CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214218Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

Date: May 10, 2022
From: G. Sachia Khasar, PhD
Pharmacology/Toxicology Reviewer
Division of Hematology Oncology Toxicology for Division of Oncology 2
Through: Claudia P. Miller, PhD
Acting Supervisory Pharmacologist
Division of Hematology Oncology Toxicology for Division of Oncology 2
To: File for NDA 214218
Re: Pharmacology and Toxicology

Hospira, Inc. (Hospira) resubmitted NDA 214218 for Pemetrexed Injection, on December 22, 2021, after it was initially given a tentative approval due to exclusivity regarding the reference listed drug, ALIMTA. As with the initial submission, Hospira relied on a prior FDA finding of safety and effectiveness for ALIMTA (NDA 21462). No new nonclinical data was submitted with the resubmission.

During the first review cycle (April 23, 2020), the Nonclinical review team responded to a request from the CMC review team regarding the acceptability of the levels of three potential leachables (from samples stored for up to 12 months) in Pemetrexed Injection. The Nonclinical team determined there were no concerns with levels of potential leachables (refer to Dr. M. Anwar Goheer's review uploaded to DARRTs on January 29, 2021).

In the current resubmission, the Applicant identified additional potential leachables in Pemetrexed Injection (Table 1) in a leachable study testing the container closure system, consisting of the (b) (4) glass vial, the (b) (4) rubber stopper and the aluminum seal with (b) (4) top of the 100 mg/4mL format of Pemetrexed Injection to represent the worst-case scenario. The CMC reviewer consulted with the Nonclinical team regarding the potential risk of the additional leachables that were above the safety concern threshold (SCT) of 1.5 μg/day in samples stored for up to 24 months. Based on information provided by the Applicant on May 10, 2022 (supporting document 24), the risk assessment for mutagenic potential was done by Quantitative Structure-Activity Relationships ((Q)SAR) prediction methodologies and literature of toxicological information and concluded that the leachables posed negligible risk to humans, (b) (4) (b) (4). Per risk assessment, analytical constraints prevented determination of individual levels of leachables identified (b) (4). As a result, a total daily intake was calculated based on the total value of each class (b) (4) Pemetrexed Injection is given once every 21 days, therefore, the approximate daily dose for the (b) (4) would be (b) (4) (b) (4) respectively; thus, the daily dose for each

individual leachable under these classes is less than [(b) (4)] µg. This dose is within the acceptable dose of ≤5 µg/day for non-mutagenic [(b) (4)] leachables for parenterally administered (IV and SC) drugs[1].

Based on the data provided by the Applicant, [(b) (4)] showed a plausible mutagenicity alert by QSAR (Derek) and was weakly mutagenic in an Ames assay; while [(b) (4)] had a plausible mutagenicity alert by QSAR. The estimated total daily intake [(b) (4)] [(b) (4)]. Thus, the total daily intake of [(b) (4)] based on the Pemetrexed Injection administration schedule is below the 1.5 µg dose for a mutagenic leachable. Moreover, the Applicant states that structurally similar compounds [(b) (4)] were negative for genotoxicity in in vivo bone marrow micronucleus and liver and duodenum comet assays. Also, structurally similar compounds [(b) (4)] [(b) (4)] were non-mutagenic in in vitro Ames assay, suggesting that the mutagenic potential of [(b) (4)] is low. Importantly, since pemetrexed is genotoxic, there is no concern that arises from levels of these compounds that can leach into Pemetrexed Injection.

In summary, although additional leachables with SCT >1.5 µg/day were identified at the 24-month time point, most of them were non-mutagenic. Five of the [(b) (4)] and one of the [(b) (4)] were identified as [(b) (4)] based on in silico prediction and existing literature but individual levels were < [(b) (4)] µg. Given the advanced cancer patient population, that pemetrexed is genotoxic, and the administration schedule for Pemetrexed Injection is once every 21 days, the daily doses of each leachable in Pemetrexed Injection is within the acceptable limit of 5 µg. From a pharmacology/toxicology perspective, the leachable levels are not a safety concern.

