submitted a 505(b)(2) New Drug Application (NDA 205580) for Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL) in a 500 mL admixture. The Agency granted a tentative approval on July 2, 2014, for the NHL indication because the listed drug upon which the 505(b)(2) application relied was subject to a period of patent protection and because Treanda (bendamustine hydrochloride) had orphan drug exclusivity that blocked approval of the application. Refer to the Tentative Approval Letter on July 2, 2014.

On January 31, 2018, the Applicant resubmitted the application which included updated CMC information and revised labeling. In the resubmission, the Applicant sought to add the CLL indication to the labeling. The Applicant identified Treanda powder 100 mg vial (NDA 22249) as the listed drug product that is the basis for the submission. In an amendment to the resubmission, the Applicant submitted new paragraph IV certifications to the following patents: U.S. Patent Nos. 8,445,524 ('524 patent), 8,791,270, 8,883,836, and 8,669,279. The Applicant provided notice of these paragraph IV certifications to Cephalon, the patent owner and NDA holder for Treanda, and submitted adequate documentation of timely sending and receipt of notice. The NDA holder for Treanda submitted information on the '524 patent to FDA before the date on which the Applicant submitted its 505(b)(2) application. Accordingly, the 45-day period provided for in section 505(c)(3)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) applied with respect to this patent. However, because the 45-day period described in section 505(c)(3)(C) of the FD&C Act had not yet expired, final approval could not be granted at that time. Thus, the application received a tentative approval on March 30, 2018, because the listed drug upon which the 505(b)(2) application relied was subject to a period of patent protection.

On April 4, 2018, the Applicant resubmitted the application for final approval. On May 14, 2018, the 45-day period described in section 505(c)(3)(C) of the FD&C Act expired. On May 15, 2018, the Applicant confirmed that no action for patent infringement had been brought by Cephalon, the NDA holder and patent owner for the '524 patent within the 45-day period.

3. Product Quality

Refer to previous CMC reviews. No issues that would preclude approval were identified.

4. Nonclinical Pharmacology/Toxicology

Refer to previous pharmacology-toxicology review. No issues that would preclude approval were identified.

5. Clinical Pharmacology

Refer to previous clinical pharmacology review. No issues that would preclude approval were identified.

6. Clinical Microbiology

No issues that would preclude approval were identified.

7. Clinical/Statistical-Efficacy

No new clinical data were submitted. The clinical review team reviewed the proposed labeling and found it acceptable for both the NHL and CLL indications.

8. Safety

No new safety issues were identified.

9. Advisory Committee Meeting

This product is not a new molecular entity.

10. Pediatrics

Pediatric study requirement for this application is waived because necessary studies are impossible or highly impracticable.

11. Other Relevant Regulatory Issues

The application was reviewed by the 505(b)(2) clearance committee.

12. Labeling

All the review teams participated in the labeling discussions. On April 25, 2018, the Applicant submitted a request to withdraw the previously proposed proprietary name.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies (REMS)

The review teams did not identify a need for a REMS for this application.

- Other Postmarketing Requirements and Commitments

Routine pharmacovigilance

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/s/

ROMEO A DE CLARO
05/15/2018

Deputy Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	R. Angelo de Claro, MD
Subject	Deputy Division Director Summary Review
NDA/BLA # and Supplement #	NDA 205580 Resubmission/Class 1
Applicant	Eagle Pharmaceuticals, Inc.
Date of Submission	31 January 2018
PDUFA Goal Date	31 March 2018
Proprietary Name	Not applicable
Established or Proper Name	Bendamustine
Dosage Form(s)	Injection: 100mg/4mL (25mg/mL)
Applicant Proposed Indication(s)/Population(s)	<ul style="list-style-type: none"> • 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.
Action or Recommended Action:	<i>Tentative Approval</i>
Approved/Recommended Indication(s)/Population(s) (if applicable)	<ul style="list-style-type: none"> • 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.

