CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209472Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 209472
Supporting document/s:	0032
Applicant's letter date:	August 9, 2019
CDER stamp date:	August 9, 2019
Product:	Pemfexy (pemetrexed injection)
Indication:	Same indications as the Listed Drug, Alimta
Applicant:	Eagle
Review Division:	Division of Hematology Oncology Toxicology (Division of Oncology Products 2)
Reviewer:	Whitney S. Helms, PhD
Supervisor/Team Leader:	Whitney S. Helms, PhD
Division Director:	John Leighton, PhD (Patricia Keegan, MD)
Project Manager:	Meredith Libeg for Autumn Zack-Taylor

Pharmacology/Toxicology Labeling Review:

Eagle Pharmaceuticals submitted a Class 1 Resubmission for Pemfexy (pemetrexed injection). Eagle previously submitted this NDA for approval on December 30, 2016 and FDA granted a tentative approval on October 26, 2017 with final approval dependent on expiring patent and exclusivity periods and the lack of changes/new information/ new manufacturing or inspection issues at the end of these periods. No new nonclinical studies were submitted to support the current submission and major labeling recommendations from the pharmacology/toxicology perspective were included with the original approval. The Applicant submitted an updated label with the current resubmission. Current FDA recommendations were based on the original label with revisions to maintain consistency with the most current labeling practices. For a full assessment of the nonclinical data used to support the tentative approval and initial labeling, refer to the original NDA review by M. Anwar Goheer, PhD. From a pharmacology/toxicology perspective there are no new issues since the tentative approval that would prevent final approval of Pemfexy for treatment of the intended patient populations.

Pemfexy Label:

The Applicant Proposed	FDA Recommends	Reasoning
Embryo-Fetal Toxicity Based on findings from animal studies and its mechanism of action, pemetrexed can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, intravenous administration of pemetrexed to pregnant mice during the period of organogenesis was teratogenic, resulting in developmental delays and increased malformations at doses lower than the recommended human dose of 500 mg/m^2. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with PEMFEXY and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during	**Embryo-Fetal Toxicity** Based on findings from animal studies and its mechanism of action, PEMFEXY can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, intravenous administration of pemetrexed to pregnant mice during the period of organogenesis was teratogenic, resulting in developmental delays and increased malformations at doses lower than the recommended human dose of 500 mg/m^2. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with PEMFEXY and for 6 months after the final dose. Advise males with female partners of reproductive potential	FDA made minor revisions to maintain consistency with current labeling practices. Eagle accepted all changes

treatment with PEMFEXY and for 3 months after the final dose *[see Use in Specific Populations (0, **Error! Reference source not found.**)* (b) (4) *(0)]*.	to use effective contraception during treatment with PEMFEXY and for 3 months after the final dose *[see Use in Specific Populations (0, **Error! Reference source not found.**)]*	
8.1 Pregnancy Risk Summary Based on findings in animal studies and its mechanism of action, pemetrexed can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (0)]*. There are no available data on pemetrexed use in pregnant women. In animal reproductive studies, intravenous administration of pemetrexed to pregnant mice during the period of organogenesis was teratogenic, resulting in developmental delays and malformations at doses lower than the recommended human dose of 500 mg/m^2 *[see Data]*. Advise pregnant women of the potential risk to a fetus. *[see use in Specific Population (**Error! Reference source not found.**)]* In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%,	**8.1 Pregnancy** Risk Summary Based on findings from animal studies and its mechanism of action, PEMFEXY can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (0)]*. There are no available data on pemetrexed use in pregnant women. In animal reproduction studies, intravenous administration of pemetrexed to pregnant mice during the period of organogenesis was teratogenic, resulting in developmental delays and malformations at doses lower than the recommended human dose of 500 mg/m^2 *(see Data)*. Advise pregnant women of the potential risk to a fetus *[see use in Specific Population (**Error! Reference source not found.**)]*. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. Data *Animal Data*	FDA only made formatting changes; Eagle accepted

respectively. Data *Animal Data* Pemetrexed was teratogenic in mice. Daily dosing of pemetrexed by intravenous injection to pregnant mice during the period of organogenesis increased the incidence of fetal malformations (cleft palate; protruding tongue; enlarged or misshaped kidney; and fused lumbar vertebra) at doses (based on BSA) 0.03 times the human dose of 500 mg/m^2. At doses, based on BSA, greater than or equal to 0.0012 times the 500 mg/m^2 human dose, pemetrexed administration resulted in dose-dependent increases in developmental delays (incomplete ossification of talus and skull bone; and decreased fetal weight).	Pemetrexed was teratogenic in mice. Daily dosing of pemetrexed by intravenous injection to pregnant mice during the period of organogenesis increased the incidence of fetal malformations (cleft palate; protruding tongue; enlarged or misshaped kidney; and fused lumbar vertebra) at doses (based on BSA) 0.03 times the human dose of 500 mg/m^2. At doses, based on BSA, greater than or equal to 0.0012 times the 500 mg/m^2 human dose, pemetrexed administration resulted in dose-dependent increases in developmental delays (incomplete ossification of talus and skull bone; and decreased fetal weight).	
8.2 Lactation Risk Summary Risk Summary There is no information regarding the presence of pemetrexed or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed infants from pemetrexed, advise women not to breastfeed during treatment	**8.2 Lactation** Risk Summary There is no information regarding the presence of pemetrexed or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed infants from PEMFEXY, advise women not to breastfeed during treatment with PEMFEXY and	No changes

