CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209472Orig1s000

PRODUCT QUALITY REVIEW(S)

CMC Review Memo

NDA: 209472 (SDN 30)
Submission Date: 8/9/2019
Drug Name: Pemfexy (Pemetrexed Injection)
Dosage Form: 500 mg/20 mL (25 mg/mL)
Applicant: Eagle Pharmaceuticals, Inc.
Submission Type: Resubmission/Class 1

Background

This is a 505(b) (2) application by Eagle Pharmaceuticals. The reference drug product is Eli Lilly and Company's Alimta (pemetrexed disodium) for injection (NDAs 021677 and 021462). PEMFEXY (pemetrexed injection) for intravenous use is a sterile, clear, colorless to yellow or green-yellow solution. Each mL contains: 25 mg pemetrexed diacid, 260 mg propylene glycol, up to 16.5-19.9 mg tromethamine, and water for injection. Additional tromethamine not exceeding 19.9 mg/mL and/or hydrochloric acid may be added for pH adjustment. During last round of review, a shelf-life of 18 months was granted to the drug product, when packaged in the proposed packaging configuration and stored at 2-8°C (36-46°F). NDA 209472 is still under tentative approval.

CMC information

There is no new CMC information submitted in this resubmission.

Labeling

The updated revised labeling is acceptable from the CMC perspective.

Action

NAI.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

XING WANG
10/02/2019 04:30:52 PM

ANAMITRO BANERJEE
10/03/2019 07:20:25 AM

Recommendation:

APPROVAL

NDA 209472
Review 1

Drug Name/Dosage Form	PEMFEXY (Pemetrexed Injection) 500 mg/vial
Strength	25 mg/mL
Route of Administration	Intravenous Injection
Rx/OTC Dispensed	Rx
Applicant	Eagle Pharmaceuticals, Inc
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0001 (1) Original NDA	*December 30, 2016*	*CMC*
0004 (4) Quality Amendment	*February 21, 2017*	*Drug Product and Facility*
0005 (5) Quality Amendment	*February 22, 2017*	*Drug Product*
0006 (6) Quality Amendment	*April 14, 2017*	*Drug Product*
0007 (7) Quality Amendment	*April 18, 2017*	*Process*
0009 (9) Quality Amendment	*May 12, 2017*	*Process*
0011 (11) Quality Amendment	*May 31, 2017*	*Drug Product and Facility*
0012 (12) Quality Amendment	*June 02, 2017*	*CMC*
0013 (13) Labeling	*June 12, 2017*	*Labeling*
0014 (14) Quality Amendment	*June 23, 2017*	*Drug Product*
0017 (17) Quality Amendment	*August 18, 2017*	*Process*
0019 (19) Quality Amendment	*September 08, 2017*	*Drug Substance*
0020 (20) Quality Amendment	*September 15, 2017*	*Drug Substance*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Haripada Sarker	Ben Stevens
Drug Product	Xing Wang	Anamitro Banerjee
Process	Zhaoyang Meng	Bogdan Kurtyka
Microbiology	Denise Miller	Bryan Riley
Facility	Wendy Zhang	Christina Capacci-Daniel
Biopharmaceutics	Zhuojun Zhao	Okpo Eradiri

Regulatory Business Process Manager	Steve Kinsley	NA
Application Technical Lead	Anamitro Banerjee	NA
Laboratory (OTR)	NA	
ORA Lead	NA	
Environmental	Xing Wang	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Pemetrexed Drug Substance (b) (4)	Adequate	9/18/2017	Review-1
	Type III			Adequate	09/05/2017	Per MAPP (b) (4)
	Type III			Adequate	09/05/2017	Per MAPP (b) (4)
	Type V			Adequate	09/05/2017	Per MAPP (b) (4)
	Type V			Adequate	09/05/2017	Per MAPP (b) (4)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	021462	Listed drug (ALIMTA)

2. CONSULTS

NA

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for APPROVAL from the CMC perspective.

