CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208194Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208194 SUPPL # N/A HFD # 161

Trade Name Bendeka granted on 6/16/15

Generic Name bendamustine hydrochloride

Applicant Name Eagle Pharmaceuticals, Inc.

Approval Date, If Known December 7, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The primary study EGL-BDM-C-1301 is a bioequivalence study. For the purposes of qualifying for exclusivity, a BE study is not considered a clinical study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data: N/A

c) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

The listed drug Treanda has Pediatric Exclusivity that expires on (b) (4). Eagle requests both (b) (4) of exclusivity.

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question is YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 022249 Treanda

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

The primary study EGL-BDM-C-1301 is a bioequivalence study.

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Laura Wall, MS
Title: Regulatory Project Manager
Date: December 7, 2015

Name of Office/Division Director signing form: Ann T. Farrell, MD (Edvardas Kaminskas, MD signed this form on behalf of Ann T. Farrell)
Title: Director/Division of Hematology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAURA C WALL
12/07/2015

EDVARDAS KAMINSKAS
12/07/2015

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 208194 | Supplement Number: N/A | NDA Supplement Type (e.g. SE5): _____

Division Name: Division of Hematology Products | PDUFA Goal Date: 12/13/2015 | Stamp Date: 2/13/2015

Proprietary Name: Bendeka granted on 6/16/15

Established/Generic Name: bendamustine hydrochloride

Dosage Form: Injection

Applicant/Sponsor: Eagle Pharmaceuticals, Inc.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 2
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Indolent Non-Hodgkin Lymphoma

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☒ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed^Δ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): ____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: chronic lymphocytic leukemia (CLL)

Q1: Does this indication have orphan designation?

- ☒ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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LAURA C WALL
11/30/2015

From:	Wall, Laura
To:	Foma Rashkovsky (frashkovsky@eagleus.com)
Cc:	Wall, Laura
Subject:	NDA 208194 - FDA Revisions to PI - Please respond by November 23, 2015 10 a.m.
Date:	Friday, November 20, 2015 10:04:59 AM
Attachments:	NDA 208194 bendamustine FDA revisions to Eagle PI 11-20-15.doc

Dear Foma,

Please refer to the attached labeling revisions in Section 11 to the prescribing information (PI) for NDA 208194 bendamustine.

I wanted to remind you to review the revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

After you have made any necessary changes, please send me the revised tracked change labeling before you make your official submission electronically.

Please send me your PI via e-mail and officially to your application by 10 a.m. Monday, November 23, 2015. If you agree with all of the FDA's changes, please send your PI formally to your application as final agreed upon labeling.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Rm 2361
Silver Spring, MD 20993
Phone: 301-796-2237 | laura.wall@fda.hhs.gov

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/s/

LAURA C WALL
11/20/2015

From: Wall, Laura
To: Foma Rashkovsky (frashkovsky@eagleus.com)
Cc: Wall, Laura
Subject: NDA 208194 - FDA Information Request
Date: Friday, November 13, 2015 11:50:00 AM

Dear Foma,

The team noted that in the prescribing information of the label for NDA 208194, there are still trailing zeros in Table A of Section 2.3 Preparation for Intravenous Administration. Please correct those. In addition, it is minor, but in the prescribing information, it appears there is a random (_) on Pg 2 in Section 2.2 (see the next to last sentence from the bottom). Please correct that as well.

To expedite the review, please send me your changes via e-mail and officially to your application as soon as possible.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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LAURA C WALL
11/13/2015

From: Wall, Laura
To: Foma Rashkovsky (frashkovsky@eagleus.com)
Cc: Wall, Laura
Subject: NDA 208194 - FDA Information Request - Please respond As Soon As Possible
Date: Thursday, November 05, 2015 12:57:00 PM

Dear Foma,

There is one patent - 8344006, that is not accounted for in the patent certifications or licensing agreement. I want to ensure that if you have not already done so, please submit the patent certification to your application as soon as possible.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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LAURA C WALL
11/05/2015

From:	Wall, Laura
To:	Foma Rashkovsky (frashkovsky@eagleus.com)
Cc:	Wall, Laura
Subject:	FDA revisions to Eagle"s NDA 208194 bendamustine PI and carton/container labeling - FDA Information Request - Please respond by Noon Tuesday, November 10, 2015
Date:	Wednesday, November 04, 2015 12:20:00 PM
Attachments:	Container carton labeling recommendations.doc FDA"s revisions to NDA 208194 PI.doc

Dear Foma,

Please refer to the attached labeling revisions to the prescribing information (PI) and the carton/container labeling comments for NDA 208194 bendamustine.

