CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209472Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 126831

MEETING MINUTES

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

Dear Mr. Rashkovsky:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Pemetrexed Injection, 25 mg/mL.

We also refer to the teleconference between representatives of your firm and the FDA on January 21, 2016. The purpose of the meeting was to discuss the proposed nonclinical study to qualify impurity and degradation products in the ready-to-dilute (RTD) product and the appropriateness to submit a waiver request for in vivo bioavailability studies in the New Drug Application (NDA).

A copy of the official minutes of the teleconference 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 (240) 402-6611.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

FOOD AND DRUG ADMINISTRATION
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MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-IND/Pre-NDA
Meeting Date and Time:	January 21, 2016 / 12:00 – 1:00 PM (EST)
Meeting Location:	Teleconference
Application Number:	126831
Product Name:	Pemetrexed Injection, 25 mg/mL
Indication:	The same indications as approved for listed product Alimta
Sponsor/Applicant Name:	Eagle Pharmaceuticals, Inc.
Meeting Chair:	Suzanne Demko
Meeting Recorder:	Leah Her

FDA ATTENDEES

Joseph Gootenberg	Deputy Director, OHOP/DOP2
Gideon Blumenthal	Clinical Team Lead, OHOP/DOP2
Barbara Scepura	Clinical Reviewer, OHOP/DOP2
Leah Her	Regulatory Project Manager, OHOP/DOP2
Whitney Helms	Nonclinical Supervisor, OHOP/DHOT
Anwar Goheer	Nonclinical Reviewer, OHOP/DHOT
Joyce Crich	CMC Lead (Acting), OPQ/ONDP/DNDPI/NDPBII
Xing Wang	CMC Reviewer, OPQ/ONDP/DNDPI/NDPBII
Om Anand	Biopharmaceutics Reviewer, OPQ/ONDP/DB
Joan Zhao	Biopharmaceutics Reviewer, OPQ/ONDP/DB
Hong Zhao	Clinical Pharmacology Team Lead, OTS/OCP/DCPV
Sriram Subramaniam	Clinical Pharmacology Reviewer, OTS/OCP/DCPV
Tamy Kim	Associate Director of Regulatory Affairs, OHOP

SPONSOR ATTENDEES

Adrian Hepner	E.V.P. of Clinical Research, Medical & Regulatory Affairs
Steven L. Krill	E.V.P. and Chief Scientific Officer
Mark Smith	V.P. of Preclinical Development
Foma Rashkovsky	V.P. of Regulatory Affairs
Feng-Jing Chen	V.P. of Pharmaceutical Development
Brian Chanas	Director Preclinical Development
Todd Jenson	Senior Director, Project Management
Sonal Patel	Senior Director, Project Management

BACKGROUND

On November 24, 2015, Eagle Pharmaceuticals (Eagle) requested a Type B meeting to discuss their 505(b)(2) development plan for a ready-to-dilute (RTD) pemetrexed product [Pemetrexed Injection for Intravenous Use, 25 mg/mL (500 mg/20 mL multiple-dose vial)] referencing the listed product, Alimta. Specifically, Eagle seeks FDA agreement on the proposed nonclinical study to qualify impurity and degradation products in the RTD product and to obtain feedback on the appropriateness to submit a waiver request for in vivo bioavailability studies in the New Drug Application (NDA). The meeting request was granted on December 8, 2015 as a teleconference meeting.

Chemistry, Manufacturing and Controls
The proposed ready-to-dilute (RTD) pemetrexed product contains drug substance pemetrexed (b) (4) (b) (4) which is different from pemetrexed disodium salt, the drug substance used for the listed drug Alimta. The chemical name for pemetrexed is: N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid. (b) (4) with a molecular formula of $C_{20}H_{21}N_5O_6$ and a molecular weight of 427.41. Commercially available Alimta (pemetrexed for injection) is a lyophilized powder which must first be reconstituted with 0.9% Sodium Chloride Injection (to yield a solution concentration of 25 mg/mL). According to the additional information provided by Eagle following the January 21, 2016, teleconference, the proposed liquid formulation contains pemetrexed (25 mg/mL) and the following excipients: propylene glycol (260 mg/mL); tromethamine (16.5-19.9 mg/mL) and hydrochloride acid for adjusting pH (b) (4); and water for injection (b) (4) It is intended to be stored at (b) (4) (2-8°C).

Nonclinical
Eagle proposes to conduct a GLP-compliant 6-week repeat dose IV study of RTD Pemetrexed solution in mice in order to provide toxicology data to support potential differences in the impurity/degradation levels for the proposed product that exceed those in the listed drug. No other nonclinical studies are planned. Eagle intends to rely on data from the listed drug to support other pharmacology/toxicology requirements for this pemetrexed solution application.

Clinical
Eagle's RTD liquid formulation pemetrexed product (b) (4) . Eagle expects that the safety and efficacy profiles of their ready to dilute liquid formulation pemetrexed product will be comparable to the listed drug, Alimta.

Eagle states that the indications and usage for their pemetrexed product are the same as for the listed drug, Alimta:

1. treatment of locally advanced or metastatic nonsquamous non-small cell lung cancer (NSCLC)
   - for initial treatment in combination with cisplatin
   - for maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy

- after prior chemotherapy as a single-agent

2. treatment of mesothelioma is in combination with cisplatin

DISCUSSION

1. Background: See Company Position on page 6 to 7 of the Briefing Document.

Does the Agency agree that a 6-week repeat dose IV mouse GLP toxicology study is appropriate to qualify impurity/degradation product levels that may be present in RTD Pemetrexed Injection?

FDA Response: Yes, the proposed toxicology study appears sufficient in design to support the qualification of impurity/degradation product levels in RTD pemetrexed; however a final determination of the adequacy of the submitted data will be determined following a full review of the reports included in the original NDA submission. In addition, develop and validate a suitable analytical method to cover the range of impurity/degradant levels in the proposed toxicology study.

Eagle Emailed Response of 1/20/16: An analytical method for the assessment of the drug product has been developed and validated to cover the range of impurity/degradant levels for the product to be used in the proposed toxicology study.

Discussion During the Meeting of 1/21/16: FDA acknowledged Eagle's response. FDA stated that Eagle submit related method and validation report in the NDA submission.

2. Background: See Company Position on page 7 of the Briefing Document.

Does the proposed IV repeat-dose study in mice obviate the need for an independent assessment of local tolerance?

FDA Response: Yes, the design of the proposed IV study in mice is sufficient to obviate the need for an independent local tolerance study.

Eagle Emailed Response of 1/20/16: We agree with your responses to questions 2 and 3 and no further discussion is requested at this time for questions 2 and 3.

Discussion During the Meeting of 1/21/16: None

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