Action letter language (to be communicated to the applicant):

An expiry dating period of 18 months may be granted for this drug product when stored in the proposed container closure system at 2-8°C (b) (4) 5-46°F)

II. Summary of Quality Assessments

A. Product Overview

This submission is a 505(b)(2) application, referencing the lyophilized (b) (4) formulation, Alimta (NDA 21462). The listed drug (LD) Alimta is available in 100 mg and 500 mg single dose vials.

The proposed Pemetrexed (as diacid) for Injection is a sterile single dose ready to dilute solution with a concentration of 25 mg/mL (500 mg/vial), intended for IV use. The solution is further diluted with 5% Dextrose in Water to a maximum of final pemetrexed concentration of 15 mg/mL prior to administration.

The drug product is a clear, colorless to yellow or green-yellow solution free from visible particles presented in Type (b) (4) Clear Glass (b) (4) Bottles. The product is (b) (4) contains no antimicrobial preservatives.

The applicant is relying on FDA's finding on safety and efficacy for the listed drug Alimta.

Proposed Indication(s) including Intended Patient Population	1. Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer a. Initial treatment in combination with cisplatin. b. Maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. c. After prior chemotherapy as a single-agent. 2. Mesothelioma: in combination with cisplatin
Duration of Treatment	For Combination Use: 500 mg/m^2 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. (b) (4) (b) (4)

	(b) (4) For Single Use: 500 mg/m^2 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle.
Maximum Daily Dose	See above
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug substance:

The applicant refers to (b) (4) **DMF** (b) (4) (LOA provided) for general properties and manufacturing information for the drug substance. The DMF was last reviewed by Dr. Haripada Sarker on September 19, 2017 and found to be adequate. The applicant provided specifications and batch data, however referred to the DMF for all other information.

(b) (4) the drug substance manufacturing facility was found acceptable based on its inspectional history.

The drug substance and facility reviewers recommended approval for this NDA.

Drug Product:

The drug product is composed of pemetrexed diacid (25 mg/mL), propylene glycol (260 mg/mL), tromethamine (for pH adjustment), hydrochloric acid (for pH adjustment), water for injection as a vehicle (b) (4).

Registration batches were manufactured at (b) (4) scale. A batch size of up to (b) (4) is proposed for commercial batches. (b) (4)

(b) (4)

The drug product is packaged in 20 mL Type (b) (4) Clear Glass (b) (4) Bottle stoppered with 20 mm Grey (b) (4) Stopper with a (b) (4) Blue 20 mm Flip-off seal.
The applicant provided 12 months stability data under long term storage conditions, and 6 months stability data under accelerated storage conditions for three (b) (4), registration batches. Based on the data presented, 18 months of expiration dating period may be granted for the drug product when stored at 2°C to 8°C (36°F to 46°F). Based on in-use stability data provided in the application, the diluted solution may be stored under refrigerated conditions (2°C to 8°C) and at ambient conditions (temperature/light) for 48 hours.

All the manufacturing and testing facilities were found acceptable based on inspection history.

The applicant is requesting categorical exclusion for EA as per 21 CFR 25.21

The drug product, process, microbiology, and facility reviewers recommended approval for this NDA.

Biopharmaceutics:
The biopharmaceutics review assessed the adequacy of the Applicant's biowaiver request for the proposed drug product, pemetrexed diacid. Per 21 CFR 320.24(b)(6), the supporting data and information for the biowaiver request were evaluated and found to adequately support bridging of the proposed drug product to the LD (pemetrexed disodium).
The Biopharmaceutics Reviewer recommends approval of this NDA.

C. Special Product Quality Labeling Recommendations (NDA only)

No labeling recommendations were made during this review cycle.
The listed drug NDA holder is currently updating the PI. Hence, the labeling submitted in this application, which is consistent with the current label of the listed drug, was not reviewed.

D. Final Risk Assessment (see Attachment)

See attached.

E. List of Deficiencies for Complete Response

None

Application Technical Lead Name and Date: Anamitro Banerjee, Ph.D., October 02, 2017

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ENVIRONMENTAL ANALYSIS

This NDA Application qualifies for categorical exclusion in accordance with 21 CFR 25.31(a), and as such, does not require the submission of an Environmental Analysis. To the best of Eagle Pharmaceuticals Inc.'s knowledge, no extraordinary circumstances exist, as described under 21 CFR 25.21 that would prohibit granting of the Claim of Categorical Exclusion.