with PEMFEXY and for one week after last dose.	for one week after last dose.	
8.3 Females and Males of Reproductive Potential *Females* Pemetrexed can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (0)]*. Because of the potential for genotoxicity, advise females of reproductive potential to use effective contraception during treatment with PEMFEXY for at least 6 months after the final dose (b) (4). *Males* Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with PEMFEXY and for 3 months after the final dose *[see Nonclinical Toxicology (0)]*. Infertility *Males* Pemetrexed may impair fertility in males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Nonclinical Toxicology (0)]*.	**8.3 Females and Males of Reproductive Potential** Pregnancy Testing Verify pregnancy status of females of reproductive potential prior to initiating PEMFEXY *[see Use in Specific Populations (0)]*. Contraception *Females* PEMFEXY can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (0)]*. Because of the potential for genotoxicity, advise females of reproductive potential to use effective contraception during treatment with PEMFEXY and for 6 months after the final dose. *Males* Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with PEMFEXY and for 3 months after the final dose *[see Nonclinical Toxicology (0)]*. Infertility *Males* PEMFEXY may impair fertility in males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Nonclinical Toxicology (0)]*.	Pregnancy Testing statement added consistent with current labelling practices and PLLR.

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12.1 Mechanism of Action Pemetrexed is a folate analog metabolic inhibitor that disrupts folate-dependent metabolic processes essential for cell replication. In vitro studies have shown that pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is taken into cells by membrane carriers such as the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are inhibitors of TS and GARFT.	**12.1 Mechanism of Action** Pemetrexed is a folate analog metabolic inhibitor that disrupts folate-dependent metabolic processes essential for cell replication. In vitro studies show that pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is taken into cells by membrane carriers, such as the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are inhibitors of TS and GARFT.	No changes
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility No carcinogenicity studies have been conducted with pemetrexed. Pemetrexed was clastogenic in an in vivo micronucleus assay in mouse bone marrow but was not mutagenic in multiple in vitro	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** No carcinogenicity studies have been conducted with pemetrexed. Pemetrexed was clastogenic in an in vivo micronucleus assay in mouse bone marrow but was not mutagenic in multiple in vitro tests (Ames assay, Chinese Hamster Ovary cell assay).	No changes

tests (Ames assay, Chinese Hamster Ovary cell assay). Pemetrexed administered intraperitoneally at doses of ≥0.1 mg/kg/day to male mice (approximately 0.006 times the recommended human dose based on BSA) resulted in reduced fertility, hypospermia, and testicular atrophy.	Pemetrexed administered intraperitoneally at doses of ≥0.1 mg/kg/day to male mice (approximately 0.006 times the recommended human dose based on BSA) resulted in reduced fertility, hypospermia, and testicular atrophy.	

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/s/

WHITNEY S HELMS
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	209472
Supporting document/s:	NDA 021462
Applicant's letter date:	December 30, 2016
CDER stamp date:	December 30, 2016
Product:	Pemetrexed Injection (PEMFEXY)
Indication:	Advanced or metastatic nonsquamous non-small cell lung cancer (NSCLC) and Mesothelioma in combination with cisplatin (same as Alimta)
Applicant:	Eagle Pharmaceuticals, Inc.
	50 Tice Boulevard, Woodcliff Lake,
	New Jersey 07677, USA
Review Division:	Division of Hematology Oncology Toxicology
	(Division of Oncology Products 2)
Reviewer:	M. Anwar Goheer, Ph.D.
Supervisor/Team Leader:	Whitney S. Helms, Ph.D.
Division Director:	John Leighton, Ph.D., D.A.B.T.
	(Patricia Keegan, M.D.)
Project Manager:	Autumn Zack-Taylor

Disclaimer
Except as specifically identified, all data and information discussed below and necessary for approval of NDA 209472 are owned by Eagle Pharmaceuticals or are data for which Eagle Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of NDA 209472 that Eagle Pharmaceuticals does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 209472.

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1 Executive Summary

1.1 Introduction:

Eagle Pharmaceuticals has submitted NDA 209472 for PEMFEXY (Pemetrexed Injection) under the 505(b)(2) pathway and is relying primarily on FDA's prior findings of safety and effectiveness for the listed drug Alimta to support the pharmacology and toxicology requirements for a new drug application. Pemetrexed Injection is a ready-to-dilute formulation of pemetrexed with different excipients than the listed drug, Alimta. Eagle has submitted limited pharmacokinetic and toxicology studies comparing its Pemetrexed Injection (PEMFEXY) to Alimta in order to help support the safety of the formulation and to qualify any novel impurities present in the Eagle pemetrexed formulation.

1.2 Brief Discussion of Nonclinical Findings

Pemetrexed is a folate analog metabolic inhibitor that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. The Applicant conducted several pharmacology/toxicology studies comparing the two products to help support the safety of the differences in formulation, including high levels of propylene glycol, and to qualify impurities in the Eagle product at levels above the ICHQ3B limits.