[1] https://pqri.org/wp-content/uploads/2022/03/PQRI-PDP-Recommendation-2022.pdf

Table 1: Estimated Dosage for Selected Leachables in Pemetrexed Injection

(b) (4)

There we no major revisions in the nonclinical sections of the labeling compared to the listed drug. Minor revisions were done to reflect current labeling practices, including revising "(b) (4) to "hazardous" in Sections 2.7 and 16 to be consistent with OSHA, and updating the OSHA Hazardous Drugs website in Section 15. In section 13.1, an error/typo in dose multiple was found to have been carried over from ALIMTA label. The exposure multiple was revised from (b) (4) to 0.0006 times to reflect the correct calculation [0.1 mg/kg/day to male mice (0.3 mg/m^2) is approximately 0.0006 times the recommended human dose of 500 mg/m^2, based on BSA]. From a pharmacology/toxicology perspective, there are no outstanding issues, therefore, the application is recommended for approval.

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/s/

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05/13/2022 10:38:34 AM

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MEMORANDUM

Date: January 29, 2021
From: M. Anwar Goheer, PhD
Nonclinical Reviewer
Division of Hematology Oncology Toxicology for Division of Oncology 2
Through: Whitney S. Helms, PhD
Supervisory Pharmacologist
Division of Hematology Oncology Toxicology for Division of Oncology 2
To: NDA 214218
Re: Pharmacology and Toxicology

On April 23, 2020 Hospira Inc. submitted a New Drug Application (NDA) for Pemetrexed Injection (pemetrexed disodium) under the 505(b)(2) pathway, identifying the listed drug as ALIMTA® under NDA 021462 held by Eli Lily, approved on February 4, 2004. There are no novel excipients or excipients at levels requiring additional toxicological assessment or impurities at specifications that required input from the nonclinical team. No pharmacology/toxicology information was included in the current submission with the exception of one GLP-compliant in vitro report on the hemolytic potential for the currently proposed formulation. Other nonclinical information included in Module 4 on dissolution was reviewed by the Biopharmaceutics team. The hemolytic report (Study 8447951: Hemolytic Potential Study with Pemetrexed Solution) investigated the potential for the formulation of Pemetrexed Injection at concentrations of 6, 9, and 12 mg/mL vs the listed drug, Alimta, at the same concentrations to cause hemolysis, flocculation, precipitation, or coagulation after incubation with human whole blood or plasma. There was no evidence of hemolysis or changes in plasma appearance with either Pemetrexed Injection or Alimta.

The CMC review team requested input on the acceptability of the levels of three potential leachables in the proposed product. Based on the Applicant's data, while each of these leachables was above the safety concern threshold of 1.5 µg/day, none of the leachables was genotoxic based on in silico data and the total amount of each leachable would be ≤ (b) (4) µg/ dose of pemetrexed. Based on current practice and a review of a test set of chemicals for which there was adequate toxicological information the FDA has agreed that a threshold of ≤ (b) (4) µg/day for non-mutagenic i (b) (4) leachables is acceptable for parentally administered (IV and SC) drugs. Therefore, the leachables in question were below the threshold of toxicological concern for this product. The nonclinical team made labeling recommendations to be consistent with current labeling policy, but not substantive changes compared to the listed drug or any changes based on data submitted by the Applicant for the current formulation. The application is approvable from a pharmacology/toxicology perspective.

Figure 1: Formulation of Pemetrexed Injection (Hospira)

Component	Quantity per Milliliter (mL)	Concentration: 25 mg/mL		
		100 mg/4 mL	500 mg/20 mL	1000 mg/40 mL
		Nominal quantity per unit[a]	Nominal quantity per unit[a]	Nominal quantity per unit[a]
Pemetrexed disodium[b] (*as pemetrexed base*)	27.57 mg (25.0 mg)	110.28 (100 mg)	551.40 (500 mg)	1102.80 mg (1000 mg)
Monothioglycerol	1.2 mg/mL	4.80 mg	24.00 mg	48.00 mg
Water for Injection	(b) (4)			
Sodium Hydroxide	(b) (4)			
	(D) (4)			
Total Volume	q.s. to 1.00 mL	4.00 mL	20.00 mL	40.00 mL

(Excerpted from the Applicant's submission)

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/s/

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01/29/2021 12:57:04 PM

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