I wanted to remind you to review the revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

After you have made any necessary changes, please send me the revised tracked change labeling before you make your official submission electronically.

Please send me your PI and c/c via e-mail and officially to your application by Noon Tuesday, November 10, 2015. If you agree with all of the FDA's changes, please send your PI and c/c labeling formally to your application as final agreed upon labeling.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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/s/

LAURA C WALL
11/04/2015

From:	Wall, Laura
To:	Adrian Hepner (ahepner@eagleus.com)
Cc:	Foma Rashkovsky (frashkovsky@eagleus.com); Wall, Laura
Subject:	NDA 208194 - FDA Information Request - Carton and Container Labeling
Date:	Wednesday, September 23, 2015 3:41:21 PM

Dear Foma and Adrian,

Please respond to the following information request with regards to the carton and container labeling for your NDA 208194 bendamustine:

A. VIAL LABEL
1. Increase font size of established name to at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2) to increase readability of this important information on the principal display panel (PDP).
2. There is a possibility that the peel-back labels may become detached from the product container under actual 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.

B. CARTON LABELING
1. See A.1and revise carton labeling accordingly.
2. Reduce the size of the company logo on the principal display panel (PDP) to assist with ensuring the most important information is the most prominent and to increase white space for ease of readability.
3. Consider bolding the portion of the sentence on the side panel, "Each mL contains 25 mg bendamustine hydrochloride," to highlight this important product information and to help increase the safe use of this product.
4. Reduce the graphic on the PDP to assist with ensuring the most important information is the most prominent.

Add names of all inactive ingredients as per 21CFR 201.100(b)(5). The immediate container label should have names of all inactive ingredients and quantity for an injectable product unless the label is too small.

Labeling, 21 CFR 201.10(g)(2), 2015

[2] Label Process Series LPS2011-04, Guidance for Designing Peel-Back and Multi-Component Labels of Domestic
Class Pest Control Products [Internet]. Ottawa (Ontario): Health Canada Pest Management Regulatory Agency.
2011 [cited 2013 Nov 6]. Available from http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/lps2011-04/index- eng.php#a5.

[3] Labeling 21 CFR 202.1(a)(1)

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
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LAURA C WALL
09/23/2015

From:	Wall, Laura
To:	Foma Rashkovsky (frashkovsky@eagleus.com)
Cc:	Wall, Laura
Subject:	FDA revisions to Eagle"s NDA 208194 bendamustine PI
Date:	Friday, September 11, 2015 12:22:49 PM
Attachments:	September 11 2015 FDA revisions to Eagle"s NDA 208194 bendamustine PI.DOC

Dear Foma,

Please refer to the attached labeling revisions to the prescribing information (PI) for NDA 208194 bendamustine. Please also make the following formatting revisions:

-All of the margins in HL should be ½ inch.
-Insert a horizontal line separating the TOC from the FPI.
-White space should be added before the major headings in HL.
-Bullet the contraindications.
-Remove the 0 in front of the (b) (4) in HL.
-The word "see" needs to be italicized in the cross-references.

I wanted to remind you to review the revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

After you have made any necessary changes, please send me the revised tracked change labeling before you make your official submission electronically.

Please send me your response by Noon on September 18, 2015.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
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LAURA C WALL
09/11/2015

From:	Wall, Laura
To:	Foma Rashkovsky (frashkovsky@eagleus.com)
Cc:	Wall, Laura
Subject:	FDA revisions to Eagle"s NDA 208194 bendamustine PI
Date:	Friday, August 07, 2015 10:22:00 AM
Attachments:	FDA revisions to Eagle"s NDA 208194 bendamustine PI 8-7-15.doc

Dear Foma,

Please refer to the attached labeling revisions to the prescribing information (PI) for NDA 208194 bendamustine.

