CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205580Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 109789

MEETING MINUTES

Eagle Pharmaceuticals, Inc.
Attention: Foma Rashkovsky
Senior Director of Regulatory Affairs
470 Chestnut Ridge Road
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 (b) (4) for Injection, 25 mg/mL, 100 mg/vial.

We also refer to the September 9, 2012, meeting request for a meeting to be held between representatives of your firm and the FDA which was held on December 12, 2012. The purpose of the meeting was to clarify the issues raised during the pre-IND teleconference since Eagle Pharmaceuticals is preparing to submit an NDA using the 505(b)(2) pathway.

A copy of the official minutes of the December 12, 2012, 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 me at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

CDR Diane Hanner
Senior Program Management Officer
Division of Hematology Products
Office of Hematology and Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

Reference ID: 4266336

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B

Meeting Category: End of Phase 2

Meeting Date and Time: December 12, 2012

Meeting Location: White Oak Bldg. 22, Room 1311

Application Number: PIND 109789

Product Name: Bendamustine Hydrochloride (b) (4) for Injection.

Indication: Chronic Lymphocytic Leukemia (CLL
Indolent Non-Hodgkin's Lymphoma (NHL)

Sponsor/Applicant Name: Eagle Pharmaceuticals, Inc.

Meeting Chair: Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC, Clinical Team Leader, DHP

Meeting Recorder: CDR Diane Hanner, M.P.H., M.S.W.

FDA ATTENDEES

- Edvardas Kaminskas, M.D., Deputy Director, DHP
- Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC, Clinical Team Leader, DHP
- Adam George, Pharm. D, Clinical Analyst, DHP
- Joyce Crich, Ph.D., CMC Reviewer, ONDQA, Division 3, Branch 5
- Janice Brown, Ph.D., CMC Lead, ONDQA, Division 3, Branch 5
- John Z. Duan, Ph.D., . Biopharmaceutics Reviewer, ONDQA
- Elizabeth Shang, Ph.D., Clinical Pharmacology Reviewer, DCP5
- Julie Bullock, Pharm.D., Team Leader, Office of Clinical Pharmacology, DCP5
- Haleh Saber, Ph.D., Supervisory Pharmacologist
- CDR Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer

SPONSOR ATTENDEES

- Paul Bruinenberg, M.D., Chief Medical Officer, Eagle Pharmaceuticals, Inc.
- Srikanth Sundaram, Ph.D., Chief Scientific Officer, Eagle Pharmaceuticals, Inc.
- Jianwei Yu, Ph.D., Senior Director, CMC, Eagle Pharmaceuticals, Inc.
- Mark Smith, Ph.D., V.P. Preclinical Development, Eagle Pharmaceuticals, Inc.
- Foma Rashkovsky, Sr. Director of Regulatory Affairs, Eagle Pharmaceuticals, Inc.
- (b) (4)
- (b) (4)
- Steven Krill, Ph.D., VP Pharmaceutical Development, Eagle Pharmaceuticals, Inc.

1.0 BACKGROUND

EAGLE PHARMACEUTICIALS REQUESTED AN END OF PHASE 2 MEETING ON SEPTEMBER 9, 2012, TO OBTAIN AGENCY FEEDBACK ON THE FOLLOWING:

The Sponsor is seeking clarification regarding the issues raised during the pre-IND teleconference. The Sponsor is preparing to submit an NDA for a bendamustine HCI ready-to dilute liquid product using the 505(b)(2) pathway. The Eagle's bendamustine hydrochloride is a pre-mixed concentrated solution that will be diluted (b) (4) final concentration (0.2 to (b) (4) mg/mL) (b) (4) prior to administration. The composition of Eagle's bendamustine has remained substantially the same as the formulation discussed during the pre-IND meeting. The meeting was granted on October 2, 2012, and it was scheduled for December 12, 2012.

DISCUSSION

Question 1
Does the Agency concur with the proposed specifications for Eagle's product?

FDA Response: No. We do not agree with your proposed drug product acceptance criteria for individual impurities and total impurities. You should establish acceptance criteria based on your batch data. New impurities above the threshold defined in ICH Q3 A/B (as appropriate) need to be qualified and impurities that are common to the Listed Drug should be no more than the level observed in the Listed Drug unless they are below the qualification threshold.

Please also see our response to Question 2 for acceptable approaches to qualify impurities.

Meeting Discussion:
No Discussion

Question 2
Does the Agency concur that no additional nonclinical studies are required for the NDA submission based on the proposed specifications and given the fact that there are no unknown impurities in Eagle's product above the ICH identification/qualification threshold?

FDA Response: We agree that for impurities that are within the threshold of ICH Q3B(R2) no toxicology study will be needed to qualify drug product-related impurities. We also agree that impurities are considered qualified if they are at or below levels detected in the Listed Drug, in a side-by-side comparison, as long as an appropriate design is utilized (e.g. solvent, dilution, etc, as applicable).

However, if your justification of a specification is based on an impurity being a metabolite (e.g. for (b) (4)), you will need to provide the data to support the claim. A justification based on information from the Summary Basis of Approval is not acceptable.

Also see our response to Question 1.

Sponsor Response: On Question 2, we would like clarification of the Agency's expectation for data needed to demonstrate that an impurity is also a metabolite.

Meeting Discussion: The Sponsor asked whether the side-by-side comparison refers to the product to be given to patients after dilution. The Agency agreed. The Sponsor will provide literature to show that impurities in their drug product are metabolites of Bendamustine.

Question 3
Based on the data provided herein, does the Agency concur that a pharmacokinetic bioequivalence study is not required for this 505(b)(2) NDA and that a Bio-Waiver will be granted?

FDA Response: It is possible to grant a biowaiver provided that you submit a comparison of the physicochemical properties to show similarities between your proposed product and the listed drug. The acceptability of your biowaiver request will be determined during the review of your NDA.

Sponsor Response: On Question 3, we have the following specific concerns about the Agency's response and would like to discuss them in more detail at the meeting:

1. We would like to clarify that the comparison of the physicochemical properties between the proposed product and the reference listed drug will be performed at the point of administration to the patient; namely TREANDA after reconstitution and dilution in either of the two diluents specified in the label, and the Eagle product after dilution to the same concentration in the same diluents.
2. We believe that the physicochemical properties reported in the briefing book (namely pH and osmolality) are adequate to establish comparison of the diluted products. Does the Agency concur?

3. We want to clarify that the grant of the biowaiver is indeed a review issue, and not an issue for acceptability of the filing for review.

Meeting Discussion:
The Agency confirmed that the biowaiver will not be a filing issue provided that the NDA includes a side-by-side comparison between the listed drug and the Eagle product. This includes a comparative characterization of the product in the vial and the admixture.

3.0 IMPORTANT MEETING INFORMATION

PREA PEDIATRIC STUDY PLAN

Please be advised that you must submit a Pediatric Study Plan within 60 days of your scheduled end-of-Phase 2 meeting. 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. For additional guidance on submission of the PSP you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues identified that required further discussion.

5.0 ACTION ITEMS

There were no action items identified.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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
12/13/2012