Reviewer's Assessment: Adequate

The EA statement is adequate (confirmed with Dr. Raanan Bloom).

Primary EA Reviewer Name and Date: Xing Wang, Ph.D., ONDP/DNDPI/NDPBII

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Anamitro Banerjee, Ph.D., Acting Branch Chief, ONDP/DNDPI/NDPBII

Xing Wang

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Anamitro Banerjee

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NDA 209472 Labeling Reivew

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

(b) (4)

[redacted]

Revised: 12/2016

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Pemetrexed Injection, for intravenous use	Edit (see below)
Dosage form, route of administration		See above
Controlled drug substance symbol (if applicable)		N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	500 mg vial for injection	Inadequate

Conclusion: Inadequate

PEMFEXY (pemetrxed injection), for intravenous use

Injection: 500 mg/20 mL (25 mg/mL) in a single-dose vial

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

3 DOSAGE FORMS AND STRENGTHS

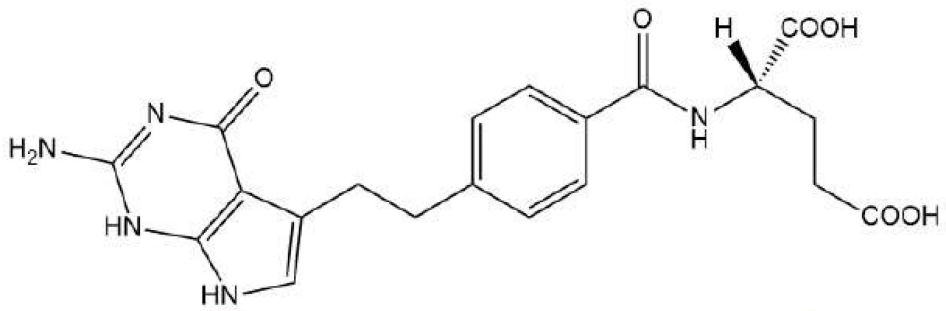
Injection: 500 mg/20 mL (25 mg/mL) (b) (4) in a single-dose vial.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Injection	adequate
Strengths: in metric system	500 mg pemetrexed (25 mg/mL)	See below
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Not provided.	Inadequate

Conclusion: Indequate
Change to
"Injection: 500 mg/20 mL (25 mg/mL) (b) (4) in a single-dose vial"

#11: Description (21CFR 201.57(c)(12))

Pemetrexed is a folate analog metabolic inhibitor. Pemetrexed diacid, the drug substance, has the chemical name N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glumatic acid. (b) (4) (b) (4) molecular formula (b) (4) $C_{20}H_{21}N_5O_6$ and (b) (4) molecular weight of 427.41. The structural formula is as follows:



PEMFEXY (pemetrexed injection) (b) (4) a sterile, clear, colorless to yellow or green-yellow (b) (4). Each mL contains: 25 mg pemetrexed diacid, 260 mg propylene glycol, (b) (4) tromethamine (b) (4) and water for injection. Additional tromethamine and/or hydrochloric acid may be added for pH adjustment.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Pemetrexed diacid (pemetrexed)	Adequate
Dosage form and route of administration	(b) (4)	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)		N/A
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	260 mg propylene glycol, (b) (4) (b) (4) tromethamine solution and water for injection	Edited
Statement of being sterile (if applicable)	sterile	Adequate
Pharmacological/ therapeutic class	a folate analog metabolic inhibitor	Adequate
Chemical name, structural formula, molecular weight	Pemetrexed (b) (4) is a folate analog metabolic inhibitor. Pemetrexed diacid (b) (4) has the chemical name N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glumatic acid. (b) (4) molecular formula of C20H21N5O6 and a molecular weight of 427.41.	Adequate
If radioactive, statement of important nuclear characteristics.		N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Color of the solution is provided. Tromethamine and hydrochloric acid may be added for pH adjustment.	Adeuqate

Conclusion:
Add pharmacological/therapeutic class of the drug. Drug product components are edited.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16.1 How Supplied

PEMEFEXY (pemetrexed Injection) is a clear, colorless to yellow or green-yellow (b) (4) solution supplied in single-dose vials for intravenous use
NDC 42367-531-32: Carton containing one (1) single-dose vial of 500 mg/20 mL (25 mg/mL) (b) (4).