I wanted to remind you to review the revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

After you have made any necessary changes, please send me the revised tracked change labeling before you make your official submission electronically.

Please send me your response by Noon on August 14, 2015.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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LAURA C WALL
08/07/2015

From:	Wall, Laura
To:	Foma Rashkovsky (frashkovsky@eagleus.com)
Cc:	Wall, Laura
Subject:	NDA 208194 - FDA Information Request - Please respond by COB July 9, 2015
Date:	Tuesday, July 07, 2015 4:30:00 PM

Dear Foma,

The review team requests that you respond to the following Information Request:

1. Please update your proposed labeling (e.g., container label, carton, labeling, PI) to contain the conditionally acceptable proprietary name, Bendeka for our evaluation of the proposed finalized labels and labeling.
2. It is unclear from your submission what "inner carton" represents. Does it mean that there is an outer carton? If so, please submit to the FDA for evaluation as well. Otherwise, please clarify what "inner carton" means.

To expedite the review, please send me your responses via e-mail and officially to your application by COB July 9, 2015.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
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/s/

LAURA C WALL
07/07/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208194

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Eagle Pharmaceuticals, Inc.
50 Tice Boulevard
Suite 315
Woodcliff Lake, NJ 07677

ATTENTION: Foma Rashkovsky
Regulatory Affairs, Vice President

Dear Mr. Rashkovsky:

Please refer to your New Drug Application (NDA) dated and received February 13, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bendamustine Injection, 25 mg/mL.

We also refer to:

- your correspondence, dated and received April 14, 2015, requesting review of your proposed proprietary name, Bendeka
- your amendment, dated and received April 20, 2015, to your request for name review

We have completed our review of the proposed proprietary name, Bendeka and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Laura Wall, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
06/16/2015

From:	Wall, Laura
To:	Foma Rashkovsky (frashkovsky@eagleus.com)
Cc:	Wall, Laura
Subject:	NDA 208194 - FDA Information Request
Date:	Monday, June 08, 2015 1:34:17 PM

Dear Foma,

The review team requests that you respond to the following Information Request:

"As described under 21 CFR 314.52(a) and 314.52(e), please provide documentation of receipt of notice by (1) each owner of the patent that is the subject of the certification or the representative designated by the owner to receive the notice and (2) the holder of the approved application under section 505(b) of the act for each drug product which is claimed by the patent or a use of which is claimed by the patent and for which the applicant is seeking approval.

In addition, please let us know whether the patent owner or its representative or approved application holder brought suit for patent infringement within 45 days of receipt of the notice of certification."

To expedite the review, please send me your response via e-mail and officially to your application as soon as possible.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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Silver Spring, MD 20993
Phone: 301-796-2237 | laura.wall@fda.hhs.gov

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/s/

LAURA C WALL
06/08/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208194

PROPRIETARY NAME REQUEST ACKNOWLEDGEMENT/WITHDRAWAL

Eagle Pharmaceuticals, Inc.
50 Tice Boulevard
Suite 315
Woodcliff Lake, NJ 07677

ATTENTION: Foma Rashkovsky
Regulatory Affairs, Vice President

Dear Mr. Rashkovsky:

Please refer to your New Drug Application (NDA) dated and received February 13, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bendamustine Hydrochloride Injection, 25 mg/mL.

We also refer to your correspondence, dated and received on April 14, 2015, notifying us that you are withdrawing your request for a review of the proposed proprietary name, (b) (4). Therefore, (b) (4) is considered withdrawn as of April 14, 2015.

Finally, we refer to your correspondence, dated and received April 14, 2015, requesting review of your proposed proprietary name, Bendeka. Upon preliminary review of your submission, we have determined that it is a complete submission as described in the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf.

Therefore, the user fee goal date is July 13, 2015.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Laura Wall, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Kevin Wright, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KEVIN WRIGHT
04/23/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208194

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Eagle Pharmaceuticals, Inc.
Attention: Foma Rashkovsky
Senior Director, Regulatory Affairs
50 Tice Boulevard, Suite 315
Woodcliff Lake, NJ 07677

Dear Mr. Rashkovsky:

Please refer to your New Drug Application (NDA) dated February 13, 2015, received February 13, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for bendamustine hydrochloride parenteral 100 mg/4 mL (25 mg/mL).