Material Reviewed/Consulted	
OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Alexandria Schwarsin / Yvette Kasamon
OPQ Review	Amit Mitra / Sherita McLamore
Clinical Pharmacology Review	John Christy / Gene Williams
OSE/DMEPA	Nicole Garrison / Hina Mehta

OND=Office of New Drugs; OPQ=Office of Pharmaceutical Quality; OPDP=Office of Prescription Drug Promotion;
 OSE= Office of Surveillance and Epidemiology; DMEPA=Division of Medication Error Prevention and Analysis

1. Regulatory Action

Recommended Regulatory Action: Tentative approval

All review team members recommend approval.

Tentative approval is the recommended regulatory action, however, because at this time there is patent protection on the listed drug relied upon. In response to FDA's information request dated March 29, 2018, regarding the requirements under 21 CFR 314.60(f), Eagle submitted new paragraph IV certifications to the following patents: U.S. Patent Nos. 8,445,524 ('524), 8,791,270 ('270), 8,883,836 ('836), and 8,669,279 ('279). Eagle has provided notice of these paragraph IV certifications to Cephalon, the NDA holder and patent owner, and submitted adequate documentation of timely sending and receipt of notice. The NDA holder submitted information on the '524 patent to FDA before the date on which Eagle submitted its 505(b)(2) application. Accordingly, the 45-day period provided for in section 505(c)(3)(C) of the FD&C Act applies with respect to this patent. Because the 45-day period described in section 505(c)(3)(C) of the Act has not yet expired, final approval cannot be granted to Eagle's pending 505(b)(2) application at this time.

This application represents a resubmission of a prior tentative approval for this NDA. The application included updated CMC information and revised labeling.

2. Background

On September 6, 2013, Eagle Pharmaceuticals, Inc. (Applicant) submitted a 505(b)(2) New Drug Application (NDA 205580) for Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL) in a 500 mL admixture. The Agency granted a tentative approval on July 2, 2014, for the NHL indication because the listed drug upon which the 505(b)(2) application relied was subject to a period of patent protection and because Treanda (bendamustine hydrochloride) had orphan drug exclusivity that blocked approval of the application. Refer to the Tentative Approval Letter on July 2, 2014.

On January 31, 2018, the Applicant resubmitted the application which included updated CMC information and revised labeling. In the resubmission, the Applicant sought to add the CLL indication to the labeling. The Applicant identified Treanda powder 100 mg vial (NDA 22249) as the listed drug product that is the basis for the submission.

3. Product Quality

From the OPQ review,

*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 retest period for the drug substance when stored in (b) (4) and an 24-month drug product expiration period when stored between 2°-8°C. There are no outstanding issues and no post-approval agreements to be conveyed to the applicant.

All facilities are acceptable and recommended for approval for the functions listed in the application.

4. Nonclinical Pharmacology/Toxicology

Refer to previous pharmacology-toxicology review. No issues that would preclude approval were identified.

5. Clinical Pharmacology

Refer to previous clinical pharmacology review. No issues that would preclude approval were identified.

6. Clinical Microbiology

No issues that would preclude approval were identified.

7. Clinical/Statistical-Efficacy

No new clinical data was submitted. The clinical review team reviewed the proposed labeling and found it acceptable for both the NHL and CLL indications.

8. Safety

No new safety issues were identified.

9. Advisory Committee Meeting

This product is not a new molecular entity.

10. Pediatrics

This product is not a new molecular entity.

11. Other Relevant Regulatory Issues

The application was reviewed by the 505(b)(2) clearance committee.

12. Labeling

All the review teams participated in the labeling discussions.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies (REMS)

The review teams did not identify a need for a REMS for this application.

- Other Postmarketing Requirements and Commitments

Routine pharmacovigilance

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/s/

ROMEO A DE CLARO
03/30/2018

Cross-Discipline Team Leader Review

Date	June 15, 2014
From	Janice Brown, M.S.
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 205580
Applicant	Eagle Pharmaceuticals, Inc.
Date of Submission	June 30, 2013 (received July 01, 2013)
PDUFA Goal Date	July 06, 2014
Proprietary Name / Established (USAN) names	Bendamustine Hydrochloride
Dosage forms / Strength	Injection, 100 mg/4 mL (25 mg/mL)
Proposed Indication(s)	For treatment of patients with: <ul style="list-style-type: none"> • Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.
Recommended:	Tentative Approval

Introduction

Bendamustine is a small molecule, alkylating agent that is approved 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.

