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APPLICATION NUMBER:

209472Orig1s000

CLINICAL REVIEW(S)

File Memorandum

Memo Date	10/4/2019
To NDA	209472
Submission Date	8/9/2019
PDFUA Date	10/9/2019
Product	Pemfexy (Pemetrexed for Injection) Ready to Dilute Solution
Dosage Form	500 mg vial for injection, (25 mg/mL)
Sponsor	Eagle Pharmaceuticals
From	Barb Scepura
Via	Erin Larkins, MD, Clinical Team Leader, DOP2
Reference Drug	Alimta (NDA 021677and 021462)

Clinical Information
No clinical data was submitted in this application.

Background
This is a 505(b) (2) application by Eagle Pharmaceuticals. Eagle Pharmaceuticals is proposing a proprietary name for their product Pemfexy (Pemetrexed for Injection). The reference drug product is Eli Lilly and Company's Alimta (pemetrexed disodium) for injection (NDAs 021677 and 021462). Alimta was initially granted traditional approval on February 4, 2004. Eagle Pharmaceuticals Pemfexy (Pemetrexed for Injection) will have the same indications as Alimta.

Eagle Pharmaceuticals, Inc. ("Eagle") requests a waiver of in vivo bioavailability studies to demonstrate the bioequivalence of Eagle's Ready-to-Dilute (RTD) aqueous solution formulation of Pemetrexed Injection, 25 mg/mL, to the listed drug Alimta.

Labeling
Please refer to the review by Associate Director for Labeling for details.

Summary of Findings
No clinical safety or efficacy data were submitted in this NDA application.
An Initial Pediatric Study Plan was submitted under IND 126831, with agreement on October 14, 2016.

Additional Background Information
Clinical studies have not been performed using Eagle's PEMFEXY product. The prepared Eagle PEMFEXY product contains relatively high levels of propylene glycol (PG), which are not present in the reference

drug ALIMTA. Although PG is generally considered safe, potential toxicity concerns with infusion of high levels of PG are renal, cardiac, neurologic, metabolic and hematologic.

Potential Safety Issues Related to PG

- Hemolysis related to osmolality.
    - The Applicant submitted a toxicology study which demonstrated no safety concern for this product.
    - Please refer to CMC review for details.
- Lactic acidosis and renal toxicity reported with cumulative doses.
    - Clinical reports of lactic acidosis and renal toxicity associated with PG have been in the setting of cumulative exposure over time, mostly associated with continuous infusions over multiple days of drug products containing PG as an excipient. A 2014 report from the European Medicines Agency (EMA) regarding the use of PG as an excipient[1] cites the report by Speth et al[2] for a dose escalation study of mitoquidone, in which the drug product had PG as an excipient. in this study, patients with cancer received PG at doses of up to 15 g/m^2 as a 4-hour IV infusion once every 3 weeks. This resulted in Cmax exposures as high as 425 μg/mL (42.5 mg/dL). There was no evidence of lactic acidosis or associated renal toxicity in this study.
    - The following information is contained in the Nonclinical Review for this application: "On a mg/m^2 basis humans would receive no more than approximately 8 g/m^2 delivered during the recommended 10-minute infusion at the maximum anticipated level of 15.6 g, though a more likely high dose would be no more than approximately 10 g, or 5.5 g/m^2, based on typical calculations using an average BSA of 1.8 m^2 rather than 3".

Reviewer comment: The anticipated maximum dose of 8 g/m^2 is well below the highest dose of 15 g/m^2 PG administered in the Speth trial. Given this, and the once every 3-week dosing of PEMFEXY, lactic acidosis and renal toxicity due to PG are not expected to be associated with use of this product.

- Cardiovascular effects with "rapid infusions"
    - As referenced by the Applicant in a September 28, 2017 response to information request from the FDA, the 2014 EMA report cites several publications describing cardiovascular effects of PG at different dose levels in nonclinical studies. One study from the mid-1970s reports antiarrhythmic effects observed in rats and dogs following IV injection of PG at doses between 193 to 289 mg/kg.[3] Another study from the mid-1980s specifically evaluated the cardiovascular effects of PG administered to dogs as an IV injection at doses of 160, 400, and 800 mg/kg. Results from this second study showed transient decrease in heart rate and blood pressure at a dose ≥400 mg/kg, with values returning to normal within 1 minute of PG administration.

Reviewer comment: These reports from nonclinical studies are for PG administered as an injection. PEMFEXY is recommended to be administered as an IV infusion over 10 minutes. Literature searches performed by the clinical reviewer and the clinical team lead revealed no clinical case reports of sudden death clearly or likely related to receipt of propylene glycol as an excipient.