We also refer to your amendments dated February 19, March 3, 13, 18, and April 2, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 13, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: *Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 15, 2015.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of

administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Laura Wall, Regulatory Project Manager, at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

EDVARDAS KAMINSKAS
04/13/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208194

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Eagle Pharmaceuticals, Inc.
50 Tice Boulevard
Suite 315
Woodcliff Lake, NJ 07677

ATTENTION: Foma Rashkovsky
Regulatory affairs, Vice President

Dear Mr. Rashkovsky:

Please refer to your New Drug Application (NDA) dated and received February 13, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bendamustine Hydrochloride Injection, 25 mg/mL.

We also refer to your correspondence dated and received February 13, 2015, requesting review of your proposed proprietary name, (b) (4).

We have completed our review of the proposed proprietary name, (b) (4), and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your February 13, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Laura Wall, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
04/02/2015

MEMORANDUM of TELECONFERENCE

MEETING DATE: March 31, 2015
TIME: 1:30 pm EST
LOCATION: CDER WO 22/4396
APPLICATION: NDA 208194
DRUG NAME: (b) (4) (bendamustine) Injection, 25 mg/mL
TYPE OF MEETING: Teleconference

MEETING CHAIR: Lubna Merchant, PharmD
MEETING RECORDER: Kevin Wright, Pharm.D.

FDA ATTENDEES:
Office of Surveillance and Epidemiology
Kevin Wright, Pharm.D., Safety Regulatory Project Manager

Office of Medication Error Prevention and Risk Management
Division of Medication Error Prevention and Analysis
Tingting Gao, Pharm.D., Safety Evaluator
Chi-Ming (Alice) Tu, Pharm.D., Team Leader, Safety Evaluator
Lubna Merchant, PharmD, Associate Director, DMEPA

SPONSOR ATTENDEES:
Adrian Hepner, Executive Vice President, Clinical Research, Medical & Regulatory Affairs
Foma Rashkovsky, Vice President, Regulatory Affairs
Steve Krill, CSO
Michael McGraw, PharmD, MS, Director, Regulatory Affairs, Teva Branded Pharmaceutical Products R&D Inc.

MEETING OBJECTIVE:
DMEPA requested this teleconference to discuss the inclusion of their company name into the proprietary name.

DISCUSSION:

- The Applicant indicated in their submission that the proposed name, (b) (4), is derived from (b) (4)
- The Agency informed the Applicant that (b) (4)
- There are currently no drug product (b) (4)
- The Agency stated because the proposed name (b) (4) The Agency stated that the proprietary name guidance could be made available for reference. The Applicant stated they are aware of the guidance and there were no questions regarding the guidance at this time. The Applicant thanked the Agency for its time.

- The call ended at approximately1:38 PM EST

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/s/

CHI-MING TU
04/01/2015

Wright, Kevin

From: Foma Rashkovsky <frashkovsky@eagleus.com>
Sent: Tuesday, March 31, 2015 11:04 AM
To: Wright, Kevin
Cc: Kang, Sue
Subject: RE: NDA 208194 bendamustine: Proposed Proprietary Name, (b) (4)

Thank you. Talk to you at 1:30 PM.

From: Wright, Kevin [mailto:Kevin.Wright@fda.hhs.gov]
Sent: Tuesday, March 31, 2015 11:03 AM
To: Foma Rashkovsky
Cc: Kang, Sue
Subject: RE: NDA 208194 bendamustine: Proposed Proprietary Name, (b) (4)
Importance: High

Mr. Rashkovsky,

Please see the updated list of FDA attendees below:

Kevin Wright, OSE Project Manager
Tingting Gao, Safety Evaluator, DMEPA
Alice Tu, Team Lead Safety Evaluator, DMEPA
Lubna Merchant, Associate Director, DMEPA

Best regards,

Kevin Wright, PharmD

Safety Regulatory Project Manager | OSE | CDER | FDA | 301.796.3621 |kevin.wright@fda.hhs.gov

