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APPLICATION NUMBER:

214657Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	May 13, 2022
From	Mei Ou, Ph.D. OPQ/ONDP/Division of Biopharmaceutics
Subject	Cross-Discipline Team Leader Review
NDA	NDA 214657-ORIG-1-RESUB-27
Type of Submission	505(b)(2)
Applicant	Sandoz Inc.
Date of Submission	November 26, 2021
PDUFA Goal Date	May 26, 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 pembrolizumab and platinum chemotherapy, in 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. Limitations of Use: pemetrexed injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer. Limitations of Use: Pemetrexed injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer. • 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**

Reference ID: 4983681

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)	05/13/2022
Drug Substance	Paresma Patel	01/18/2022
Drug Product	Rajiv Agarwal/Xing Wang	02/23/2021, 08/16/2021, 04/25/2022, 05/12/2022
Process/Facility	Steve Hertz/James Norman	04/25/2022
Quality Microbiology	Jason God/Julie Nemecek	01/18/2022
Biopharmaceutics	Gerlie Gieser	01/18/2022
Clinical	Satinder (Mona) Choudhary	N/A
Non-Clinical (Pharmacology/Toxicology)	Emily Wearne/Claudia Miller	05/02/2022
Clinical Pharmacology	Suryatheja Ananthula/ Jeanne Fourie Zirkelbach	N/A
Division of Medication Error Prevention and Analysis	Tingting Gao/Janine Stewart	05/03/2022
505(b)(2) Committee	Mary Ann Holovac	N/A

Reference ID: 4983681

Cross Discipline Team Leader Review

1. Background

This NDA for Pemetrexed Injection (25 mg/mL) relies for approval on the FDA's previous findings of safety and efficacy for the Listed Drug (LD) product, ALIMTA® (pemetrexed) lyophilized powder for injection (NDA 021462), approved on February 4, 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 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.
- in combination with cisplatin, for the initial treatment 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 dosage form (i.e., ready-to-dilute (RTD) solution formulation vs. lyophilized powder formulation for reconstitution and further dilution), drug substance hydrate form (i.e., hemipentahydrate vs. heptahydrate), and excipients (i.e., absence of mannitol, and addition of sodium thiosulfate pentahydrate (b) (4) and propylene glycol (b) (4)).

The original 505(b)(2) application by Sandoz Inc. submitted on July 7, 2020 received a Tentative Approval Letter on May 06, 2021. The Applicant resubmitted the NDA 214657 on July 23, 2021 but withdraw the resubmission on November 18, 2021. The Applicant resubmitted this NDA again on November 26, 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, safety or efficacy data were submitted in this NDA application.

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2. Product Information

The proposed Pemetrexed Injection is clear colorless to yellow or green-yellow 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 in single-dose vials. 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 25 mg/mL solution 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- ADEQUATE

The OPQ review teams recommended APPROVAL for the current resubmission.

Drug Substance: No Action Indicated (NAI)

This NDA was recommended for approval during review of the original submission by Katherine Windsor on 18-Feb-2021. The current resubmission provides no additional drug substance information. The cross referenced DMF (b) (4) was last reviewed by Donglei Yu on 04-Jan-2022. There are no unreviewed amendments. The DMF remains adequate. *The Drug Substance remains* ***Approval****.*

Drug Product: ADEQUATE

Applicant has performed a root cause analysis. (b) (4) (b) (4) (b) (4) The newly proposed acceptance criteria for impurities are consulted to the assigned Pharmacology/Toxicology (P/T) reviewer and on 7/27/2021, P/T reviewer confirmed that the newly proposed acceptance criteria for (b) (4) total impurities are safe from a P/T standpoint. Therefore, widening of the acceptance criteria for these impurities is acceptable. Provided information for quality labeling is adequate. *The Drug Product recommends for* ***Approval****.*

Process and Facilities: NAI

The Process and Facilities remains ***Approval****.*

Quality Microbiology: NAI

The Microbiology remains ***Approval.***

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Biopharmaceutics: NAI
*The Biopharmaceutics remains **Approval**.*

