CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214218Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	June 7, 2022
From	Mei Ou, Ph.D. OPQ/ONDP/Division of Biopharmaceutics
Subject	Cross-Discipline Team Leader Review
NDA	NDA 214218-ORIG-1-RESUB-21
Type of Submission	505(b)(2)
Applicant	Hospira, Inc., a Pfizer Company
Date of Submission	December 22, 2021
PDUFA Goal Date	June 22, 2022
Established or Proper names	Pemetrexed Injection Solution
Dosage forms / Strength	Solution for Intravenous Injection 25 mg/mL (100 mg/4 mL, 500 mg/20 mL, 1000 mg/40 mL)
Proposed Indications	The same as Alimta®: • In combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC); • As a single agent for the maintenance treatment of patients with locally advanced or metastatic, non - squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy; • As a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy; • Limitations of Use: Pemetrexed Injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer; and • Initial treatment, in combination with cisplatin, of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.
Recommendation:	**APPROVAL**

This CDTL review is based on the primary reviews/memos of:

DICIPLINE	PRIMARY REVIEWER/TL	FINAL REVIEW DATE
Quality IQA	Mei Ou (Application Technical Lead)	05/20/2022
Drug Substance	Rajan Pragani/Haripada Sarker	03/25/2022
Drug Product	Tefsit Bekele/Xing Wang	05/13/2022
Process/Facility	Ruth Moore/Kshitij Patkar	04/11/2022
Quality Microbiology	Marla Stevens-Riley/ Yeissa Chabrier-Rosello	04/202022
Biopharmaceutics	Gerlie Gieser	05/10/2022
Clinical	Satinder (Mona) Choudhary	N/A
Non-Clinical (Pharmacology/Toxicology)	Sachia Khasar/Claudia Miller	05/13/2022
Clinical Pharmacology	Lingshan Wang/Hong Zhao	N/A
Division of Medication Error Prevention and Analysis	Ruth Mayrosh/Rachael Conklin	05/25/2022, 05/27/2022
505(b)(2) Committee	Mary Ann Holovac	N/A

Cross Discipline Team Leader Review

1. Background

The Applicant submitted the original NDA 214218 on April 23, 2020, for Pemetrexed Injection, a sterile, ready-to-dilute (RTD) solution, 25 mg/mL (100 mg/4 mL, 500 mg/20 mL, 1000 mg/40 mL). This 505(b)(2) NDA relies, at least in part, on the FDA's previous findings of safety and efficacy for the Listed Drug (LD) product, ALIMTA® (pemetrexed) lyophilized powder for injection (NDA 021462), for approval. ALIMTA was approved on February 04, 2004, for the treatment of patients with locally advanced or metastatic non-squamous non-small cell lung cancer as well as mesothelioma and is available as a lyophilized powder (containing 100 mg and 500 mg pemetrexed per vial).

The proposed Pemetrexed Injection has the same indications as described for ALIMTA, as:

- In combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC);
- As a single agent for the maintenance treatment of patients with locally advanced or metastatic, non -squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy;
- As a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy;
- Limitations of Use: Pemetrexed Injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer; and
- Initial treatment, in combination with cisplatin, of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.

The proposed drug product also has the same route of administration and contains the same active moiety (pemetrexed) as the approved LD. There is no difference in dosing regimen (500 mg/m^2 as an intravenous infusion over 10 minutes).

The proposed drug product differs from LD product in terms of (i) dosage form (i.e., RTD solution formulation vs. lyophilized powder formulation for reconstitution and further dilution), (ii) drug substance hydrate form (i.e., hemipentahydrate vs. heptahydrate), (iii) formulation composition/excipients (i.e., addition of monothioglycerol (b) (4) vs. absence of (b) (4) mannitol), (iv) long-term storage conditions during shelf-life (i.e., refrigerated vs. room temperature), (v) physico-chemical properties of the RTD solution and the final infusion product (has a lower osmolality and slightly higher surface tension, (vi) minor difference in the characteristics of the container-closure system.

The original NDA received a Tentative Approval Letter on February 23, 2021. The Applicant resubmitted the NDA 214218 on November 24, 2021 but withdraw the resubmission on December 22, 2021. The Applicant resubmitted this NDA again on December 22, 2021 and requested the final approval upon the expiry of the pediatric exclusivity (May 24, 2022) associated with U.S. Pat. No. 7,772,209 which is the sole patent listed in the Orange Book for the LD.

No clinical pharmacology, nonclinical, safety or efficacy data were submitted in this NDA application.