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From: Foma Rashkovsky [mailto:frashkovsky@eagleus.com]
Sent: Thursday, March 26, 2015 8:36 AM
To: Wright, Kevin
Cc: Kang, Sue; Foma Rashkovsky
Subject: RE: NDA 208194 bendamustine: Proposed Proprietary Name, (b) (4)

Dear Dr. Wright,

We have some changes to the attendees' list. The new list of attendees is as follows:

- Adrian Hepner, Executive Vice President, Clinical Research, Medical & Regulatory Affairs

- Foma Rashkovsky, Vice President, Regulatory Affairs
- Steve Krill, CSO
- Michael McGraw, PharmD, MS, Director, Regulatory Affairs, Teva Branded Pharmaceutical Products R&D Inc.

Best regards,
Foma

From: Foma Rashkovsky
Sent: Tuesday, March 24, 2015 7:26 AM
To: Wright, Kevin
Cc: Kang, Sue; Foma Rashkovsky
Subject: RE: NDA 208194 bendamustine: Proposed Proprietary Name, (b) (4)

Dr. Wright,

We are available for a teleconference on Tuesday, **March 31, 2015 from 1:30-2:00 PM EST**.
The following is call-in information:

- Toll free number: (b) (4)
- Participant passcode: (b) (4)

Eagle attendees:
- Adrian Hepner, Executive Vice President, Clinical Research, Medical & Regulatory Affairs
- Foma Rashkovsky, Vice President, Regulatory Affairs
- Linda Dell, Vice President, Portfolio & Project Management

Let me know if you have any questions.

Foma

From: Wright, Kevin [mailto:Kevin.Wright@fda.hhs.gov]
Sent: Monday, March 23, 2015 9:47 AM
To: Foma Rashkovsky
Cc: Kang, Sue
Subject: NDA 208194 bendamustine: Proposed Proprietary Name, (b) (4)

Mr. Rashkovsky,

Good morning, the Division of Medication Error Prevention and Analysis (DMEPA) review team would like to schedule a 30 minute teleconference with you and your review team regarding your proprietary name submission under NDA 208194 bendamustine.

Please let me know if you are available for this teleconference on Tuesday, March 31, 2015 from 1:00 - 1:30 ***or*** 1:30-2:00 PM EST. Also, please provide me with call-in information and a list of attendees.

The agenda is as follows:

Agenda
1) Introductions
2) Purpose of meeting - Discuss the proposed proprietary name, (b) (4).
3) Closing remarks

Please confirm receipt of this email.

Best regards,

Kevin Wright, PharmD

Safety Regulatory Project Manager | OSE | CDER | FDA | 301.796.3621 |kevin.wright@fda.hhs.gov

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/s/

KEVIN WRIGHT
03/31/2015

From:	Wall, Laura
To:	Foma Rashkovsky (frashkovsky@eagleus.com)
Cc:	Wall, Laura
Subject:	NDA 208194 - FDA Information Request - Please respond by COB March 18, 2015
Date:	Monday, March 16, 2015 9:29:53 AM

Dear Foma,

The review team requests that you respond to the following Information Request:

Please provide table of each section in modules 2 and 3 where the information in NDA 208194 (b) (4) (b) (4) Provide a brief summary describing the new CMC information in NDA 208194.

To expedite the review process, please send me your responses via e-mail and officially to your application by COB Wednesday, March 18, 2015.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Rm 2361
Silver Spring, MD 20993
Phone: 301-796-2237 | laura.wall@fda.hhs.gov

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/s/

LAURA C WALL
03/16/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208194

NDA ACKNOWLEDGMENT

Eagle Pharmaceuticals, Inc.
Attention: Foma Rashkovsky
Senior Director, Regulatory Affairs
50 Tice Boulevard, Suite 315
Woodcliff Lake, NJ 07677

Dear Mr. Rashkovsky:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Bendamustine hydrochloride parenteral 100 mg/4 mL (25 mg/mL)

Date of Application: February 13, 2015

Date of Receipt: February 13, 2015

Our Reference Number: NDA 208194

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 14, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Laura Wall, MS, APHN, OCN
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

LAURA C WALL
02/27/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 116448

MEETING MINUTES

Eagle Pharmaceuticals, Inc.
Attention: Foma Rashkovsky
Vice President of Regulatory Affairs
50 Tice Boulevard, Suite 315
Woodcliff Lake, NJ 07677

Dear Mr. Rashkovsky:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for bendamustine hydrochloride injection for intravenous infusion.