EMA Statement on PG

The 2014 EMA report regarding PG as an excipient concludes "the safe maximum daily dose of PG for adults is 500 mg /kg".[1] In a letter dated October 2, 2017 Eagle Pharmaceuticals confirmed that the maximum level of PG to be delivered at the maximum expected pemetrexed dose of 1500 mg is 15.6 g, which is equivalent to approximately 222 mg/kg, which is less than half the maximum daily dose considered safe for adults per the EMA report.

FDA Statement on PG

The FDA Inactive Ingredient Database (IID) for Drug Products includes a maximum potency of 30% for propylene glycol administered as an administered as an intravenous infusion.[5] The anticipated maximum potency of PG Pemetrexed Injection for the expected highest total dose of 1,500 mg of pemetrexed, administered IV as a 100-mL admixture over a 10-minute infusion to a very large patient with 3 m^2 BSA, is 15.6%. This potency of 15.6% is approximately 50% lower than the IID-allowed maximum potency for an IV infusion (30%), and approximately one fifth of the maximum potency IID-allowed for an IV injection (82.04%).

Reviewer comment: The dose of PG in Eagle's prepared PEMFEXY product is within the safety limits defined by both the FDA and the EMA.

Reviewer comment: Based on biopharmaceutical review, nonclinical assessment and literature references, Eagle's prepared PEMFEXY product contains safe levels of PG.

References

1. European Medicines Agency. Background review for the excipient propylene glycol. November 20, 2014, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/12/WC500177937.pdf Accessed on September 28, 2017.
2. Speth P and Vree T. Propylene glycol pharmacokinetics and effects after intravenous infusion in humans. Therapeutic Drug Monitoring, 1987, 9:255-258.
3. Eichbaum FW and Yasaka WJ. Antiarrhythmic effect of solvents: propylene glycol, benzyl alcohol. Basic Res Cardiology, 1976, 71:355-370.
4. Al-Khudhairi D and Whitman JG. Autonomic reflexes and the cardiovascular effects of propylene glycol. Br J Anaesth, 1986, 58:897-902.
5. U. S. Food and Drug Administration. Inactive Ingredient Search for Approved Drug Products. Available at: https://www.accessdata.fda.gov/scripts/cder/iig/getiigWEB.cfm Accessed on October 3, 2017.

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Cross-Discipline Team Leader Review

Date	October 03, 2019
From	Anamitro Banerjee, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	2084742
Type of Application	505(b)(2)
Applicant	Eagle Pharmaceuticals, Inc.
Date of Receipt	August 09, 2019 (original submission: (December 30, 2016)
PDUFA Goal Date	October 09, 2019
Proposed Proprietary/Established Name	PEMFEXY (pemetrexed injection)
Dosage forms / Strength	Injection/ 25 mg/mL (500 mg/vial)
Route of Administration	Intravenous injection
Proposed Indication(s)	Pemetrexed for injection is a folate analog metabolic inhibitor indicated for: • Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer: • Initial treatment in combination with cisplatin. • 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. •Mesothelioma: in combination with cisplatin.
Recommended:	**TENTATIVE APPROVAL**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Product Quality (Xing Wang), dated October 03, 2019
- Clinical (Barbara Scepura); in DARRTS, dated October 02, 2019
- Pharmacology/Toxicology (M. Anwar Goheer, NAI); in DARRTS, dated September 30, 2019
- Pharmacology/Toxicology Labeling Review (Whitney Helms); in DARRTS, dated October 04, 2019
- Clinical Labeling Review (Stacy Shord); in DARRTS, dated October 04, 2019
- OPDP (Susan Redwood), dated September 27, 2019

- OPDP (Fatima Nazia), dated September 26, 2019
- Clinical Pharmacology (Safaa Burns), dated October 02, 2019

1. Introduction

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 submission is a 505(b)(2) application, referencing the lyophilized (b) (4) formulation, Alimta (NDA 021462). The listed drug (LD) Alimta is available in 100 mg and 500 mg single dose vials. The therapeutic active moiety (pemetrexed), route of administration (b) (4) of the proposed drug product is identical to the listed rug product. However, the listed and the proposed drug product differ in salt form of the active moiety, excipients, dosage form, and the solution for dilution. In support of the equivalence of the LD and the proposed drug product, the applicant provided comparative physicochemical properties and a bio-waiver request. Clinical data was not submitted in the application. Other than the pemetrexed in disodium salt form, Alimta contains mannitol, and hydrochloric acid or sodium hydroxide for pH adjustment (b) (4) Alimta is reconstituted with 0.9% sodium chloride injection solution followed by further dilution prior to administration. The proposed drug product contains pemetrexed (as diacid), propylene glycol as stabilizer, tromethamine and hydrocholic acid as pH adjusters, and water for injection (b) (4) The proposed Eagle product may be diluted with 5% Dextrose Injection while the LD may only be diluted with 0.9% Sodium Chloride Injection.