The current application for Bendamustine Hydrochloride Injection is submitted as a 505(b)(2) NDA. The innovator product, Treanda (bendamustine hydrochloride) for Injection, is supplied as a single-use vial containing either 100 mg or 25 mg of bendamustine hydrochloride as a lyophilized powder that requires reconstitution with 20 mL (for the 100 mg vial) or 5 mL (for the 25 mg vial) of sterile water for injection. The solution is further diluted into 500 mL (of either normal saline or 2.5% dextrose/0.45% saline prior to administration.

In this NDA, the product is ready-to-dilute solution, and will not require reconstitution as is the case for the reference drug, Treanda®, which is a lyophilized powder. This product is a self-preserving, multiple-use drug product. Similar to the innovator product, the proposed bendamustine hydrochloride injection also must be diluted in 500 mL of 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP prior to intravenous infusion.

The applicant is seeking approval for the NHL drug indication only. The Agency is not able to approve the marketing application submitted by Eagle Pharmaceuticals for the use of bendamustine for the treatment of Indolent B-Cell Non-Hodgkin's Lymphoma prior to the expiration of exclusivity afforded Treanda for the Indolent B-Cell Non-Hodgkin's Lymphoma that expires October 31, 2015.

1. Background

The subject of the current NDA application is a new formulation for bendamustine hydrochloride. The applicant for this NDA is relying upon information in the public domain (labeling for approved bendamustine hydrochloride product and published studies about bendamustine hydrochloride) to support the safety and efficacy of the new product. No clinical data was submitted to support the application.

This NDA application was originally submitted on June 30, 2013 (received July 01, 2013). The initial submission was deemed insufficiently complete since the DMF holder did not submit a minimum of 12 months long term stability testing on at least three primary drug substance batches and a Refusal to File letter was sent to the applicant on August 28, 2013.

The NDA was resubmitted on September 6, 2014 (received September 6, 2014). The application was filed and Biopharmaceutics deficiencies were identified and communicated to the applicant in a filing letter on September 16, 2013.

2. CMC

Drug Substance

The CMC information for the drug substance was provided in DMF No. (b) (4) from (b) (4). The applicant provided adequate reference to their Type II DMF (b) (4) for information pertaining to the drug substance, bendamustine hydrochloride. The DMF contains the necessary information related to manufacturing, characterization, physical properties, manufacture, process controls, analytical methods, specifications, validation, container closure system, reference standard and stability data for bendamustine hydrochloride. DMF (b) (4) was reviewed and found adequate to support the manufacture of a drug product as a solution dosage form by Joyce Crich, Ph.D. on May 6, 2014.

Bendamustine hydrochloride is a white crystalline powder that is slightly soluble in water. (b) (4)

Drug Product

This NDA was jointly reviewed by Gaetan Ladouceur, Ph.D. who performed the drug product review and Erika Pfeiler, Ph.D. who performed the manufacturing process review and was a member of the facility inspection team. No product quality issues which preclude approval were found and the CMC Review (Gaetan Ladouceur, Ph.D. and Erika Pfeiler, Ph.D. final signature May 14, 2014) recommended approval of the NDA.

The drug product is a multiple use, ready-to-dilute, clear and colorless yellow non-aqueous solution of bendamustine hydrochloride. Each vial contains 25 mg/mL of bendamustine hydrochloride, 5 mg/mL of monothioglycerol (b) (4) and 0.1 mL/mL of propylene glycol (b) (4) in polyethylene glycol 400. The drug product does not contain an antimicrobial preservative, since it demonstrates self-preserving characteristics.

The drug product is sterilized by (b) (4) (b) (4) (b) (4). The container closure system consists of a 5 mL glass vial with 20 mm rubber stopper and 20 mm aluminum flip-off seal. The equipment used for equipment and container closure (b) (4) is appropriately qualified and operated using validated loading patterns.