16.2 Storage and Handling

Refrigerate at 2° to 8°C (36° to 46°F). Pemetrexed is a cytotoxic drug. Follow applicable special handling and disposal procedures. *[see References (15)]*

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	500 mg	500 mg/ 20 mL (25 mg/mL)
Available units (e.g., bottles of 100 tablets)	Single-dose vials	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC 42367-531-32: single-dose vial with blue flip-off cap individually packaged in a carton.	Revised to NDC 42367-531-32: Carton containing one (1) single-dose vial of 500 mg/mL (25 mg/mL) (b) (4)
Special handling (e.g., protect from light, do not freeze)	(b) (4)	Removed "(b) (4)". Add" Pemetrexed is a cytotoxic drug. Follow applicable special handling and disposal procedures. (b) (4)
Storage conditions	(b) (4)	Refrigerated at 2° to 8°C (36° to 46°F).

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Marketed by: Marketed by: Eagle Pharmaceuticals, Inc. Woodcliff Lake, NJ 07677	Either the manufacturer's name, packer's name, or distributor's name is acceptable. "Marketed by" is allowed when indicating the distributor's name on the labeling.

Conclusion:
"Marketed by" is allowed when indicating the distributor's name on the labeling.

2. Container and Carton Labeling

1) Immediate Container Label

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QUALITY ASSESSMENT

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	PEMFEXY (PEMETEXED INJECTION)	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	500 mg/vial	500 mg/20 mL (25 mg/mL)
Route of administration 21.CFR 201.100(b)(3))	(b) (4)	Adequate
Net contents* (21 CFR 201.51(a))	500 mg/vial	See above
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Not provided	Not required for vial labeling.
Lot number per 21 CFR 201.18	Reseved space for lot number	Adequate
Expiration date per 21 CFR 201.17	Not provided	Inadequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Provided	Adequate
Storage (not required)	Refrigerate at 2°C-8°C (36°F to 46°F) (b) (4) (b) (4)	Edit
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC 42367-531-32	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Not provided	Inadequate
Name of manufacturer/distributor (21 CFR 201.1)	Marketed by: Eagle Pharmaceuticals, Inc. Woodcliff Lake, NJ 07677	"Marketed by" is allowed when indicating the distributor's name on the labeling.
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Inadequate
The changes/edits will be conveyed to the applicant by OND.

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

QUALITY ASSESSMENT

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	PEMFEXY (PEMETRXED INJECTION)	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	(b) (4)	500 mg/20 mL (25 mg/mL)
Net contents (21 CFR 201.51(a))		See above
Lot number per 21 CFR 201.18	Not provided	Inadequate
Expiration date per 21 CFR 201.17	Not provided	Inadequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Name of all inactive ingredients are provided. Quantitavie ingredient information is not provided.	Inadequte
Sterility Information (if applicable)	(b) (4)	Adequte
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Rx ONLY provided	Adequate
Storage Conditions	Refrigerate at 2°C-8°C (36°F to 46°F)	Inadequte
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC 42367-531-32	Adequte
Bar Code per 21 CFR 201.25(c)(2)**	UPC code space reserved but not provided	Inadequate
Name of manufacturer/distributor	Only provided "Marketed by"	Inadequate
"See package insert for dosage information" (21 CFR 201.55)	Provided	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	N/A	N/A

QUALITY ASSESSMENT

Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	(b) (4) Must be futher diluted before administration	Adequate

Conclusion: Inadequate
The changes/edits will be conveyed to the applicant by OND.