To investigate whether changes to the formulation would result in any changes in plasma protein binding which might affect the PK of the active pharmaceutical ingredient (API), pemetrexed, the Applicant tested pemetrexed injection and Alimta at final assay concentrations of 10, 100, and 1000 µg/mL in an equilibrium dialysis assay system. Results showed that protein binding of Pemetrexed Injection and Alimta to human plasma, human serum albumin, and human α1-acid glycoprotein was comparable. In a safety study investigating the hemolytic potential of the Eagle formulation of pemetrexed, Pemetrexed Injection diluted in 5% Dextrose Injection to 15 mg/mL 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.

The toxicities of pemetrexed injection compared to Alimta were assessed in a repeat dose toxicity study in Crl:CD1 (IRC) mice. Animals (15/sex/group) received 315 mg/kg (945 mg/m^2) of pemetrexed injection or Alimta given once weekly for a total of 7 doses. While several deaths occurred in the pemetrexed injection and vehicle arms, the pathologist attributed these deaths to the infusion procedure rather than the drug and no treatment-related effects were noted in body weight, food consumption, clinical observations, and ophthalmic examinations in either early death animals or animals that survived until sacrifice. Similar procedural deaths also occurred in Alimta-treated animals in the toxicokinetic groups. No propylene glycol was present in the vehicle control formulation, suggesting that the high levels of this excipient were also not related to these mortalities. Clinical pathology findings were generally comparable between the pemetrexed injection and Alimta groups. Findings included minor hepatocellular effects in pemetrexed-treated females indicated by mild increases in alanine aminotransferase

(ALT) and aspartate aminotransferase (AST) activities, as well as minimal to mild decreases in neutrophil and/or lymphocyte counts in both sexes of the Alimta-treated group and in females in the pemetrexed injection-treated group. Treatment-related changes occurred in the testes and epididymides of mice given Alimta or pemetrexed injection; the incidence and intensity of these findings were comparable for both groups and correlated with reduction in testes weights.

Systemic exposure (C_{max} and $AUC_{0\text{-}24hr}$) following once weekly IV administration of pemetrexed injection or Alimta for seven doses was similar between the two treatment groups. Overall, the results of this study were comparable to those results previously reported for pemetrexed and indicate that pemetrexed injection administered weekly for seven doses is comparable to Alimta administered weekly for seven doses. No clear pemetrexed injection-related local tolerance effects or impurity-related toxicities (Section 2.5) were observed in this study, providing safety data to support the requested specifications.

From a pharmacology/toxicology perspective the submitted studies are supportive of the comparability of pemetrexed-related toxicity and exposure between the listed drug and Eagle's pemetrexed injection and sufficient to support the final impurity specifications. While the nonclinical data is also reasonably supportive of the safety of the high levels of propylene glycol included in this formulation of pemetrexed, there is clinical data in the literature suggesting that such high levels of propylene glycol may represent an added risk to patients. While there is no additional nonclinical data needed to support this formulation, given the literature suggesting the potential for propylene glycol mediated toxicity (primarily metabolic acidosis and hyperosmolarity, and sequalae of those toxicities) at clinical pharmacokinetic concentrations above 25 mg/dL[1], and potential propylene glycol Cmax concentrations that exceed this level even in patients with a small BSA at the recommended pemetrexed injection dose of 500 mg/m^2, a determination of the safety of the levels of propylene glycol in the currently proposed formulation cannot be made on the basis of nonclinical data alone.

1.3 Recommendations

1.3.1 Approvability

There are no outstanding issues from a pharmacology/toxicology perspective that would prevent approval of Pemfexy.

1.3.2 Additional Non Clinical Recommendations

None

[1] Background Review for the Excipient Propylene Glycol, European Medicines Agency (EMA) Report, 20 November 2014

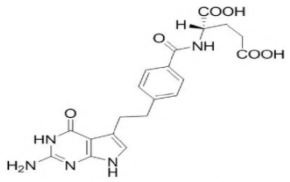
1.3.3 Labeling

The nonclinical recommendations to the Applicant's proposed labeling are primarily based on the listed drug, were discussed internally, and will be communicated to the Applicant.

2 Drug Information

2.1 Drug

Generic Name
Pemetrexed Injection
Code Name
None
Chemical Name
N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid
Molecular Formula/Molecular Weight
$C_{20}H_{21}N_5O_6$ / 427.41
Structure or Biochemical Description:



Pharmacologic Class: Folate antimetabolite

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 021462

2.3 Drug Formulation

Table 1: Composition of Pemetrexed Injection, 25 mg/mL (500 mg/vial)

Ingredient	Quality Standard	Amount per Vial (mg)	Concentration (mg/mL)	Function
Pemetrexed[a]	In-House	500	25	Active Ingredient
Propylene Glycol	USP/EP	5,200	260	
Tromethamine	USP/EP	pH adjustment to	(b) (4	
Hydrochloric Acid	NF/EP	pH adjustment to		
Water for Injection	USP/EP		(b) (4	
			(b) (4	

(b) (4)

Composition after Reconstitution for Alimta and before Dilution for Eagle's Proposed Drug Product (500 mg vial)	Pemetrexed 25 mg/mL Propylene Glycol 260 mg/mL Tromethamine pH adjustment Hydrochloric Acid pH adjustment WFI qs. to volume

(b) (4)

(Excerpted from Applicant's submission)

2.4 Comments on Novel Excipients

The maximum level of tromethamine to be delivered at the maximum pemetrexed dose of 1500 mg is (b) (4). This amount of tromethamine is significantly lower than the dose given as a drug for acidosis (Tham), which is (b) (4). Thus, there is sufficient clinical safety data to justify the potential levels of tromethamine administered in Pemetrexed Injection.