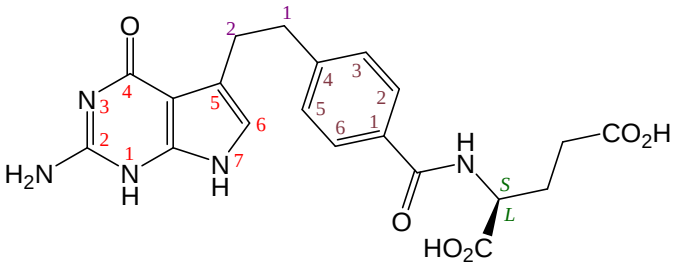
2. Background

The current application relies on the Agency's determination of human safety and efficacy for the pemetrexed lyophilized powder for injection (Alimta), which has been previously approved for marketing under NDA 021462 and NDA 021677.

This NDA was given a tentative approval on October 26, 2017. In this resubmission, the applicant is seeking full approval of the ready to dilute solution of pemetrexed ditromethamine for the same indication granted for Alimta. Alimta is indicated for the initial treatment of nonsquamous non-small cell lung cancer in combination with cisplatin, as a single agent treatment for nonsquamous non-small cell lung cancer after prior chemotherapy, and for the treatment of mesothelioma in combination with cisplatin.

3. Chemistry, Manufacturing and Controls (CMC)

The drug substance for NDA 208472 is pemetrexed diacid (b) (4) Labeling and strength designation is on the basis of the pemetrexed (b) (4), consistent with the listed product, Alimta. Chemical Name: (4-(2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzoyl)-L-glutamic acid.



(4-(2-(2-amino-4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl)benzoyl)-*L*-glutamic acid
Chemical Formula: $C_{20}H_{21}N_5O_6$
Molecular Weight: 427.4170

The applicant did not provide any new CMC information in this resubmission. No CMC deficiencies were identified in the previous review cycle.

Overall CMC recommendation
The Office of Pharmaceutical Quality recommendation remains APPROVAL action for NDA 208472.

4. Pharmacology/Toxicology
No new information provided in this resubmission

5. Clinical
No clinical safety or efficacy data were submitted in this NDA application.

6. Clinical Pharmacology
This NDA does not contain any clinical or clinical pharmacology studies as the Applicant requested a biowaiver. No new information submitted in this resubmission.

7. Advisory Committee Meeting
N/A

9. Other Relevant Regulatory Issues
The application may not be approved for marketing until patent/s for the listed drug expires or the current patent infringement lawsuit is settled.

10. Labeling
The applicant updated the label as suggested by the review team. The label is now acceptable.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This drug product differs with the listed drug, Alimta, in the salt form of active moiety and in the composition of the product. No clinical studies were conducted to assure safety and efficacy and a bio-waiver request will be granted for this 505(b)(2) application when it can be approved. The cross disciplinary team lead recommendation is for a **Tentative Approval** for this NDA. The drug product may not be approved for marketing until pertinent patents for the listed drug "Alimta" expire or the current patent infringement lawsuit is settled in Eagles's favor.

- **Risk Benefit Assessment**

Please refer to NDA 021462

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/s/

ANAMITRO BANERJEE
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File Memorandum

Memo Date	10/4/2019
To NDA	209472
Submission Date	8/9/2019
PDFUA Date	10/9/2019
Product	Pemfexy (Pemetrexed for Injection) Ready to Dilute Solution
Dosage Form	500 mg vial for injection, (25 mg/mL)
Sponsor	Eagle Pharmaceuticals
From	Barb Scepura
Via	Erin Larkins, MD, Clinical Team Leader, DOP2
Reference Drug	Alimta (NDA 021677and 021462)

Clinical Information
No clinical data was submitted in this application.

Background
This is a 505(b) (2) application by Eagle Pharmaceuticals. Eagle Pharmaceuticals is proposing a proprietary name for their product Pemfexy (Pemetrexed for Injection). The reference drug product is Eli Lilly and Company's Alimta (pemetrexed disodium) for injection (NDAs 021677 and 021462). Alimta was initially granted traditional approval on February 4, 2004. Eagle Pharmaceuticals Pemfexy (Pemetrexed for Injection) will have the same indications as Alimta.