2. Product Information

The proposed Pemetrexed injection is a clear colorless to pale yellow (b) (4) RTD solution for intravenous administration. Proposed Pemetrexed injection is available in three presentations of 100 mg/4 mL, 500 mg/20 mL and 1000 mg/40 mL, presented in 6 mL, 20 mL and 50 mL clear (b) (4) glass vials, representatively. To deliver the required pemetrexed dose (calculated based on the patient's body surface area (BSA), 500 mg/m^2), the appropriate volume of the RTD Pemetrexed Injection solution 25 mg/mL is to be withdrawn from the vial(s) and then diluted with 0.9% Sodium Chloride Injection to achieve a total volume of 100 mL for intravenous infusion for over 10 minutes.

3. Pharmaceutical Quality

The OPQ review teams recommended APPROVAL for the current resubmission.

Drug Substance: ADEQUATE
The drug substance pemetrexed disodium was previously reviewed in the original CMC submission (assessment cycle #1) and determined to be adequate (review #1 on 01/07/2021). Since then, cross-referenced DMF (b) (4) has been updated and a quality amendment has also been submitted to this NDA. The most recent DMF major amendments have been reviewed for an ANDA and the current status of DMF (b) (4) is adequate. Additional test data was submitted to the DMF in response to an additional comment from the last review (R06_AQAC), and the data do not impact the adequate status of the DMF. The CMC information referenced in DMF (b) (4) demonstrates a control of the quality for the manufacture of the drug substance. The NDA amendment was also reviewed and appears reasonable. The drug substance pemetrexed disodium is a disodium salt that is (b) (4) a hydrate. The impurity control strategy follows the USP monograph for pemetrexed disodium. The proposed retest date of (b) (4) from the original submission is still acceptable for pemetrexed disodium. *The Drug Substance recommends for* ***Approval****.*

Drug Product: ADEQUATE
The CMC updates or changes in this review cycle is related to (b) (4) risk assessment, updated leachable report of pemetrexed injection at the end of its shelf life, minor change to the container closure system and updated stability data. The (b) (4) risk assessment performed per FDA's guidance is adequate and there is no risk for the presence of (b) (4) impurities in the drug product. There is no safety risk with the level of nine leachables identified in pemetrexed injection stored for 24 months at long term storage conditions. For commercial pemetrexed, the (b) (4) top that is not part of the primary packaging will be different in color from the exhibit batches. However, this change in the secondary packaging material will not have an impact on stability of the product. The minor change in the container closure system is acceptable from the CMC perspective. Pemetrexed injection continued to show stability at 2–8 °C for 24 months. No request is made to extend the shelf-life. The 24 months expiration date granted in the first review cycle for pemetrexed remains unchanged.

*The Drug Product recommends for **Approval**.*

Process and Facilities: ADEQUATE

The manufacturing process involves (b) (4) [redacted]. No Pre-approval inspection of facilities were requested. Review of the submission information and inspection history for the drug product manufacturer facility show the site has the capability to manufacture the product and implement the manufacturing control strategy in compliance with CGMPs. All facilities in the application have satisfactory CGMP compliance status and are recommended for approval. *The Process and Facilities remains **Approval**.*

Quality Microbiology: ADEQUATE

Prior to the resubmission, the product quality microbiology information was deemed adequate. The drug product is (b) (4) [redacted]. All proposed changes to the drug substance and drug product in current resubmission do not affect sterility assurance/product quality microbiology of the final drug product. The changes to the aluminum seal are not considered to be changes to the primary container closure system. (b) (4) [redacted]. *The Microbiology recommends for **Approval.***

Biopharmaceutics: ADEQUATE

The Biopharmaceutics Review of the original NDA, APPROVAL was recommended, based on submission of adequate comparative in vitro data and additional supporting data/information/justification to establish the scientific bridge between the proposed drug product and the relied upon LD product, i.e., in accordance with 21 CFR 320.24 (b)(6). For current resubmission, based on the information in the Summary of Changes document and considering the Applicant's updated (24-month) drug product stability summary, it was determined that for the identified minor CMC changes introduced after this NDA's tentative approval, a biowaiver request is not needed. Additionally, submission of in vitro bridging data (e.g., from additional in vitro protein binding, in vitro hemolysis, and physicochemical characterization studies) is not warranted to support the final approval of the proposed drug product. *The Biopharmaceutics recommends for **Approval**.*

4. Nonclinical Pharmacology/Toxicology

During the first review cycle (April 23, 2020), the Nonclinical review team determined there were no concerns with levels of potential leachables in Pemetrexed Injection from samples stored for up to 12 months. In the current resubmission, the Applicant identified additional

potential leachables in Pemetrexed Injection 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. Based on the information provided and per risk assessment, although additional leachables with safety concern threshold (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). 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. From a pharmacology/toxicology perspective, there are no outstanding issues, therefore, the application is recommended for approval.