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). In an email communication on September 15, 2017, the Applicant confirmed that PG was present in the pemetrexed injection formulation used in their comparative mouse toxicology study (b) (4) and, in a follow-up communication on September 25, 2017, that PG was not present in the vehicle control administered in the same study. In the Applicant's toxicology study mice received 21 mL/kg of pemetrexed—which would result in approximately 98 mg of PG using an average mouse weight of 30 g (21 mL/kg*0.03 kg=0.63 mL; 0.63 mL* 156 mg/mL PG= 98 mg PG) or approximately 9.8 g/m^2 (3200 mg/kg),. Per the protocol, injections in this toxicology study occurred over 5 minutes. Compared to the listed drug, there were no significant differences in clinical observations or changes in clinical chemistry recorded in this study; while transient changes in clinical chemistry immediately after infusion cannot be excluded based on the study design, no effects were apparent by scheduled sacrifice. 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, based on typical calculations using an average BSA of 1.8m^2 rather than 3. Thus, there is nonclinical data with the formulation to support the high levels of PG delivered in the 10 minute time interval, though based on the EMA background review for propylene glycol[1], saturation of propylene glycol metabolism occurs at lower doses for humans than for rats/rabbits (0.2 g/kg vs. 2 g/kg, respectively). In response to a nonclinical information request, the Applicant submitted additional supportive nonclinical information based on literature reports that LD_{50s} for IV administration of propylene glycol in multiple animal species occurred at doses greater than 6 g/kg (**Error! Reference source not found.**), or approximately 36 g/m^2 in rats, 18 g/m^2 in mice.

Table 2: LD_{50s} for PG

Animal Species	EMA Report (mg/kg)	Expert Panel Report (mg/kg)	(b) (4) (mg/kg)
Mouse	5,000-8,000	6,081	N.A
Rabbit	4,000-6,000	N.A.	6,500
Rat	N.A.	5,985	6,800

N.A.: not applicable

(Excerpted from Applicant's submission)

There is, however, also clinical data regarding PG administration by the IV route available in the published scientific literature. At a PG dose of 213 g/day for 7 days given by continuous infusion (1699 g total) some clinical toxicity (confusion,

hyperosmolality, lactic acidosis, and acute kidney injury) occurred, but the effects were recoverable[2]. In the same review documenting this clinical high dose PG toxicity, animal LD_{50} doses were (b) (4) g/kg by oral administration in all species tested. The 2014 EMA review on propylene glycol toxicity suggests limits in patients ≥5 years old of up to 500 mg/kg/day based on clinical data described by Yaucher et al[3] and Yahwak et al[4]. This document also refers to a study described by Speth et al[5],[6] in which patients with cancer received propylene glycol at a once every 3 week dose of up to 15 g/m^2 over a 4 hour IV infusion resulting in Cmax exposures as high as 425 µg/mL (42.5 mg/dL) as a part of a Phase 1 study of mitoquidone (600 mg/m^2) with no evidence of lactic acidosis, hemolysis, or increase in osmolarity.

2.5 Comments on Impurities/Degradants of Concern

The pharmacology/toxicology team received questions from the CMC review team regarding the safety of the levels propylene glycol (PG) and tromethamine that will be delivered to patients at the maximum pemetrexed dose in the Eagle formulation as well as questions about the justification of the specifications for Impurities (b) (4) in the drug product. Impurities (b) (4) were present at levels of (b) (4)% in the toxicology batch for the Pemetrexed Injection lot used in the repeat dose toxicology study comparing Pemetrexed Injection and Alimta. There were no clear differences in toxicity between animals treated weekly with Pemetrexed Injection versus Alimta at doses approximately twice the recommended once every 3 weeks human dose in this study and no drug-related deaths (reviewed below). For this reason, the proposed specifications for Impurities (b) (4) of no more than (b) (4)% are justified based on the submitted nonclinical data.

The Applicant identified the structure of Impurities (b) (4) as stereoisomers of a published metabolite of pemetrexed. This pemetrexed metabolite is present following administration of the drug in both animal and human samples at levels higher than the proposed specification of no more than (b) (4)%. Consistent with the recommendations in

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[2] Fowles JR, Banton MI, Pottenger LH. A toxicological review of the propylene glycols. Crit Rev Toxicol. 2013 Apr;43(4):363-90.

[3] Yaucher, N. and Fish, J. (2003). Propylene Glycol-Associated Renal Toxicity from Lorazepam Infusion. Pharmacotherapy 23, 1094–1099.