Eagle Pharmaceuticals, Inc. ("Eagle") requests a waiver of in vivo bioavailability studies to demonstrate the bioequivalence of Eagle's Ready-to-Dilute (RTD) aqueous solution formulation of Pemetrexed Injection, 25 mg/mL, to the listed drug Alimta.

Labeling
Please refer to the review by Associate Director for Labeling for details.

Summary of Findings
No clinical safety or efficacy data were submitted in this NDA application.
An Initial Pediatric Study Plan was submitted under IND 126831, with agreement on October 14, 2016.

Additional Background Information
Clinical studies have not been performed using Eagle's PEMFEXY product. The prepared Eagle PEMFEXY product contains relatively high levels of propylene glycol (PG), which are not present in the reference

drug ALIMTA. Although PG is generally considered safe, potential toxicity concerns with infusion of high levels of PG are renal, cardiac, neurologic, metabolic and hematologic.

Potential Safety Issues Related to PG

- Hemolysis related to osmolality.
    - The Applicant submitted a toxicology study which demonstrated no safety concern for this product.
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- Lactic acidosis and renal toxicity reported with cumulative doses.
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    - The following information is contained in the Nonclinical Review for this application: "On a mg/m^2 basis humans would receive no more than approximately 8 g/m^2 delivered during the recommended 10-minute infusion at the maximum anticipated level of 15.6 g, though a more likely high dose would be no more than approximately 10 g, or 5.5 g/m^2, based on typical calculations using an average BSA of 1.8 m^2 rather than 3".

Reviewer comment: The anticipated maximum dose of 8 g/m^2 is well below the highest dose of 15 g/m^2 PG administered in the Speth trial. Given this, and the once every 3-week dosing of PEMFEXY, lactic acidosis and renal toxicity due to PG are not expected to be associated with use of this product.

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    - As referenced by the Applicant in a September 28, 2017 response to information request from the FDA, the 2014 EMA report cites several publications describing cardiovascular effects of PG at different dose levels in nonclinical studies. One study from the mid-1970s reports antiarrhythmic effects observed in rats and dogs following IV injection of PG at doses between 193 to 289 mg/kg.[3] Another study from the mid-1980s specifically evaluated the cardiovascular effects of PG administered to dogs as an IV injection at doses of 160, 400, and 800 mg/kg. Results from this second study showed transient decrease in heart rate and blood pressure at a dose ≥400 mg/kg, with values returning to normal within 1 minute of PG administration.

Reviewer comment: These reports from nonclinical studies are for PG administered as an injection. PEMFEXY is recommended to be administered as an IV infusion over 10 minutes. Literature searches performed by the clinical reviewer and the clinical team lead revealed no clinical case reports of sudden death clearly or likely related to receipt of propylene glycol as an excipient.

EMA Statement on PG

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Reviewer comment: The dose of PG in Eagle's prepared PEMFEXY product is within the safety limits defined by both the FDA and the EMA.

Reviewer comment: Based on biopharmaceutical review, nonclinical assessment and literature references, Eagle's prepared PEMFEXY product contains safe levels of PG.

References

1. European Medicines Agency. Background review for the excipient propylene glycol. November 20, 2014, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/12/WC500177937.pdf Accessed on September 28, 2017.
2. Speth P and Vree T. Propylene glycol pharmacokinetics and effects after intravenous infusion in humans. Therapeutic Drug Monitoring, 1987, 9:255-258.
3. Eichbaum FW and Yasaka WJ. Antiarrhythmic effect of solvents: propylene glycol, benzyl alcohol. Basic Res Cardiology, 1976, 71:355-370.
4. Al-Khudhairi D and Whitman JG. Autonomic reflexes and the cardiovascular effects of propylene glycol. Br J Anaesth, 1986, 58:897-902.
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BARBARA A SCEPURA
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ERIN A LARKINS
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

Date: January 22, 2018

From: Autumn Zack-Taylor, M.S., Regulatory Health Project Manager
DOP2/OHOP/CDER

Subject: Financial Disclosure Review

Financial disclosures were not required for review of this application because there were no clinical studies submitted supporting the application.