We also refer to the meeting between representatives of your firm and the FDA on December 17, 2014. The purpose of the meeting was to seek the Agency's advice on the strategy for filing data as an amendment (b) (4)

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Laura Wall, Regulatory Project Manager at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, MS, RN, ACNP-BC
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	pre-NDA
Meeting Date and Time:	December 17, 2014 from 2:00 p.m. to 3:00 p.m. (EST)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application Number:	IND 116448
Product Name:	bendamustine hydrochloride injection for intravenous infusion
Indication:	for the treatment of chronic lymphocytic leukemia (CLL) and indolent B-cell non-Hodgkin's lymphoma (NHL)
Sponsor/Applicant Name:	Eagle Pharmaceuticals, Inc.
Meeting Chair:	Virginia Kwitkowski, MS, RN, ACNP-BC, Clinical Team Leader
Meeting Recorder:	Laura Wall, MS, APHN, OCN, Regulatory Project Manager

FDA ATTENDEES

Division of Hematology Products
Ann Farrell, MD, Division Director
Edvardas Kaminskas, MD, Deputy Director
Virginia Kwitkowski, MS, RN, ACNP-BC, Clinical Team Leader
Alexandria Schwarsin, MD, Clinical Reviewer
Nicole Gormley, MD, Clinical Reviewer
Tamy Kim, PharmD, Associate Director of Regulatory Affairs
Theresa Carioti, MPH, Chief Project Management Staff
Laura Wall, MS, Regulatory Project Manager

Division of Hematology Oncology Toxicology
Christopher Sheth, PhD, Pharmacologist/Toxicologist Team Leader
Haw-Jyh Chiu, PhD, Pharmacologist/Toxicologist Reviewer

Office of New Drug Quality Assessment (ONDQA)
Janice Brown, MS, Chemistry, Manufacturing & Controls Lead
Elsbeth Chikhale, PhD, Biopharmaceutics Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology
Bahru Habtemariam, PharmD, Clinical Pharmacology Team Leader

Olanrewaju Okusanya, PharmD, Clinical Pharmacology Reviewer

Division of Medication Error Prevention and Analysis (DMEPA)
Michelle Rutledge, PharmD, DMEPA Reviewer

Office of Executive Programs (OEP)
Virginia Behr, BS, Ombudsman

Division of User Fee Management & Budget Formulation
Beverly Friedman, RPh, MBA, Division of User Fee Management & Budget Formulation
Jeen Min, RPh, Division of User Fee Management & Budget Formulation
Teresa Ramson, PharmD, Division of User Fee Management & Budget Formulation
Kristan Callahan, Esq, Regulatory Counsel, Division of User Fee Management & Budget Formulation

SPONSOR ATTENDEES
Paul Bruinenberg, MD, Chief Medical Officer, Eagle Pharmaceuticals, Inc.
Steve Krill, PhD, Chief Scientific Officer, Eagle Pharmaceuticals, Inc.
Mark Smith, PhD, VP Preclinical Development, Eagle Pharmaceuticals, Inc.
Foma Rashkovsky, VP, Regulatory Affairs, Eagle Pharmaceuticals, Inc.
Linda Dell, VP, Portfolio & Project Management, Eagle Pharmaceuticals, Inc.
Peter Grebow, PhD, Executive VP of Research and Development, Eagle Pharmaceuticals, Inc.
(b) (4)

1.0 BACKGROUND

The purpose of this Type B meeting request is to seek the Agency's advice on the strategy for filing data as an amendment (b) (4) NDA 205580 was submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for bendamustine hydrochloride injection. The application was tentatively approved on July 2, 2014 for the use of bendamustine hydrochloride injection for Indolent Non-Hodgkin Lymphoma (NHL). (b) (4)

(1) the compatibility of bendamustine hydrochloride injection in a new diluent (5% dextrose water)

(2) the bioequivalence to the currently approved bendamustine hydrochloride injection product (in terms of area under the curve [AUC])

(3) a safety and tolerability profile of bendamustine hydrochloride injection when infused over 10 minutes in an admixture volume - 50 mL infusion bag

Objectives and expected outcomes of the meeting are to obtain the Agency's concurrence on acceptability of the following:

(b) (4)

2.0 DISCUSSION

2.1. Regulatory

Question 1: Eagle is planning to submit an amendment (b) (4) labeling "Dosage and Administration" section, supported by the submission of CMC and clinical BE study data (Study EGL-BDM-C-1301). Does the Agency agree that the proposed submission can be filed as an amendment (b) (4) ?