[4] Yahwak, J., Riker, R. and Fraser, G. (2008). Determination of a lorazepam dose threshold for using the osmol gap to monitor for propylene glycol toxicity. Pharmacotherapy 28, 984–991.

[5] Speth, P. and Vree, T. (1987). Propylene glycol pharmacokinetics and effects after intravenous infusion in humans. Therapeutic drug monitoring 9, 255–258.

[6] Speth P, Gore M, Pateman A, Newell D, Bishop J, Ellis W, Gumbrell L, Linssen P, Miller A, Smith I, McVie G, de Mulder P, de Pauw B, Griggs J, and Brown G (1988). Phase I and pharmacokinetic studies with the pentacyclic pyrroloquinone mitoquidone. Cancer Chemother Pharmacol. 21(4):343-6.

ICH S9, no further nonclinical qualification is necessary to support the safety of the 0.6% specification for this metabolite.

3 Studies Submitted

3.1 Studies Reviewed

PHARMACOKINETICS/TOXICOKINETICS
Distribution

1. Pemetrexed Injection: Human Plasma Protein Binding Study. (b) (4) Study Number 1773-040, Sponsor Study Number EGL-PTX-NC-1602.

TOXICOLOGY
Repeat-dose toxicity

1. Pemetrexed Injection: A 6 Week Intravenous Impurity Qualification Toxicity Study in Male and Female Mice. (b) (4) Study Number: 1773-032, Sponsor Study Number EGL-PTX-NC-1601.

Special toxicology studies

1. Pemetrexed Injection in 5% Dextrose: Hemolytic Potential and Plasma Compatibility of Pemetrexed Injection in Human Whole Blood (GLP). (b) (4) Study Number MP20SY.

3.2 Studies Not Reviewed

1. Validation of a Method for the Determination of Pemetrexed in Mouse Plasma by HPLC with MS/MS detection.
2. Comparison of Pharmacokinetics and Tolerability of Alimta (Pemetrexed) Following Intraperitoneal and Intra Venous Dosing To Male CD-1 Mice. (b) (4) (b) (4) Study Number 1773-029.

3.3 Previous Reviews Referenced

None

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME:

Distribution

Study title: Pemetrexed Injection: Human Plasma Protein Binding Study.
Study no.: (b) (4)
Study report location: eCTD
Conducting laboratory and location: (b) (4)

(b) (4)

Date of study initiation:	September 19, 2016
GLP compliance:	No
QA statement:	Yes
Drug, lot #, and % purity:	Pemetrexed Injection (25 mg/mL), lot # EPD002,
Formulation/Vehicle:	5% Dextrose Injection

Key Study Findings

- Protein binding of Pemetrexed Injection and Alimta to human plasma, human serum albumin, and human α1-acid glycoprotein were comparable
- Pemetrexed Injection and Alimta demonstrated a similar concentration-dependent decrease in percent binding to human plasma proteins

Methods

The Applicant determined binding of both Pemetrexed Injection and the comparator article, Alimta, to human plasma, human serum albumin, and human α-1 acid glycoprotein by rapid equilibrium dialysis at 37°C for 4 hours. The Applicant demonstrated the stability of pemetrexed injection in PBS and each of the human protein solutions prior to analysis of specific binding at concentrations of approximately 6 µg/mL and 600 µg/mL. Recovery was generally ≥90% in all conditions tested over the 4 hour time period at each concentration, suggesting low non-specific binding to the apparatus under the conditions tested.

Observations and Results

Table 3: Protein Binding of Pemetrexed Injection and Alimta in Human Plasma

Concentration (µg/mL)	% Bound	
	Pemetrexed	Alimta
10	86.7	86.6
100	85.4	86.4
1000	64.8	63.2

Table 4: Protein Binding of Pemetrexed Injection and Alimta in Human Albumin

Concentration (µg/mL)	% Bound	
	Pemetrexed	Alimta
10	90.9	90.9
100	89.5	89.2
1000	70.4	70.7

Table 5: Protein Binding of Pemetrexed Injection and Alimta in Human α1-Acid Glycoprotein

Concentration (µg/mL)	% Bound	
	Pemetrexed	Alimta
10	29.3	35.0
100	30.8	31.0
1000	31.5	26.6

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: Pemetrexed Injection: A 6 Week Intravenous Impurity Qualification Toxicity Study in Male and Female Mice.

Study no.: (b) (4)

Study report location: eCTD

Conducting laboratory and location: (b) (4)

Date of study initiation: May 3, 2016

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: Pemetrexed – lot # EPD002T, 95.5%purity; Impurity (b) (4) and Impurity (b) (4) – (b) (4) %
Alimta – lot # C514165A & C514163A,

Key Study Findings

- Weekly IV administration of 315 mg/kg (945 mg/m^2) Alimta or Pemetrexed Injection for 7 doses did not cause any mortality in mice.
- Clinical pathology and microscopic findings were similar among both groups
- Systemic exposure (C_{max} and $AUC_{0\text{-}24hr}$) was similar between the two treatment groups.