Bendamustine hydrochloride injection is further diluted into either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, prior to intravenous administration. Bendamustine is susceptible to hydrolysis and undergoes rapid degradation in the presence of water to form mainly one degradant, monohydroxy bendamustine. Monohydroxy bendamustine (also known as HP1), is a metabolite and a not more than (NMT)

(b)
(4) % limit is established for HP1 in the admixture and is controlled in the drug product specification.

An 18-month expiration dating period is granted for the drug product when stored at 2° to 8°C (36° to 46°F). Since the drug product is light sensitive the following statement is included in the label “Retain in original package until time of use to protect from light” and “After first use, the multi-use vial should be stored in original carton at 2 °C to 8 °C, and then discarded after 28 days.”

Facilities review and inspection

An Establishment Evaluation Request (EER) was submitted to the Office of Compliance, and an overall acceptable recommendation was issued for the application on June 2, 2014.

3. Nonclinical Pharmacology/Toxicology

Pharmacology/Toxicology has no concerns with the nonclinical findings and the excipients used for Eagle’s bendamustine HCl injection at the defined levels. No pharmacology/toxicology issues which preclude approval were found and the Pharmacology/Toxicology Review (Christopher Sheth, Ph.D., final signature December 20, 2013) recommended approval of the NDA.

According to the nonclinical review, “Eagle conducted local tolerance studies in rabbits, in addition to in vitro hemolytic potential studies in human whole blood, comparing their bendamustine HCl product with the LD (Treanda®). There was no indication of hemolysis in human blood exposed to EPI’s bendamustine HCl. Intravenous administration of EPI’s bendamustine HCl was well tolerated in the rabbit local tolerance study, as exemplified by results typical of minor trauma associated with injection procedures. Eagle did not perform any animal pharmacology studies in support of the NDA approval for bendamustine HCl.”

4. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology

This submission contains no clinical pharmacology information. The Clinical Pharmacology review (Young Jin Moon, Ph.D. signed May 29, 2014) recommended approval of the NDA from a clinical pharmacology perspective.

Biopharmaceutics

The NDA includes a request for a waiver of the CFR requirement to submit data from an *in vivo* bioequivalence study, based on the similarity between the proposed product and the listed product. Comparative data showed very similar pH values but differences were observed in the osmolality range for the diluted admixture solutions for the proposed and the listed drug products. The proposed admixture drug product’s osmolality is hypertonic and is higher than

that of Treanda which is consistently hypotonic. Based on the nonclinical information provided by the application to support the osmolality, sufficient data was provided justifying that the higher osmolality range of their product when compared to that of the listed product, and will not have an impact on the clinical safety profile. The Clinical Reviewer, Dr. Adam George, agrees with this conclusion (see his review in DARRTS dated 5/13/14).

According to the biopharmaceutics review, data was provided that adequately supports the absence of mannitol and the inclusion of monothioglycerol, propylene glycol, and PEG 400 in the proposed formulation do not affect the distribution and/or elimination of bendamustine HCl when compared to those of the listed product. According to the biopharmaceutics review, the applicant provided evidence from literature supporting the safety of the intravenous infusions of bendamustine HCl solutions containing the proposed concentrations of monothioglycerol, propylene glycol, and PEG 400. The applicant adequately resolved the outstanding issues and the biopharmaceutics review (Elsbeth Chikhale, Ph.D., final signature May 13, 2014) recommended approval of the NDA.

5. Clinical Microbiology

No Clinical Microbiology review was required for this NDA.

6. Clinical/Statistical- Efficacy

Eagle did not conduct any human clinical studies and therefore no efficacy information is included in the NDA. No Statistical Review was done for this NDA.

7. Safety

A potential safety issue was identified by the biopharmaceutics reviewer regarding the increased osmolality of the proposed drug product once diluted into either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. According to the clinical review, “the increased osmolality of the Eagle formulation of bendamustine will not result in a clinically meaningful increase in toxicities associated with administration of a hyperosmotic intravenous solution (i.e., phlebitis and/or infusion site reactions). In clinical practice chemotherapy is typically administered to patients via central venous access (e.g., peripherally inserted central catheter or Hickman catheter). Administration of chemotherapeutic agents through central venous access minimizes the risks of phlebitis associated with drugs that are hyperosmolar due the increased venous blood flow with central venous access.”