4. Nonclinical Pharmacology/Toxicology

The nonclinical team recommended approval for the original submission. The resubmission includes a proposal to widen the release and shelf life specification limits fo (b) (4) (b) (4) total impurities) in all three presentations (100 mg/4 mL, 500 mg/20 mL, 1000 mg/40 mL) of the Drug Product (DP) specifications. There were no new nonclinical studies provided in the current resubmission. The Applicant used the previously submitted toxicology study #31777 and a statistical evaluation of long term stability data to justify widening the specification limits for Pemetrexed injection. Overall, there were no clear toxicological differences between the pemetrexed active control and pemetrexed enriched with related impurities, suggesting the presence of these impurities did not change the toxicity profile of pemetrexed. The Applicant's new proposed specifications for (b) (4) (b) (4) at levels above the ICH Q3B thresholds are justified by the available nonclinical toxicology data. There are no outstanding issues from a pharmacology/toxicology perspective that would prevent final approval of this 505(b)(2) application for the proposed indications.

5. Clinical Pharmacology - NAI

No new clinical pharmacology information was included in the resubmission.

6. Clinical - NAI

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. The Applicant can use the previously printed container labels and carton labeling for product launch and implement the FDA recommended changes at next printing.

11. Risk Benefit Assessment

Please refer to NDA 021462 (Alimta)

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12. Recommendations

The cross disciplinary team lead recommendation for NDA-214657-ORIG-1-RESUB-27 is **APPROVAL**.

Reference ID: 4983681

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/s/

MEI OU
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Cross-Discipline Team Leader Review

Date	April 30, 2021
From	Banu Zolnik, Ph.D. Biopharmaceutics Team Leader, ONDP/Division of Biopharmaceutics
Subject	Cross-Discipline Team Leader Review
NDA	NDA 214657
Type of Submission	505(b)(2)
Applicant	Sandoz Inc.
Date of Submission	July 7, 2020
PDUFA Goal Date	May 5, 2021
Proprietary Name / Established (USAN) names	Pemetrexed Injection
Dosage forms / Strength	Intravenous Injection, (infusion) 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:
	  • In combination with pembrolizumab and platinum chemotherapy when your lung cancer with no abnormal EGFR or ALK gene has spread (advanced NSCLC).
	  • 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**

Reference ID: 4788732

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)	04/19/2021
Drug Substance	Katherine Windsor Ali Al Hakim	02/18/2021
Drug Product	Rajiv Agarwal/ Anamitro Banerjee	02/23/2021
OPMA/Facility	Steven Hertz/Yiwei Li	03/31/2021
Quality Microbiology	KellyAnn Miller/Julie Nemecek	09/24/2020
Biopharmaceutics	Gerlie Gieser/Banu Zolnik	04/02/2021
Clinical	Nicole Drezner	04/23/2021
Non-Clinical (Pharmacology/Toxicology)	Anwar Goheer/Whitney Helms	03/04/2021
Non-Clinical (Pharmacology/Toxicology) Addendum	Emily Wearne/John Leighton	03/31/2021
Clinical Pharmacology	Yibo Wang/Hong Zhao	04/12/2021
Office of Prescription Drug Promotion (OPDP)	Nazia Fatima (refers to combined review OPDP/DMMP below)	02/19/2021
Patient Labeling (DMPP and OPDP)	Susan Redwood/Nazia Fatima (Barbara Fuller/Lashawn Griffiths	02/16/2021
PREA waiver memo	Kwadwo Korsah	03/17/2021
Medication Error Prevention and Analysis	Janine Stewart/Ashleigh Lowery	12/10/2020 01/28/2021
505 (b) (2) Committee	Mary Ann Holovac (email memo)	04/02/2021

Reference ID: 4788732

Cross Discipline Team Leader Review

1. Introduction

This is a 505 (b) (2) application by Sandoz submitted on July 7, 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 parenteral solution which was developed to eliminate the reconstitution step required for the Alimta lyophilized powder.

The proposed drug product has the same 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.

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 (contains (b) (4) sodium thiosulfate and (b) (4) propylene glycol in place of (b) (4) mannitol found in Alimta);

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.