Methods

Doses: 315 mg/kg/week (945 mg/m^2)
Frequency of dosing: Weekly
Route of administration: IV, 5 minutes intravenous infusion
Dose volume: 21 mL/kg
Formulation/Vehicle: 5% Dextrose Injection
Species/Strain: Crl:CD1® (ICR) mice
Age: 12 – 14 weeks
Weight: Males - 31 to 39 g
Females 22 to 30 g

Satellite groups: Yes
Unique study design: No
Deviation from study protocol: None

Table 6: Treatment Groups

Group	Number of Animals		Treatment				Necropsy (Day 43)	
	M	F	Identity	Dose Level (mg/kg/week)	Conc. (mg/mL)	Dose Volume (mL/kg)	M	F
Main Study								
1	15	15	Control (5% Dextrose Injection)	0	0	21	15	15
2	15	15	Alimta	315	15		15	15
3	15	15	Pemetrexed Injection	315	15		15	15
Toxicokinetic[a]								
4	6	6	Control (5% Dextrose Injection)	0	0	21	-	-
5	15	15[b]	Alimta	315	15		-	-
6	15[c]	15	Pemetrexed Injection	315	15		-	-

Toxicokinetic groups were sampled on Day 43 for composite analysis by sex. For the Toxicokinetic groups, 6 animals/sex (control) or 15 animals/sex (treated groups) were dosed throughout the study. Control animals were bled at 0.0166 hours post end of infusion. For treated groups, 3/sex/group (total of 12 animal/sex) were bled at alternating time points (0.0166, 0.50, 1, 2, 4, 8, 12, and 24 hours post end of infusion).
[b]Animal 5502 (female Group 5) died on Day 8 and was replaced by animal 5513 for the Day 43 blood collections.
[c]Animal 6006 (male Group 6) died prior to bleeding on Day 43 and was replaced by animal 6013 for the Day 43 blood collections. Animal 6009 (male Group 6) died after the first scheduled blood collection on Day 43 and was replaced by animal 6014 for the second scheduled bleed on Day 43.

Observations and Results

Mortality: (twice daily)

No treatment-related deaths occurred. Accidental deaths attributed to the infusion procedure occurred in three control and two Pemetrexed Injection treated main study mice. There were no macroscopic or microscopic findings in any of these animals with the exception of pulmonary emboli without inflammatory reactions in one of the pemetrexed injected treated animals. Animals died shortly after infusion. Two Pemetrexed Injection-treated and one Alimta-treated toxicokinetic mice died during dose administration; these deaths were also attributed to infusion procedures.

Table 7: Summary of Mortality of mice

Main

Animal Number/ Sex	Dose Level (mg/kg/week)	Fate/ Animal Disposition	Fate Day	Cause of Death/Euthanasia
1003M	0	AD	15	Undetermined/Likely procedure related
3002M	315 Pemetrexed Injection	AD	29	Undetermined/Likely procedure related
3003M	315 Pemetrexed Injection	AD	15	Pulmonary Emboli/Likely procedure related
1506F	0	AD	36	Undetermined/Likely procedure related
1513F	0	AD	8	Undetermined/Likely procedure related
Toxicokinetic				
5502	Female	315 (Alimta)	8	Accidental death – died post dosing
6006	Male	315 (Pemetrexed Injection)	43	Accidental death – died post dosing
6009	Male	315 (Pemetrexed Injection)	43	Found dead – died after the first blood collection

(Excerpted from Applicant's submission)

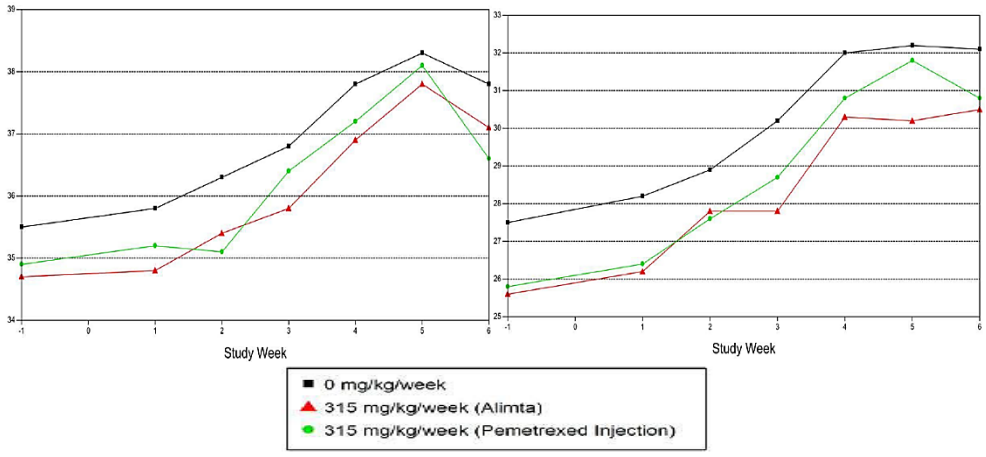
Clinical Signs: (daily)

Alimta group – Scar, skin discolored, swelling,
Pemetrexed group – Skin discolored, scabbed area

Body Weights; (weekly)

No treatment-related effects

Figure 1: Mean Body Weights of Male and Female Mice



(Excerpted from Applicant's submission)

Feed Consumption: (weekly)

No effect on food consumption

Ophthalmoscopy: (pretest and prior to terminal sacrifice)

No treatment related effects

Hematology: (scheduled sacrifice)

Alimta and Pemetrexed – Small and comparable decreases in neutrophil (maximum -35%) and/or lymphocyte (up to -31%) counts

Clinical Chemistry (scheduled sacrifice)

Alimta and Pemetrexed Injection increased ALT (up to +2.2x) and AST (up to 2.2x) comparably and with no microscopic correlates.

