CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215179Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

Date: March 28, 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 215179
Re: Pharmacology and Toxicology

Shilpa Medicare, Ltd (Shilpa) resubmitted NDA 215179 for Pemetrexed Injection, on October 14, 2021, after it was initially given a complete response (CR) due to quality and facility inspection deficiencies. As with the initial submission, Shilpa relied on a prior FDA finding of safety and effectiveness for the listed drug, ALIMTA (NDA 21462). The resubmitted NDA did not contain any nonclinical data.

During the review cycle, the CMC review team requested input regarding the acceptability of citing ICH M7 guidelines to support the total extractable levels for (b) (4) In response to CMC, we cited ICH S9 Q&A which states that the scope of ICH M7 does not apply to "drug substances and products intended for advanced cancer indications as defined in the scope of ICH S9". Given that Pemetrexed Injection is indicated for treatment of patients with advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) or mesothelioma, ICH M7 is not the appropriate guidance to justify levels for Pemetrexed Injection. Regarding the extractable levels, per Applicant, at a worse-case scenario with a maximum exposure of 48 hours, the concentration of extractable is (b) (4) µg/mL (b) (4) mg total extractable / (b) (4) L minimum batch size). Considering a maximum daily do 1000 mg in 100 mL, the overall total concentration of extractable is (b) (4) From a nonclinical perspective, the level of the extractables from (b) (4) is not a safety concern since pemetrexed is genotoxic and Pemetrexed Injection will be used in an advanced cancer population. In addition, Pemetrexed Injection will be administered once every 21 days; thus, based on the total concentration of extractables at worse-case scenario (b) (4) the daily intake is (b) (4) / 21 days), which is within the safety concern threshold (SCT).

Relevant sections of the label for Pemetrexed Injection were reviewed, with no major revisions. 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 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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03/31/2022 01:06:39 PM

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03/31/2022 04:41:12 PM

MEMORANDUM

Date: May 18, 2021
From: M. Anwar Goheer, PhD
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Through: Emily F. Wearne, PhD
Acting Pharmacology/Toxicology Team Leader
Division of Hematology Oncology Toxicology for Division of Oncology 2
To: NDA 215179
Re: Pharmacology and Toxicology

On August 27, 2020 Shilpa Pharmaceuticals submitted a New Drug Application (NDA) for Pemetrexed Injection (pemetrexed disodium hemi pentahydrate) under the 505(b)(2) pathway, identifying the listed drug as ALIMTA® under NDA 021462 held by Eli Lily, approved on February 4, 2004. No new pharmacology/toxicology information was included in the submission and there are no novel excipients included in the current formulation. This formulation includes mannitol at a 1:1 ratio with pemetrexed, consistent with the listed drug. The proposed formulation is at a lower concentration compared to the listed drug: 10 mg/mL with a maximum volume of 100 mL at the maximum projected dose of 1000 mg. The cysteine excipient was not present in the listed drug. The Applicant justified the proposed level based on the IV administration of cysteine as a parenteral nutrition product at up to 490 mg (vs up to 100 mg in Pemetrexed Injection); thus, there is no further safety qualification necessary for cysteine.

The CMC review team requested input on the acceptability of the levels of one potential extractable (b) (4) (b) (4) 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 safety concern threshold (SCT) of ≤5 µg/day for non-mutagenic irritant/sensitizer leachables is acceptable for parentally administered (IV and SC) drugs, though higher levels may be justifiable based on information for a specific compound. Using this 5-µg threshold, the CMC team calculated an analytic evaluation threshold (AET) of (b) (4) µg/mL considering a pemetrexed volume of (b) (4) mL at the 500 mg/m2 dose of pemetrexed. This delivered volume assumes an average BSA of (b) (4), consistent with many guidance documents, though not a worst-case scenario.

Using the assumptions discussed above, the delivered dose of (b) (4) While toxicological data on (b) (4) itself is limited, there is data on related compounds. (b) (4) and a (b) (4) representing up to (b) (4) exposure in

rats[1]. [redacted] itself has high oral bioavailability and LD_{50s} in animal studies were similar between oral and IV routes of administration, over 1000 mg/kg. [redacted] has a similar lethal dose to [redacted] with a lowest lethal dose of [redacted] mg/kg by intraperitoneal injection in guinea pigs; reported oral LD_{50s} were [redacted] g/kg or greater in multiple species. In addition, the EPA has established an oral reference dose for [redacted]. Considering the subsequent exposure of [redacted] due to metabolism of [redacted] there is no safety concern with the potential levels of [redacted].

Name of the Ingredient	Compendium	mg/mL	Quantity/Vial				Function
			100 mg/10 mL	500 mg/50 mL	1 g/100 mL	%	
Pemetrexed disodium hemipentahydrate equivalent to Pemetrexed®	IH	10.0 mg	100 mg	500 mg	1000 mg	1% w/v	Active Ingredient
Mannitol	USP-NF/Ph.Eur	10.0 mg	100 mg	500 mg	1000 mg	1% w/v	[redacted]
Sodium Chloride	USP/Ph.Eur	9.0 mg	90 mg	450 mg	900 mg	0.9% w/v	
[redacted] L-Cysteine hydrochloride	USP/Ph.Eur	1.0 mg	10 mg	50 mg	100 mg	0.1% w/v	
Sodium Hydroxide	USP/Ph.Eur	q.s to adjust pH	q.s to adjust pH	q.s to adjust pH	q.s to adjust pH	q.s to adjust pH	pH adjusting Agent
Hydrochloric acid [redacted]	USP/Ph.Eur	q.s to adjust pH	q.s to adjust pH	q.s to adjust pH	q.s to adjust pH	q.s to adjust pH	pH adjusting Agent
Water for Injection	USP/Ph.Eur	q.s to 1 mL	q.s to 10 mL	q.s to 50 mL	q.s to 100 mL	q.s to 100%	[redacted]
[redacted]	USP-NF/Ph.Eur	[redacted]					[redacted]

[redacted]

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/s/

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