Reviewer's Assessment and Signature:

Secondary Review Comments and Concurrence:

Xing Wang

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Anamitro Banerjee

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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: 209472

Drug Product Name / Strength: Pemetrexed Injection 25 mg/mL, Injection

Route of Administration: Intravenous

Applicant Name: Eagle Pharmaceuticals, Inc

Review Summary:

Eagle Pharmaceuticals, Inc.'s proposed Pemetrexed Injection, 25 mg/mL, is a ready-to dilute (RTD) new formulation submitted in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The listed drug (LD) is Eli Lilly's Alimta® (pemetrexed) for injection (NDA 021462, approved on 2/4/2004), 100 and 500 mg. The Applicant requests to bridge the proposed drug product to Alimta® under 21 CFR 320.24 (b) (6) as stated in FDA's WRO letter dated 9/23/2016 (IND 126831)[1].

The proposed Pemetrexed Injection, 25 mg/mL is intended for the same indications as Alimta®. It is noted that the proposed pemetrexed injection is to be diluted directly with 5% Dextrose in water, while Alimta® is supplied as lyophilized powder for reconstitution with 0.9% sodium chloride. The Applicant did not conduct any clinical studies.

This review evaluates the following data in support of the Applicant's bridging request.

- Drug substance
  The comparison between the pemetrexed diacid in the proposed drug product and pemetrexed disodium in Alimta® demonstrate that the structures of the drug substance are equivalent.

- Drug product formulation
  Two excipients, Propylene Glycol and Tromethamine, are present in the proposed drug product and found not likely to affect the in vivo disposition of pemetrexed. The proposed formulation is therefore acceptable.

- Physicochemical characteristics
  The proposed drug product has higher osmolality than Alimta® due to the presence of propylene glycol, which was evaluated in the Applicant's Hemolysis study and does not cause safety concerns. In addition, the physicochemical characteristics of the admixtures of Eagle's proposed drug product and Alimta® are similar.

- In vitro Protein binding study
  Results of an in vitro protein binding study indicate that the proposed product is comparable to Alimta®.

Review Recommendation:
From the Biopharmaceutics perspective, the Applicant has bridged the proposed drug product to Alimta® (pemetrexed disodium) IV injectable (infusion) under *21CFR 320.24 (b) (6)* and thus NDA 209472 for Pemetrexed for Injection is recommended for **APPROVAL**.

List Submissions being reviewed: Original submission (12/30/2016)

Highlight of Key Outstanding Issues from Last Cycle: N/A (First cycle)

Concise Description of Outstanding Issues : None

This proposed drug product was previously discussed in IND 126831[1]. The Applicant was advised to bridge the proposed drug product to the listed drug, Eli Lilly and Co.'s NDA 021462 Alimta® (pemetrexed disodium) IV injectable (infusion), under *21CFR 320.24 (b) (6)*.

The firm provided the following data in this application.

Drug Substance
The drug substance in the proposed drug product is pemetrexed diacid, while the API in the listed drug Alimta® is pemetrexed disodium.

(b) (4)

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(b) (4)

List of Deficiencies: None

Recommendation: From the Biopharmaceutics perspective, the Applicant has bridged the proposed drug product to Alimta® (pemetrexed disodium) IV injectable (infusion) under *21CFR 320.24 (b) (6)* and NDA 209472 for Pemetrexed for Injection is therefore recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date: Zhuojun Zhao, Ph.D. 8/23/2017

Secondary Reviewer Name and Date: Okpo Eradiri, Ph.D.8/24/2017

Zhuojun Zhao

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Okponanabofa Eradiri

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QUALITY ASSESSMENT

MICROBIOLOGY

Product Background: This is a chemotherapy agent for the treatment of locally advanced or metastatic Non-squamous Non-Small Cell Lung Cancer and Mesothelioma. It is manufactured as a ready to dilute solution and provided in 20 mL vials (b) (4) (500 mg/vial).

NDA: **209-472**

Drug Product Name / Strength: Pemetrexed Injection 25 mg/mL

Route of Administration: Intravenous

Applicant Name: Eagle Pharmaceuticals, Inc.

Manufacturing Site:

(b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: Adequate

Review Summary: The drug product (b) (4)

(b) (4)

Highlight Key Outstanding Issues from Last Cycle: NA

Remarks:
The proposed manufacturer (b) (4) was recently reviewed by the Division of Microbiology Assessment for NDA (b) (4). The DMA review (File (b) (4)) was used to supplement the manufacturing information for the subject NDA.