Urinalysis (scheduled sacrifice)

No effect

Gross Pathology

Table 8: Gross pathology

Dose (mg/kg/week	0		315 (Alimta)		315 (Pemetrexed)	
	DOS	SNC	DOS	SNC	DOS	SNC
Number Examined	1	14	0	15	2	13
Testes, small, mild	0	0	0	8	0	5

DOS – Died on study SNC – Scheduled Necropsy

Organ Weights

Treatment related decreases in testes and epididymides.

Table 9: Organ Weight Changes –Terminal Sacrifice

Dose level: mg/kg/week	0	315 (Alimta)		315 (Pemetrexed Injection)	
Number Examined	14	15		13*	
Mean Body Weight (g)	36.3	35.3	(↓2.75)	36.3	(0.00)
Testes (g)	0.270	0.103[b]	(↓61.85)	0.102[b]	(↓62.22)
Testes/BWt%	0.7429	0.2938[b]	(↓60.45)	0.2819[b]	(↓62.05)
Testes/BrWt ratio	0.5526	0.2107[b]	(↓61.87)	0.2119[b]	(↓61.65)
Epididymides (g)	0.112	0.089[a]	(↓20.54)	0.087[b]	(↓22.32)
Epididymides/BWt%	0.3071	0.2516[a]	(↓18.07)	0.2379[b]	(↓22.53)
Epididymides/BrWt ratio	0.2294	0.1817[a]	(↓20.79)	0.1805[b]	(↓21.32)

a - Significantly different from 0 mg/kg/week; ($p<0.05$)
b - Significantly different from 0 mg/kg/week; ($p<0.01$)
BWt - Body Weight; BrWt - Brain Weight
*A terminal body weight was not collected at necropsy for animal number 3006 and is excluded from the mean of n=13.

Histopathology

Adequate Battery: Yes
Peer Review: Yes

Table 10: Histological Findings

Dose (mg/kg/week	0		315 (Alimta)		315 (Pemetrexed)	
	DOS	SNC	DOS	SNC	DOS	SNC
Number Examined	1	14	0	15	2	13
Epididymides, oligospermia/germ cell debris, bilateral, minimal	0	0	0	15	2	13
Mild	0	0	0	0	2	0
Moderate	0	0	0	10	0	7
Testes, degeneration/atrophy, seminiferous tubules, bilateral, minimal	0	0	0	15	2	13
Mild	0	0	0	0	1	1
Moderate	0	0	0	10	0	7

DOS – Died on study SNC – Scheduled Necropsy

Special Evaluation: None

Toxicokinetics:

(0.017, 0.50, 1, 2, 4, 8, 12, and 24 hours postdose on Day 43)

Table 11: Toxicokinetics

Treatment	C_0 (µg/mL)	C_{max} (µg/mL)	T_{max} (hr)	T_{last} (hr)	AUC_{Tlst} (hr*µg/mL)	$AUC_{0\text{-}24hr}$ (hr*µg/mL)	EqR[a]	$T_{1/2}$[b] (hr)	Adjusted R^2[b]
Alimta	796	758	0.0166	8	467	468	NA	0.861	0.947
Pemetrexed Injection	681	656	0.0166	12	575	587	1.25	0.814	0.992

NA- Not Applicable
a: EqR for $AUC_{0\text{-}24hr}$ = $AUC_{Pemetrexed\ Injection} \div AUC_{Alimta}$
b: Half-life values ($T_{1/2}$) and adjusted Rsq values (R^2) determined using lambda z lower set to 0.5 hours and lambda z upper set to 8 hours

(Excerpted from Applicant's submission)

Histopathology inventory:

Study	1773-032
Species	Mice
Adrenals	X*
Aorta	X
Bone Marrow smear	X
Bone (femur)	X
Brain	X*
Cecum	X
Cervix	

Study	1773-032
Species	Mice
Colon	X
Duodenum	X
Epididymis	X*
Esophagus	X
Eye	X
Fallopian tube	
Gall bladder	X
Gross lesions	X
Harderian gland	
Heart	X*
Ileum	X
Injection site	X
Jejunum	X
Kidneys	X*
Lachrymal gland	X
Larynx	X
Liver	X*
Lungs	X
Lymph nodes, cervical	
Lymph nodes mandibular	X
Lymph nodes, mesenteric	X
Mammary Gland	X
Nasal cavity	
Optic nerves	X
Ovaries	X*
Pancreas	X
Parathyroid	X*
Peripheral nerve	
Pharynx	
Pituitary	X
Prostate	X*
Rectum	X
Salivary gland	X
Sciatic nerve	X
Seminal vesicles	X
Skeletal muscle	X
Skin	X
Spinal cord	X
Spleen	X*
Sternum	