The clinical reviewer also cites an article by Gazitua et. al. that evaluated the risk of phlebitis based upon the osmolality of the infusion solution. The lowest identified risk group was solutions with an osmolality lower than 450 mOsm/L. The upper limit for the range of osmolality with the proposed Eagle formulation is ^{(b) (4)} mOsm/kg. Dr. George also stated that “it would not be feasible to conduct a clinical trial to quantify the possible increased risk of phlebitis with the Applicant’s hyperosmolar formulation compared to Treanda as this would require an extremely large number of patients.”

The Clinical Review of the NDA was completed by Adam George, Pharm.D. (final signature on May 13, 2014). The reviewer found no new safety concerns from review of the recent literature and recommended approval of the NDA from a clinical perspective.

8. Advisory Committee Meeting

There was no Advisory Committee meeting held for this application.

9. Pediatrics

The labeling for the LD contains information in the Pediatric Use section based upon a study conducted by the LD applicant. Information from the study regarding pediatric experience was placed into the label based on safety concerns that could arise should the product be used off label in pediatric patients. Consequently, this information was retained in the label for the new Eagle bendamustine product.

10. Other Relevant Regulatory Issues

None.

11. Labeling

General

The proposed labeling for the Eagle's bendamustine is essentially the same in content as that of the innovator LD product, except for the relevant sections of the Dosage and Administration section on the dilution of the drug product, How Supplied, Description, and Storage and Handling sections of the labeling. The formatting of the applicant's proposed labeling has been constructed to comply with the requirements of the Physician's Labeling Rule (PLR).

The exact wording of the labeling in the PLR format has been reviewed and comments from all disciplines (including DMEPA) were conveyed to the applicant on April 11, 2014. The most recent DRAFT labeling text was received from the Applicant on June 18, 2014.

In this application, the Applicant included the FDA Form 256h, which requested only the NHL indication. Both the existing CLL and NHL indications for the Treanda NDA are currently protected by orphan drug and pediatric exclusivity. This application cannot be granted final approval until all exclusivities expire. For purposes of attaching labeling to the approval letter, the labeling will contain the NHL indication only, because it is the only indication requested in the FDA Form 256h submitted by the Sponsor. The final indications included in labeling at the time of final approval of this Eagle application, will depend upon existing exclusivities remaining. The last exclusivity expiration date for the CLL indication is September 20, 2015. The last exclusivity expiration date for the NHL indication is May 1, 2016.

Proprietary name

There was no proprietary name proposed for this product.

DMEPA comments

In an initial review dated December 24, 2014, the DMEPA reviewer (Tingting Gao, PharmD.) and again on April 9, 2014 and identified several specific deficiencies in the proposed container and carton labeling.

These deficiencies were conveyed to the applicant and .

Patient labeling/Medication guide

This is not required for this product.

12. Recommendations/Risk Benefit Assessment

• Recommended Regulatory Action

No clinical, pharmacology/toxicology, CMC or clinical pharmacology issues have been found to preclude approval. EES gave an overall acceptable recommendation for the manufacturing sites. From a technical review discipline viewpoint, this application may be approved, provided regulatory legal requirements are met for existing exclusivity for the innovator bendamustine product (tentative approval).

• Risk Benefit Assessment

The review of this NDA is based primarily on chemistry, manufacturing and controls and nonclinical data. Pharmacology/Toxicology has no concerns with the nonclinical findings and the excipients used for Eagle's bendamustine HCl injection at the defined levels. The Applicant has satisfactorily responded to the identified CMC and biopharmaceutics deficiencies, and the application has received an overall acceptable recommendation from the Office of Compliance.

• Recommendation for Postmarketing Risk Management Activities

This does not apply to this NDA.

• Recommendation for other Postmarketing Study Commitments

None

• Recommended Comments to Applicant

The standard language for conveying a tentative approval should be inserted into the action letter.