Cross-Discipline Team Leader Memo

Date	October 26, 2017
From	Okpo Eradiri, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	209472
Type of Application	505(b)(2)
Applicant	Eagle Pharmaceuticals, Inc.
Date of Receipt	December 30, 2016
PDUFA Goal Date	October 30, 2017
Proposed Proprietary/Established Name	PEMFEXY (pemetrexed injection)
Dosage forms / Strength	Injection/ 25 mg/mL (500 mg/vial)
Route of Administration	Intravenous injection
Proposed Indication(s)	Pemetrexed for injection is a folate analog metabolic inhibitor indicated for: • Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer: • Initial treatment in combination with cisplatin. • 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. •Mesothelioma: in combination with cisplatin.
Recommended:	**TENTATIVE APPROVAL**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Drug Substance (Haripada Sarker), dated September 18, 2017
- Drug Product (Xing Wang), dated September 05, 2017
- Microbiology (Denise Miller), dated July 28, 2017
- Manufacturing Facilities (Wenzheng Zhang), dated September 28, 2017
- Manufacturing Process (Zhaoyang Meng), dated August 28, 2017
- Biopharmaceutics (Zhuojun Zhao), dated August 24, 2017
- Clinical (Barbara Scepura); in DARRTS, dated October 20, 2017
- Pharmacology/Toxicology (M. Anwar Goheer); in DARRTS, dated October 03, 2017

- Patient Labeling (Susan Redwood); in DARRTS, dated October 20, 2017
- Medication Error Prevention and Analysis (Janine Stewart), dated October 25, 2017

1. Introduction

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 final pemetrexed concentration of 15 mg/mL prior to administration. The submission is a 505(b)(2) application, referencing the lyophilized (b) (4) formulation, Alimta (NDA 021462). The listed drug (LD), Alimta, is available in 100 mg and 500 mg single dose vials. The therapeutic active moiety (pemetrexed), route of administration (b) (4) of the proposed drug product are identical to the listed drug product. However, the listed and the proposed drug products differ in salt form of the active moiety, excipients, dosage form, and the solution for dilution. In support of the equivalence of the LD and the proposed drug product, the applicant provided comparative physicochemical properties and a bio-waiver request. Clinical data were not submitted in the application. Other than the pemetrexed in disodium salt form, Alimta contains mannitol and hydrochloric acid or sodium hydroxide for pH adjustmen (b) (4) Alimta is reconstituted with 0.9% sodium chloride injection solution followed by further dilution prior to administration. The proposed drug product contains pemetrexed (as diacid), propylene glycol as stabilizer, tromethamine and hydrochloric acid as pH adjusters, and water for injection (b) (4) . The proposed Eagle product may be diluted with 5% Dextrose Injection while the LD may only be diluted with 0.9% Sodium Chloride Injection.

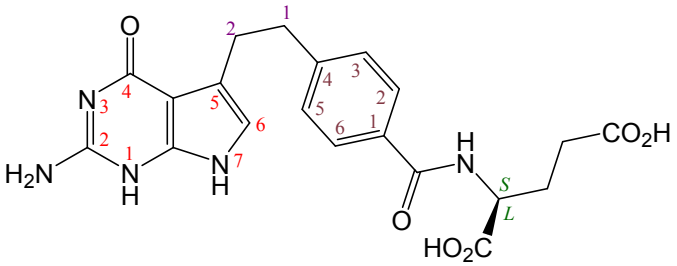
2. Background

The current application relies on the Agency's determination of human safety and efficacy for the pemetrexed lyophilized powder for injection (Alimta), which has been previously approved for marketing under NDA 021462 and NDA 021677; Alimta was granted traditional approval on February 4, 2004.

The applicant is seeking approval of a ready to dilute solution of pemetrexed ditromethamine for the same indications granted for Alimta. Alimta is indicated for the initial treatment of nonsquamous non-small cell lung cancer in combination with cisplatin, as a single agent treatment for nonsquamous non-small cell lung cancer after prior chemotherapy, and for the treatment of mesothelioma in combination with cisplatin.

3. Chemistry, Manufacturing and Controls (CMC)

The drug substance for NDA 208472 is pemetrexed diacid (b) (4)). Labeling and strength designation are based on the pemetrexed (b) (4), consistent with the listed product, Alimta.
Chemical Name: (4-(2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzoyl)-L-glutamic acid.



(4-(2-(2-amino-4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl)benzoyl)-*L*-glutamic acid
Chemical Formula: $C_{20}H_{21}N_5O_6$
Molecular Weight: 427.4170

The applicant refers to [redacted] (b) (4) **DMF** [redacted] (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.

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, [redacted] (b) (4) Prior to intravenous infusion, the drug product is reconstituted and further diluted with 5% dextrose in water to a maximum final concentration of not more than 15 mg/mL. Proposed maximum commercial scale batch size up to [redacted] (b) (4) is proposed for commercial batches.

The drug product specifications include testing for appearance of the solution, volume, identification, pH, assay, related substances, enantiomeric purity, particulate matter, bacterial endotoxin, sterility, and elemental impurities.

The drug product is packaged in 20 mL Type [redacted] (b) (4) Clear Glass [redacted] (b) (4) Bottle stoppered with 20 mm Grey [redacted] (b) (4) Stopper [redacted] (b) (4) and a [redacted] (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 [redacted] (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 substance, 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.