5. Clinical Pharmacology

No new clinical pharmacology information was included in the resubmission.

6. Clinical

No clinical studies have been conducted under the submitted original NDA and the current resubmission and no clinical issues need to be addressed related to this NDA. The clinical team recommended approval in original submission upon satisfactory review from other FDA disciplines.

7. Pediatric Research Equity Act Waiver – NAI

8. Advisory Committee Meeting – NAI

9. Other Relevant Regulatory Issues - None

10. Labeling

The Applicant accepted FDA's edits and recommendations.

11. Risk Benefit Assessment

Please refer to NDA 021462 (Alimta)

12. Recommendation

The cross disciplinary team lead recommendation for NDA-214218-ORIG-1-RESUB-21 is **APPROVAL**.

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/s/

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Cross-Discipline Team Leader Review

Date	February 5, 2021
From	Banu Zolnik, Ph.D. Biopharmaceutics Team Leader, ONDP/Division of Biopharmaceutics
Subject	Cross-Discipline Team Leader Review
NDA	NDA 214218
Type of Submission	505(b)(2)
Applicant	Hospira Inc.
Date of Submission	April 23, 2020
PDUFA Goal Date	February 23, 2021
Proprietary Name / Established (USAN) names	Pemetrexed Injection
Dosage forms / Strength	Injection, Solution/ 25 mg/mL (100 mg/4 mL, 500 mg/20 mL, and 1000 mg/40 mL)

Proposed Indications	Pemetrexed for injection is a folate analog metabolic inhibitor indicated for:
	• Locally Advanced or Metastatic Non-Squamous Non-Small Cell Lung Cancer:
	  • Initial treatment in combination with cisplatin.
	  • Maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.
	  • After prior chemotherapy as a single-agent.
	• Mesothelioma: in combination with cisplatin.

Recommendation:	**TENTATIVE APPROVAL**

This CDTL review is based, on the primary reviews/memos of:

DICIPLINE	PRIMARY REVIEWER/TL	FINAL REVIEW DATE
Quality IQA	Banu Zolnik (Application Technical Lead)	02/02/2021
Drug Substance	Rajan Pragani/ Ali Al Hakim	12/17/2020
Drug Product	Tefsit Bekele/ Anamitro Banerjee	12/18/2020
OPMA/Facility	Ruth Moore/David Anderson	11/25/2020
Quality Microbiology	Christine Craig/ Marla Stevens-Riley	11/18/2020
Biopharmaceutics	Gerlie Gieser/Banu Zolnik	12/17/2020
Clinical	Katie Chon/Erin A. Larkins	02/03/2021
Non-Clinical (Pharmacology/Toxicology)	M. Anwar Goheer/ Whitney S. Helms	01/29/2021
Clinical Pharmacology	Yibo Wang/Hong Zhao	01/29/2021
Medication Error Prevention and Analysis	Janine Stewart/Ashleigh Lowery	12/18/2020 01/26/2021
505 (b) (2) Committee	Mary Ann Holovac (email memo)	01/11/2021

Cross Discipline Team Leader Review

1. Introduction

This is a 505 (b) (2) application by Hospira submitted on April 23, 2020 for Pemetrexed for Injection, 100 mg/4 mL, 500 mg/20 mL, and 1000 mg/40 mL. The proposed pemetrexed injection is a sterile, ready-to-dilute solution which was developed to eliminate the reconstitution step required for the Alimta lyophilized powder. An additional presentation 1000 mg/40 mL is proposed to facilitate ease of administration.

The proposed drug product is a parenteral solution intended solely for intravenous route of administration and contains the same active moiety (pemetrexed) in the same concentration as the approved listed drug. There is no difference in dosing regimen. This application has the same indications as Alimta, except for use in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations as this indication is under patent protection.