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/s/

JANICE T BROWN
06/19/2014

ALI H AL HAKIM
06/19/2014

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # Supplement #	205580
Applicant Name	Eagle Pharmaceuticals
Date of Submission	September 6, 2013
PDUFA Goal Date	July 6, 2014
Proprietary Name / Established (USAN) Name	Bendamustine Hydrochloride Concentrate for Injection
Dosage Forms / Strength	25 mg/mL
Proposed Indication(s)	For the treatment of non-Hodgkin's Lymphoma (NHL) and for the treatment of chronic Lymphocytic Leukemia (CLL)
Action/Recommended Action for NME:	Tentative Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Adam George, Pharm.D./ Virginia Kwitkowski, RNP
Statistical Review	N/A
Pharmacology Toxicology Review	Christopher M. Sheth, Ph.D./Todd Palmby, Ph.D.
CMC Review/OBP Review	Gaetan Ladoucer, Ph.D./Ali H Al-Hakim, Ph.D.
Microbiology Review	Erika Pfeiler, Ph.D./John Metcalfe, Ph.D.
Clinical Pharmacology Review	Young Jin Moon, Ph.D./Julie Bullock, Ph.D.
OPDP	Richard Lyght, Pharm.D./Karen Rulli, Ph.D.
DSI	N/A
CDTL Review	Janice Brown, M.S.
OSE/DMEPA	Tingting Gao, Pharm.D./Yelena Maslov, Pharm.D.
OSE/DDRE	
OSE/DSRCS	
Other -MHT	

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMETS=Division of Medication Errors and Technical Support

DSI=Division of Scientific Investigations

DDRE= Division of Drug Risk Evaluation

DSRCS=Division of Surveillance, Research, and Communication Support

CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

This submission for NDA 205580, a 505 b2 application for bendamustine hydrochloride concentrate for injection.

2. Background

The Reference Listed Drug (RLD) for this submission is Treanda (bendamustine hydrochloride) (NDA)22249 and 022303), which is currently marketed by Teva Pharmaceuticals.

3. CMC/Device

From the product quality review:

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...

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.

No issues were identified which would preclude approval.

4. Nonclinical Pharmacology/Toxicology

Drs. Sheth and Palmby noted in their review:

EPI's to-be-marketed formulation that is the subject of this NDA is different from the Treanda® formulation, in that it will be supplied as a ready-to-dilute concentrated sterile solution containing bendamustine HCl (100 mg), monothioglycerol (20 mg), propylene glycol (0.4 mL), and polyethylene glycol 400 (QS to 4 mL), rather than a

lyophilized powder of bendamustine HCl (100 mg) and mannitol (170 mg). Prior to IV administration, both reconstituted Treanda (5 mg/mL in sterile water) and EPI's ready-to-dilute (25 mg/mL) formulation of bendamustine HCl require further dilution into 500 mL of 0.9% Sodium Chloride Injection or, alternatively, 500 mL of 2.5% Dextrose / 0.45% Sodium Chloride Injection.

The final concentrations of both Treanda- and EPI-bendamustine HCl will be 0.2^{(b) (4)} mg/mL.

No issues that would preclude approval were identified.

5. Clinical Pharmacology/Biopharmaceutics

No issues that would preclude approval were identified.

6. Microbiology

No issues that would preclude approval were identified.

7. Clinical/Statistical-Efficacy

No new clinical data was submitted. The clinical review team reviewed the proposed labeling.

8. Safety

No new safety issues have been identified.

9. Advisory Committee Meeting

This product is not a NME.

10. Pediatrics

This product is not a NME.

11. Other Relevant Regulatory Issues

This application is currently blocked by Orphan Drugs exclusivity for both the CLL (expiring March 20, 2015) and indolent Non-Hodgkins Lymphoma (expiring October 31 2015). In addition, the Teva Pharmaceuticals has filed a suit against Eagle Pharmaceuticals for patent infringement. Thus this application will receive a tentative approval.

12. Labeling

All disciplines made recommendations for labeling.

13. Decision/Action/Risk Benefit Assessment

- - Recommended regulatory action
Tentative Approval
 - Risk Benefit Assessment
N/A
 - Recommendation for Post marketing Risk Management Activities
None
 - Recommendation for other Post marketing Study Requirements/
Commitments
None

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/s/

ANN T FARRELL
06/17/2014