CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208194Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 208194	NDA Supplement #: S- N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: With submission dated 2/13/15, Eagle initially requested "(b) (4) which was concluded conditionally acceptable on 4/2/15. Then Eagle withdrew "(b) (4) and requested "Bendeka," which was concluded conditionally acceptable on June 16, 2015. Established/Proper Name: bendamustine hydrochloride Dosage Form: Injection Strengths: 100 mg/4 mL (25 mg/mL)		
Applicant: Eagle Pharmaceuticals, Inc.		
Date of Receipt: February 13, 2015		
PDUFA Goal Date: December 13, 2015	Action Goal Date (if different):	
RPM: Laura Wall		
Proposed Indication(s): (1) Treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil. (2) Treatment of patients with indolent B cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab containing regimen.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
TREANDA® (bendamustine HCl) for injection (the listed drug)	*Various sections of the label*
Published literature	*Product quality, nonclinical; and clinical*

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

In order to bridge the proposed product, Eagle-BDM, to the listed drug, Treanda®, the Applicant conducted an open-label, randomized, crossover (partially replicated) phase 1 study in cancer patients to demonstrate the bioequivalence of the two drug products.
Both Treanda® and Eagle-BDM were administered at the same dose of 120 mg/m^2. However, Treanda® was diluted into 500 mL infusion and infused over 60 minutes, while Eagle-BDM was diluted into 50 mL infusion and infused over 10 minutes.
Plasma PK of bendamustine was measured and statistical analysis was performed using both the average BE and reference-scaled BE approaches due to the high within-subject variability. It was agreed upon by the Agency at the IND116448 meeting held in 2013, that only AUCs would be used for BE determination, because C_{max} would be different due to the differences in concentration and administration duration of the two drug products. The results showed that the AUCs (AUC_{0-t} & $AUC_{0-\infty}$) of bendamustine met the bioequivalence criteria in both FDA-recommended PK evaluation populations, though the C_{max} of bendamustine of Eagle-BDM was about 2.5 fold higher than that of Treanda®. The safety profiles of the two products are similar.
Overall, the proposed product is bioequivalent to Treanda® based on AUCs comparison, and the bridge between the proposed product and the listed drug was established.

RELIANCE ON PUBLISHED LITERATURE

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
TREANDA® (bendamustine HCl) for injection	NDA # 022249	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

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