FDA Response to Question 1:
Based on the labeling as proposed under Appendix B, you will need to submit (b) (4)

Meeting Discussion December 17, 2014:

(b) (4)

Question 2: Eagle proposes to submit the Integrated Summary of Safety (ISS) in Section 2.7.4 of the NDA amendment instead of Section 5.3.5.3. Does the Agency agree with this approach?

FDA Response to Question 2:
Given that you propose to include only two studies in the amendment, Study EGL-BDM-C-1301(the bioequivalence study) (b) (4) **it is acceptable to submit the integrated summary of safety in section 2.7.4 of the NDA amendment. Bear in mind that the ISS is not a summary, but rather a detailed integrated analysis of all relevant data from the clinical study reports. If you decide to place this information in section 2.7.4, it will need to be adequately detailed, and meet the suggested size limitations of Module 2.**

Meeting Discussion December 17, 2014:
No discussion occurred.

2.2. Pharmacokinetic

Question 3: Does the Agency agree with including the 6 patients in the PKE population who were part of the IA and whose PK sample collection was done improperly?

FDA Response to Question 3:
See Response to Question 4.

Meeting Discussion December 17, 2014:
The Sponsor presented bioequivalence data describing the AUC $_{0\text{-}t\ and}$ AUC $_{0\text{-}inf}$ for four populations who received either the Eagle or Teva bendamustine products. The Sponsor proposed that the most relevant population for the BE analysis is the n=38 which includes all subjects who completed the PK component of the study successfully with no major protocol deviations. As noted in the background document, the Sponsor became aware of patients who had missing or incorrectly obtained PK samples (i.e., blood sample drawn from same extremity as administration of drug). The Sponsor requested clarification on why FDA wanted the n=60 population as the primary BE population. FDA stated that they recommended that the n=60 population (Primary BE population) be used for the primary BE analyses and that they conduct subset analyses for the other sub-populations and include justification for why a given subset is most relevant to the BE evaluation.

Question 4: Does the Agency agree that the primary PKE analysis should include the 6 patients from the IA with the improper PK sample collection or would the Agency rather limit the primary PKE analysis only to include patients with proper PK sample collection and instead include the 6 patients from the IA in the secondary sensitivity analysis?

FDA Response to Question 4:
Your primary analysis should include patients that received all 3 doses. However, the sponsor should provide sensitivity analyses for the following:

a. The population that includes the PKE analysis population and the 19 patients with incomplete sampling route (n=38 + 19),
b. The patients (per protocol) (n=38)

The sponsor may also provide a BE power and sample-size calculation based on the variability estimated using the per protocol PKE patients.

Meeting Discussion December 17, 2014:
See meeting discussion under Question 3.

Question 5: In addition to the primary and secondary sensitivity BE analyses described above, Eagle plans to also include in the final CSR the descriptive statistics PK analysis which will include all patients who had at least one dose of study drug (i.e., including proper and improper PK sample collection). Does the Agency agree?

FDA Response to Question 5:
See response to Question 4 above. The calculated PK parameters and individual concentration data for the BE analyses should be provided as SAS transport files along

with the associated program files. Ensure that the patients and PK concentrations that were incorrectly collected are flagged, where applicable.

Meeting Discussion December 17, 2014:
The Agency requested that in the datasets patients be flagged for dose and "proper/improper" sample collection.

2.3. Clinical Safety

Question 6: Eagle will include the final CSR for the BE Study [EGL-BDM-C-1301] in the NDA amendment. In addition, (b) (4) Is this acceptable to the Agency?

FDA Response to Question 6:
Refer to question 1. We remind you of the meeting we held with you in January 2013 when we stated that we could not determine whether we needed additional (b) (4) until the results of the BA/BE studies are available.