Overall CMC recommendation
The Office of Pharmaceutical Quality recommends an APPROVAL action for NDA 208472.

4. Pharmacology/Toxicology
The applicant is relying on the findings described in the label for Alimta to support the nonclinical requirements for evaluation of the proposed product. The nonclinical data submitted to support this NDA was limited to qualification of any novel impurities or high levels of excipients or degradants and the comparability of the proposed Eagle product to the LD.
In this submission, the applicant included:

1. *in vitro* human plasma protein binding study, a 6-week repeat dose GLP intravenous toxicity study in mice

The toxicities of the proposed product and Alimta were compared in repeat dose toxicity studies in Crl:CD1(IRC) mice. Animals (15/sex/group) received 315 mg/kg of the Eagle pemetrexed injection and Alimta given once weekly for s total of 7 doses.

2. An assessment of hemolytic potential

The diluted solution (15 mg/mL) of Eagle pemetrexed injection in 5% dextrose solution had no hemolytic potential in human whole blood and was negative for protein precipitation and aggregation in human plasma at a final pemetrexed concentration of 7.5 mg/mL (similar to Alimta).

3. Plasma compatibility of pemetrexed in human blood and plasma (*in vitro*).

The plasma protein binding study data submitted in this application indicates that the protein binding of Eagle pemetrexed injection and Alimta to human plasma, human serum albumin, and human α1-acid glycoprotein are comparable. Clinical pathology findings were generally comparable between the pemetrexed injection and Alimta groups.
Systemic exposure (C_{max} and $AUC_{0\text{-}24h}$) following once weekly IV administration of Eagle pemetrexed injection and Alimta for seven dozes were similar between two treatment groups.

The maximum level of tromethamine to be delivered is 1.08 g, which is significantly lower than the dose of 35 g for acidosis (Tham). Hence, tromethamine levels are not a concern.

Propylene Glycol:
The maximum level of propylene glycol (PG) to be delivered at the maximum expected pemetrexed dose of 1500 mg is 15.6 g (~222 mg/kg). PG was present in the formulation but not in the vehicle control used for mouse toxicology study. Per protocol, approximately 98 mg of PG were administered to mouse over 5 minutes. No significant clinical observations or changes in clinical

chemistry were recorded in this study compared to Alimta at the time of scheduled sacrifice, although transient changes in clinical chemistry cannot be ruled out. On an mg/m^2 basis humans would receive no more than approximately 8 g/m^2 delivered during the recommended 10-minute infusion at the maximum anticipated level of 15.6 g, though a more likely high dose would be no more than approximately 10 g, or 5.5 mg/m^2. While the nonclinical data supports the high levels of PG delivered in the 10-minute time interval, EMA background review for propylene glycol indicates saturation of propylene glycol metabolism occurs at lower doses for humans than for rats/rabbits (0.2 g/kg vs. 2 g/kg, respectively). Clinical data regarding PG administration by the IV route in literature indicates that a PG dose of 213 g/day for 7 days given by continuous infusion (1699 g total) leads to some clinical toxicity (confusion, hyper osmolality, lactic acidosis, and acute kidney injury), but the effects were recoverable. The 2014 EMA review on propylene glycol toxicity suggests limits in patients ≥5 years old of up to 500 mg/kg/day based on published clinical data.

Degradants:
Based on the nonclinical data presented in this applicant, the proposed limits for the impurities (b) (4) are acceptable.

The Pharmacology/Toxicology Reviewer recommends approval of the application.

5. Clinical
No clinical safety or efficacy data were submitted in this NDA. The clinical team recommends approval of this product contingent upon satisfactory reviews by other FDA disciplines.

6. Clinical Pharmacology
This NDA does not contain any clinical or clinical pharmacology studies as the Applicant requested a biowaiver, which was assessed by the biopharmaceutics review team. A biowaiver will be granted for this 505(b)(2) application when it can be approved.

7. Advisory Committee Meeting
N/A

8. Pediatrics
An Initial Pediatric Study Plan was submitted under IND 126831, with agreement on October 14, 2016. At its September 27, 2017 meeting, a full waiver of pediatric studies was granted by the PeRC. This information will be transmitted to Eagle at the time of final approval.

9. Other Relevant Regulatory Issues
This application is the subject of Patent Infringement Lawsuit Civil Action No. 17-cv-1293 filed September 11, 2017 in the District Court of Delaware by the patent owner of Patent 7,772,209 against Eagle Pharmaceuticals regarding the Listed Drug. The application may not be approved for marketing until this patent for the listed drug expires or the current patent infringement lawsuit is settled. This application is currently under a 30-month marketing stay.