Concise Description Outstanding Issues Remaining: NA

Supporting Documents:
DMF (b) (4)**:** DMF update dated (b) (4) for the Bacterial Endotoxin Reduction studies for the (b) (4) family of stoppers. The DMF was reviewed by the Division of Microbiology Assessment for the (b) (4) family on (b) (4) and determined that the DMF was adequate.

(b) (4)**:** DMA review dated (b) (4) was a review of the same manufacturing facility and manufacturing line. The facility was acceptable. (Reviewer Note: there are instances where the subject application only provided the most recent re-qualifications to support the (b) (4) process. In those instances, the cited DMA review supports the facility and therefore additional information was not requested).

List Number of Comparability Protocols (ANDA only): NA

S Drug Substance: NA

Reviewer's Assessment: ***Drug substance is not sterile.***

P Drug Product

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – Sterile ready to dilute solution. The product is to be stored at 2-8°C. Provided as a 20 mL fill in a 20 mL vial. Diluted in (b) (4) of 5% dextrose in water for administration.
- **Drug product composition** – The composition of the drug product is in table 1 below (copied from Application Section 3.2.P.3.2 Table 1):

Table 1: Batch Formula

Ingredient	Composition	NDA Registration Batches	Proposed Commercial Batches
	mg/mL	(b) (4)	
Pemetrexed[a]	25		
Propylene Glycol, USP/EP	260		
Tromethamine, USP/EP	Q.S. to pH	(b) (4)	
Hydrochloric Acid, NF/EP	Q.S. to pH		
Water for Injection, USP/EP	(b) (4)		

(b) (4)

Note: A response to an information request sent by the Process Reviewer stated that the maximum commercial batch will be (b) (4). If they find that a batch (b) (4) is needed, they state that the hold time limit (b) (4) of NMT (b) (4) hours will not change.

- **Description of container closure system –**
  - **Vials:** 20 mL, 20 mm Type (b) (4) clear glass vials, (b) (4)
  - **Stoppers**: 20 mm gray (b) (4) stoppers, (b) (4) (b) (4)

Reviewer's Assessment: ***Adequate; the information provided is of adequate detail.***

P.2 Pharmaceutical Development

(b) (4)

Antimicrobial Effectiveness Testing: NA.

Reviewer's Assessment: ***Drug product is single use and is not preserved.***

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(b) (4)

Reviewer's Assessment: ***Adequate; the study supports the proposed*** (b) (4) ***time limit for storing the diluted drug product in 5% Dextrose.***

Post-Approval Commitments: NA

List of Deficiencies: NA

Primary Microbiology Reviewer Name and Date:
Denise A. Miller 07/28/17
Senior Microbiologist

Secondary Reviewer Name and Date:
Bryan Riley Ph.D.
Acting Branch Chief

Denise Miller

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Bryan Riley

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Date: 8/02/2017 08:54:15AM
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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H	(b) (4)	Acceptable	
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M	Testing included in DP release specification. Method supported by suitability studies.	Acceptable	
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Included in DP specifications.	Acceptable	
Assay (anti-oxidant)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M	Large amount of propylene glycol in formulation which has anti-oxidant property. DP stability data is ok.	Acceptable	
Uniformity of Dose (Fill volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L	Fill volume Included in DP specifications	Acceptable	
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	The sponsor provided a hemolysis study report. Pharm Tox assessed and had no concern because there were no	Acceptable	

			differences detected in the hemolytic potential and plasma compatibility of Pemetrexed Injection in human whole blood relative to Alimta.		
pH (High)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Included in DP specifications.	Acceptable	
pH (Low)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Included in DP specifications.	Acceptable	
Particulate Matter	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	M	Included in DP specifications.	Acceptable	
Leachables extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Extractable study reports of glass vials and stoppers from (b) (4)	Acceptable	
Appearance (color/turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Included in DP specifications.	Acceptable	

Anamitro Banerjee -S

Digitally signed by Anamitro Banerjee -S
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Date: 2017.10.02 15:37:58 -04'00'