Meeting Discussion December 17, 2014:
(b) (4) **f they file the PK-safety data from the BE study, they will submit all safety data.** (b) (4)

Question 7: Eagle refers to the response from the Agency to Question 8 (page 8) in the pre-IND Meeting Minutes for IND 116448 regarding sufficient characterization of safety findings for Eagle's ready-to-dilute BDM HCl formulation. Eagle will submit safety data as part of the final CSR for the 81 patients dosed in the BE Study [EGL-BDM-C-1301]. The dosing of these patients in this study results in 133 individual doses of Eagle-BDM HCl injection and 151 doses of the Listed Drug ('comparator') TREANDA. (b) (4)

FDA Response to Question 7:
The adequacy of the exposure data to allow for sufficient characterization of safety will be a review issue after submission of the bioequivalence (b) (4)

Meeting Discussion December 17, 2014:
No discussion occurred.

Question 8: (b) (4) [redacted]

FDA Response to Question 8:
Yes.

Meeting Discussion December 17, 2014:
No discussion occurred.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records,

IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

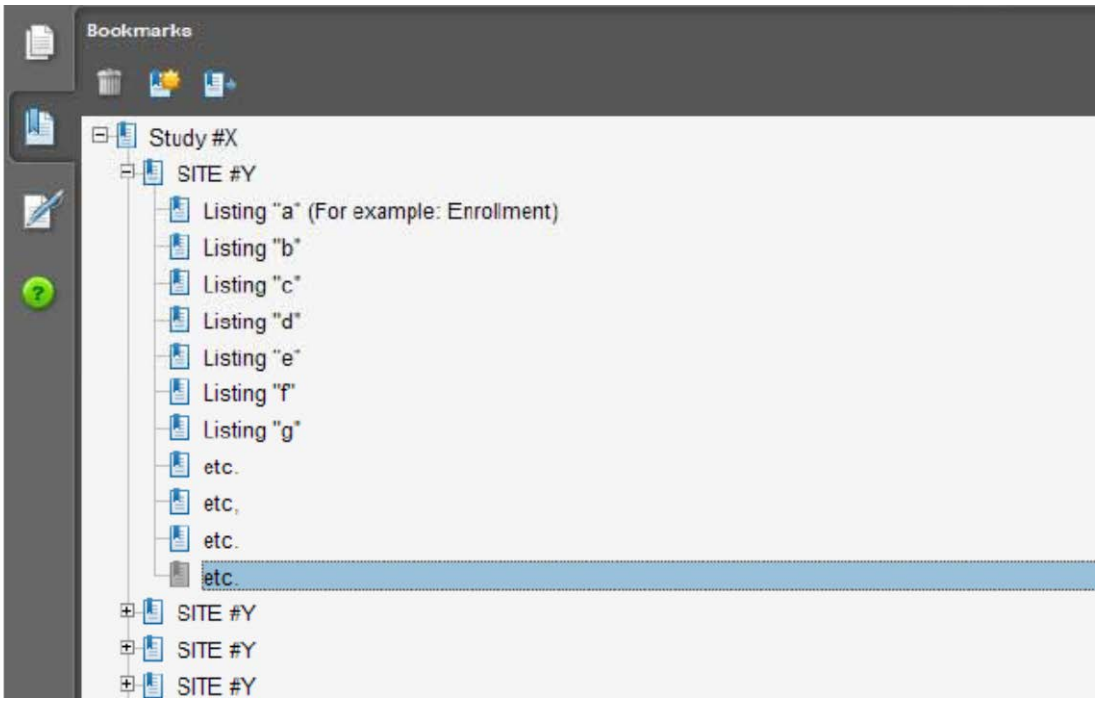
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submission of supplemental letter	Sponsor	Within 3 days of this meeting
Response to supplemental letter	Agency (User Fee Staff)	Will respond as soon as possible after appropriate consideration and review

6.0 ATTACHMENTS AND HANDOUTS

Eagle's presentation slides are attached and were received via e-mail on December 18, 2014. Also, attached are (b) (4) that were presented by the Agency.

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

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VIRGINIA E KWITKOWSKI
12/30/2014