10. Labeling

FDA edited Eagle's proposed label ensuring compliance with the Pregnancy and Lactation Labeling Final Rule (PLLR). Agreed upon labeling will be issued at the time of tentative approval. The Applicant has been made aware that the USPI for the reference product, ALIMTA, has been recently updated, and these updates include the addition of new warnings and precautions. The Applicant has stated that at the time of resubmission following resolution of pending patent issues, the NDA will contain revised proposed labeling based upon the most current USPI for the reference product. The Division of Medical Policy Programs (DMPP) has deferred review of the PPI to a future review cycle when they are consulted.

11. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This drug product differs from the listed drug, Alimta, in the salt form of the active moiety and in the composition of the drug product. Pre-clinical studies were conducted to qualify the proposed formulation (tromethamine and propylene glycol). No clinical studies were conducted to assure safety and efficacy and a biowaiver request will be granted for this 505(b)(2) application when it can be approved. The cross disciplinary team leader recommendation is for a **Tentative Approval** for this NDA. The drug product may not be approved for marketing until pertinent patents for the listed drug Alimta expire or the current patent infringement lawsuit is settled in Eagles' favor.

- **Risk Benefit Assessment**

Please refer to NDA 021462

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/s/

OKPONANABOFA ERADIRI
10/26/2017

JOSEPH E GOOTENBERG
10/26/2017

I agree with the conclusions reached by the CDTL, as embodied in this review, that Patent Infringement Lawsuit issues preclude full approval of this NDA. I recommend that this NDA be issued a TENTATIVE APPROVAL.

File Memorandum

Memo Date:	October 20, 2017
To NDA:	209472
Submission Date:	12/30/2016
FDA Received Date:	12/30/2016
PDFUA Date:	10/30/2017
Product:	Pemfexy (Pemetrexed for Injection) Ready to Dilute Solution
Dosage Form:	500 mg vial for injection, (25 mg/mL)
Sponsor:	Eagle Pharmaceuticals
From:	Barb Scepura
Via:	Erin Larkins, MD, Clinical Team Leader, DOP2
Reference Drug:	Alimta (NDA 021677and 021462)

Clinical: No clinical data was submitted in this application.

Background: This is a 505(b) (2) application by Eagle Pharmaceuticals. Eagle Pharmaceuticals is proposing a proprietary name for their product Pemfexy (Pemetrexed for Injection). The reference drug product is Eli Lilly and Company's Alimta (pemetrexed disodium) for injection (NDAs 021677and 021462). Alimta was initially granted traditional approval on February 4, 2004. Eagle Pharmaceuticals Pemfexy (Pemetrexed for Injection) will have the same indications as Alimta.

Eagle Pharmaceuticals, Inc. ("Eagle") requests a waiver of in vivo bioavailability studies to demonstrate the bioequivalence of Eagle's Ready-to-Dilute (RTD) aqueous solution formulation of Pemetrexed Injection, 25 mg/mL, to the Reference Listed Drug (RLD) Alimta.

Labeling: FDA edited Eagle's proposed label ensuring compliance with the Pregnancy and Lactation Labeling Final Rule (PLLR). Agreed upon labeling will be issued at the time of tentative approval. The Applicant has been made aware that the USPI for the reference product, ALIMTA, has been recently updated, and these updates include the addition of new warnings and precautions. The Applicant has stated that at the time of resubmission following resolution of pending patent issues, the resubmission will contain revised proposed labeling based upon the most current USPI for the reference product.

Summary of Findings: No clinical safety or efficacy data were submitted in this NDA application.
An Initial Pediatric Study Plan was submitted under IND 126831, with agreement on October 14, 2016.

Other Background Information:
Clinical studies have not been performed using Eagle's PEMFEXY product. The prepared Eagle PEMFEXY product contains relatively high levels of propylene glycol (PG), which are not present in the reference

listed drug ALIMTA. Although PG is generally considered safe, potential toxicity concerns with infusion of high levels of PG are renal, cardiac, neurologic, metabolic and hematologic.

Potential issues related to PG:

1) Hemolysis related to osmolality.

The Applicant submitted a toxicology study which demonstrated this is not an issue for this product. See CMC review for details.

2) Lactic acidosis and renal toxicity reported with cumulative doses.