The proposed drug product differs from the LD in terms of:

i) drug substance hydrate form (hemipentahydrate vs. heptahydrate);
ii) dosage form (ready-to-dilute solution versus lyophilized powder);
iii) formulation composition (proposed product contains (b) (4) monothioglycerol whereas Alimta contains (b) (4) mannitol); and
iv) long-term storage conditions during shelf-life (refrigerated vs room temperature);

No clinical safety or efficacy data were submitted in this NDA application. The Applicant provided adequate comparative in vitro and additional CMC and nonclinical data/information to justify that the aforementioned pharmaceutical quality differences between the proposed RTD solution drug product and the relied upon LD would not significantly impact the clinical PK/efficacy/safety/tolerability of the proposed drug product

2. Background

The Applicant is relying on FDA findings of safety and efficacy for Alimta (Pemetrexed for Injection), 100 and 500 mg per vial), NDA 021462 which was approved on February 4, 2004. Alimta has the following indications:

- in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
- in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC).
- as a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.
- as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy.

- initial treatment, in combination with cisplatin, of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.

3. Pharmaceutical Quality

Drug Substance:
The drug substance pemetrexed disodium is a disodium salt that is (b) (4) a hemipentahydrate. The CMC information referenced in DMF (b) (4) demonstrates a control of the quality for the manufacture of the drug substance. The impurity control strategy follows the USP monograph for pemetrexed disodium. The most recent DMF amendments have been reviewed and the current status of DMF (b) (4) is adequate.

Based on the stability data provided in the DMF, a proposed retest date of (b) (4) is acceptable for pemetrexed disodium.

Drug Product:
The applicant provided satisfactory drug product information including stability of the product. Pemetrexed injection is a sterile solution containing no antimicrobial preservatives. The overall formulation development indicates that the quality and chemical stability of the proposed product is equivalent to the listed drug. The proposed pemetrexed injection is a (b) (4) product containing no antimicrobial preservatives. (b) (4) . Three registration batches of each strength were manufactured that conform to the proposed specifications. (b) (4) when stored in the proposed primary container at the proposed storage temperature. The product is required to be diluted in 0.9% NaCl infusion solution before administration. The admixture can be stored under refrigerated conditions for up to 24 hours which is supported by in-use stability data. Pemetrexed injection is stable at 2–8 °C for up to 18 months and up to 6 months at (b) (4) . Based on the available 18 months stability data at 2–8 °C, the requested 24 months expiration date is granted. This determination is based on ICH Q1A (R2) and ICH Q1E.

Process and Facilities:

(b) (4)

[redacted] (b) (4)

No Pre-approval inspection of facilities were requested. Review of the submission information and inspection history for the drug product manufacturing facility show that the site has the capability to manufacture the drug product and implement the manufacturing control strategy in compliance with CGMPs. All facilities listed in the application have satisfactory CGMP compliance status and are recommended for approval.

Quality Microbiology:
The microbiology review covers sterility assurance and microbiological quality of the drug product. The applicant has met regulatory expectations regarding the information related product quality microbiology

Biopharmaceutics:
Overall, the submitted comparative and additional supporting data/information/justification are deemed sufficient to establish the scientific bridge between the proposed drug product and the relied upon LD product, i.e., in accordance with 21 CFR 320.24 (b)(6).

The application is approvable from Quality Review Team

4. Nonclinical Pharmacology/Toxicology

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.

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 [redacted] (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.

5. Clinical Pharmacology

No clinical pharmacology studies have been conducted with the proposed pemetrexed product and there are no clinical pharmacology issues to be addressed in this NDA. The proposed labeling does not contain any changes to the clinical pharmacology sections compared to the labeling of the LD Alimta®.

6. Clinical

No clinical safety or efficacy data were submitted in this NDA application. Due to the difference in the pharmaceutical dosage form, Hospira, is required under PREA, submitted their agreed initial pediatric study plan requesting a full waiver for all pediatric age groups. Initial Pediatric Study Plan: was submitted under PIND 138218 with agreement on April 29, 2019.
For recommendation regarding this NDA, clinical team refers to review by other disciplines.

7. Advisory Committee Meeting

Current submission did not go to an Advisory Committee Meeting.

8. Other Relevant Regulatory Issues

Per email by Mary Ann Holovac dated 1/11/2021, NDA 214218 is cleared for ******tentative approval****** action because the applicant provided a paragraph III patent certification to the unexpired patent.

9. Labeling

Labeling has been updated to align with the listed drug Alimta with the exception of use in combination with pembrolizumab and platinum chemotherapy. DMEPA evaluated revised container and carton labeling to determined that it is acceptable from a medication error perspective (refer to DMEPA reviews dated 12/18/2020 and 01/26/2021).

10. Risk Benefit Assessment

Please refer to NDA 021462 (Alimta)

11. Recommendations

The cross disciplinary team lead recommendation for NDA 214218 is **TENTATIVE APPROVAL.**

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/

BANU S ZOLNIK
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