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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

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