Study	1773-032
Species	Mice
Stomach	X
Testes	X*
Thymus	X*
Thyroid	X*
Tongue	X
Trachea	X
Urinary bladder	X
Uterus	X
Vagina	X
Zymbal gland	

X, histopathology performed
*, organ weight obtained

10 Special Toxicology Studies

Study title: Pemetrexed Injection in 5% Dextrose: Hemolytic Potential and Plasma Compatibility of Pemetrexed Injection in Human Whole Blood (GLP)

Study no.: (b) (4) Study Number MP20SY.
Study report location: electronic
Conducting laboratory and location: (b) (4)
Date of study initiation: August 8, 2016
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Pemetrexed Injection, lot # EPD002, 98.7% pure,
Alimta, lot # C503573A and C568247A

Key Study Findings

- The hemolytic potential and plasma compatibility of Pemetrexed Injection (test) and Alimta (comparator) were negative and no differences were detected.

Observations and Results

Table 12: Hemolytic potential of Pemetrexed and Alimta

Tube	Contents	Mean Hb Concentration (g/dL)	% Hemolysis*
1	Human Whole Blood + (TA) Pemetrexed Injection in 5% Dextrose (15 mg/mL)	0.0	0.0
2	Human Whole Blood + (CA) Alimta® in 0.9% Sodium Chloride (15 mg/mL)	0.0	0.0
3	0.9% Sodium Chloride + (TA) Pemetrexed Injection in 5% Dextrose (15 mg/mL)	0.0	0.0
4	Human Whole Blood + 5% Dextrose (Vehicle Control)	0.0	0.0
5	Human Whole Blood + 0.9% Sodium Chloride (Negative Control)	0.0	0.0
6	Human Whole Blood + 1% Saponin (Positive Control) + 0.9% Sodium Chloride	5.5 ± 0.2	86.6
7	Human Whole Blood (Untreated Control)	0.0	0.0
8	0.9 Sodium Chloride + (CA) Alimta® in 0.9% Sodium Chloride (15 mg/mL)	0.0	0.0

Hb = Hemoglobin Hct = Hematocrit CA = comparator article TA = test article
* Calculated as: [(Mean Hb/Total donor Hb)*dilution factor (2)] *100

Table 13: Plasma Compatibility

Tube No.	Contents	Mean OD (600 nm)	Ratio*	Interpretation
Assays (13-Sep-16)				
1	Human Plasma + (TA) Pemetrexed Injection in 5% Dextrose (15 mg/mL)	0.067	0.9	Negative
2	Human Plasma + (CA) Alimta® in 0.9% Sodium Chloride (15 mg/mL)	0.061	1.0	Negative
3	Water + (TA) Pemetrexed Injection in 5% Dextrose (15 mg/mL) (IC)	0.048	-	
4	Water + (CA) Alimta® in 0.9% Sodium Chloride (15 mg/mL) (IC)	0.041	-	
5	Human Plasma + 0.9% Sodium Chloride (NC)	0.061	1.5	Negative
6	Human Plasma + 5% Dextrose (VC)	0.067	1.3	Negative
7	Water + 0.9% Sodium Chloride (IC)	0.040	-	
8	Water + 5% Dextrose (IC)	0.040	-	
9	Human Plasma + 0.5% Sulfosalicylic Acid (PC)	1.763	82.1	Positive
10	Water + 0.5% Sulfosalicylic Acid (IC)	0.039	-	

Protocol criteria:

Positive control ratio > 6.3
NC/NIC Ratio < 3.15
Positive Interpretation ratio > 1.7
Negative Interpretation ratio ≤ 1.7

Key to table:

* Ratio = NC/NIC (for controls) NIC = Negative interference control
Ratio = (Sample OD - Sample IC)/MNC (for study samples)
MNC = Mean negative corrected OD value (NC-NIC)
a = Did not meet run acceptance criteria OD = Optical density
CA = Comparator article PC = Positive control
IC = Interference Control Pos = Positive
NC = Negative control TA = Test article
Neg = Negative VC = Vehicle control

12 Appendix/Attachments: None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

M A GOHEER
10/02/2017

WHITNEY S HELMS
10/03/2017

Eagle Pharmaceuticals has submitted a marketing application for PEMFEXY (pemetrexed injection) under the 505(b)(2) pathway, identifying ALIMTA as the listed drug. Under this pathway, only minimal nonclinical safety data was required or submitted; however the Applicant did conduct a GLP-compliant repeat-dose study in mice comparing the proposed formulation and the listed drug to help support the safety of the proposed formulation and to qualify the proposed impurity specifications. Through this study, the Applicant has also provided some justification for the proposed levels of propylene glycol to be delivered to patients in PEMFEXY. While this study in mice does provide minimal coverage for the proposed levels of propylene glycol, I concur with Dr. Goheer's conclusion that given the reasonably extensive literature describing clinical concerns with high levels of propylene glycol, a final determination of the safety of the proposed amount cannot be made on the basis of nonclinical data alone. There are no additional nonclinical studies that would adequately address any outstanding clinical concerns with the levels of propylene glycol in the proposed formulation. With this caveat, I concur with Dr. Goheer's conclusion that there are no outstanding issues from a nonclinical perspective that would prevent approval of PEMFEXY under the 505(b)(2) pathway.