Clinical reports of lactic acidosis and renal toxicity associated with PG have been in the setting of cumulative exposure over time, mostly associated with continuous infusions over multiple days of drug products containing PG as an excipient. A 2014 report from the European Medicines Agency (EMA) regarding the use of PG as an excipient[1] cites the report by Speth et al[2] for a dose escalation study of mitoquidone, in which the drug product had PG as an excipient. in this study, patients with cancer received PG at doses of up to 15 g/m^2 as a 4-hour IV infusion once every 3 weeks. This resulted in Cmax exposures as high as 425 μg/mL (42.5 mg/dL). There was no evidence of lactic acidosis or associated renal toxicity in this study.

The following information is contained in the Nonclinical Review for this application: "On a mg/m^2 basis humans would receive no more than approximately 8 g/m^2 delivered during the recommended 10-minute infusion at the maximum anticipated level of 15.6 g, though a more likely high dose would be no more than approximately 10 g, or 5.5 g/m^2, based on typical calculations using an average BSA of 1.8 m^2 rather than 3".

Reviewer comment: The anticipated maximum dose of 8 g/m^2 is well below the highest dose of 15 g/m^2 PG administered in the Speth trial. Given this and once every 3-week dosing of PEMFEXY, lactic acidosis and renal toxicity due to PG are not expected to be associated with use of this product.

3) Cardiovascular effects with "rapid infusions"

As referenced by the Applicant in a September 28, 2017 response to information request from the FDA, the 2014 EMA report cites several publications describing cardiovascular effects of PG at different dose levels in nonclinical studies. One study from the mid-1970s reports antiarrhythmic effects observed in rats and dogs following IV injection of PG at doses between 193 to 289 mg/kg.[3] Another study from the mid-1980s specifically evaluated the cardiovascular effects of PG administered to dogs as an IV injection at doses of 160, 400, and 800 mg/kg. Results from this second study showed transient decrease in heart rate and blood pressure at a dose ≥400 mg/kg, with values returning to normal within 1 minute of PG administration.[4]

Reviewer comment: These reports from nonclinical studies are for PG administered as an injection. PEMFEXY is administered as an IV infusion over 10 minutes. Literature searches performed by the clinical reviewer and the clinical team lead revealed no clinical case reports of sudden death clearly or likely related to receipt of propylene glycol as an excipient.

The 2014 EMA report regarding PG as an excipient concludes "the safe maximum daily dose of PG for adults is 500 mg /kg". [1] In a letter dated October 2, 2017 Eagle Pharmaceuticals confirmed that the maximum level of PG to be delivered at the maximum expected pemetrexed dose of 1500 mg is 15.6 g, which is equivalent to approximately 222 mg/kg, which is less than half the maximum daily dose considered safe for adults per the EMA report.

The FDA Inactive Ingredient Database (IID) for Drug Products includes a maximum potency of 30% for propylene glycol administered as an administered as an intravenous infusion.[5] The anticipated maximum potency of PG Pemetrexed Injection for the expected highest total dose of 1,500 mg of pemetrexed, administered IV as a 100-mL admixture over a 10-minute infusion to a very large patient with 3 m^2 BSA, is 15.6%. This potency of 15.6% is approximately 50% lower than the IID-allowed maximum potency for an IV infusion (30%), and approximately one fifth of the maximum potency IID-allowed for an IV injection (82.04%).

Reviewer comment: The dose of PG in Eagle's prepared PEMFEXY product is within the safety limits defined by both the FDA and the EMA.

Pharmacovigilance

On September 28, 2017, Eagle submitted for FDA review a copy of their standard operating procedure (SOP) for pharmacovigalence.

Reviewer comment: Eagle's SOP requires that all unexpected or severe adverse reactions be reported to the FDA in a timely manner, according to severity and appears adequate to detect potential adverse reactions related to the use of PG as an excipient in this product.

References:

1. European Medicines Agency. Background review for the excipient propylene glycol. November 20, 2014, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/12/WC500177937.pdf Accessed on September 28, 2017.
2. Speth P and Vree T. Propylene glycol pharmacokinetics and effects after intravenous infusion in humans. Therapeutic Drug Monitoring, 1987, 9:255-258.
3. Eichbaum FW and Yasaka WJ. Antiarrhythmic effect of solvents: propylene glycol, benzyl alcohol. Basic Res Cardiology, 1976, 71:355-370.
4. Al-Khudhairi D and Whitman JG. Autonomic reflexes and the cardiovascular effects of propylene glycol. Br J Anaesth, 1986, 58:897-902.
5. U. S. Food and Drug Administration. Inactive Ingredient Search for Approved Drug Products. Available at: https://www.accessdata.fda.gov/scripts/cder/iig/getiigWEB.cfm Accessed on October 3, 2017.

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/s/

BARBARA A SCEPURA
10/20/2017

ERIN A LARKINS
10/20/2017