CENTER FOR DRUG EVALUATION AND RESEARCH

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.

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

/s/

BARBARA A SCEPURA
10/02/2019 11:06:04 AM

ERIN A LARKINS
10/02/2019 12:20:53 PM

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.