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3. Pharmaceutical Quality

Drug Substance:
The drug substance is isolated as the hemipentahydrate, which is freely soluble in water. There is a USP monograph for pemetrexed disodium (listing heptahydrate, anhydrous, and free acid forms, but not the hemipentahydrate form).
The Applicant cross-referenced the CMC information for pemetrexed disodium drug substance to DMF (b) (4). DMF (b) (4) was reviewed by Donglei Yu Ph.D. (final signature 08-JAN-2021) and was found adequate to support ANDA-202111-ORIG-1-AMEND-20. There have been no quality amendments submitted since the last assessment; the DMF remains adequate to support NDA 214657. Specified and unspecified impurity controls are sufficient. Stability data in the referenced DMF support the proposed retest period of (b) (4) months for pemetrexed disodium drug substance (b) (4)

Drug Product:
The applicant provided satisfactory drug product information including stability of the product. Pemetrexed injection, 25 mg/mL is a clear colorless to yellow or green-yellow solution for intravenous administration. Pemetrexed injection is available in three presentations of 100 mg/4mL, 500 mg/20mL and 1000 mg/40mL. All excipients used for Pemetrexed injection formulation were of pharmacopoeia grade (USP). The amounts of Sodium thiosulfate and propylene glycol excipients appears to be higher than what is listed in IID for IV route of administration. Applicant has provided the justification via safety report in 3.2.P.2 (document 2020_TRA_163_MW). Pharmacology/Toxicology reviewer is contacted to comment on the safety of these excipients. The Pharmacology/Toxicology team has no safety issues with the levels of excipient used in the formulation.
Stability data from formulation development does not indicate any incompatibilities between the excipients. Stability study of Pemetrexed injection, 25 mg/mL contains testing at 25°C ± 2°C / 60% ±5% RH, 30°C ± 2°C/75% ± 5% RH and at 40°C ± 2°C/75% ± 5% RH (accelerated condition) in both inverted and upright configurations. Over the 18 months (500 mg and 1000 mg presentations) and 12 months (100 mg presentation) testing times, the parameters, such as, color, assay, chromatographic purity, pH and (b) (4) content were found to be within the shelf-life specification limits. There was no change observed in (b) (4) identity, sub-visible particles, clarity, microbial testing (sterility and bacterial endotoxins) and extractable volume. Tightness of closure (Container Closure Integrity Test) was performed at initial time point. All tested vials were leak tight and no sample showed any blue coloration. Under the thermal stress conditions, the tested parameters remained within the release specification limits over the period of cycles 1, 2 and 3 at -20°C to 40°C/75% RH and within the shelf life specification limits over the tested time period of 12 months. Based on the results of the present study, it can be concluded that temperature variations had no impact on the stability of Pemetrexed injection, 25 mg/mL.
During photo stability testing, data indicate that the drug product is light sensitive as impurity levels are higher in illuminated samples. Therefore, the use of a carton box for storage of the drug product until the moment of use is proposed by the applicant as it provides protection from light. This information is captured in all drug product labels.
Infusion solutions: Infusion solutions prepared from Pemetrexed injection, 25 mg/mL were stable for 7 days at room temperature protected from light and for 14 days at refrigerated

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condition (2-8 °C, protected from light) for the 500 mg and 1000 mg presentations. For the 100 mg presentation the prepared infusion solution was stable for 3 days at refrigerated condition (2-8 °C, protected from light). In PI label, the recommendation will be captured as (b) (4)

Original drug vial: The proposed expiration dating period of 24 months for drug product when stored at 25°C (77°F), excursions permitted to 15° - 30°C (59° - 86°F) in the proposed primary container and secondary closure system may be granted.

Process and Facilities:
The manufacturing process development was performed applying a QbD approach, and manufacturing process parameters were proposed based on laboratory studies. A 704a4 was performed for the drug product facility, and after reviewing the facility's 704a4 responses, the primary manufacturing reviewer and lead ORA officer determined that the 704a4 response mitigates the need for a PAI.

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:
The Applicant provided adequate comparative in vitro data, additional CMC and nonclinical data/information, and published literature to justify that the 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.

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 in accordance with 21 CFR 320.24(b)(6).

The application is approvable from Pharmaceutical Quality Review Team

4. Nonclinical Pharmacology/Toxicology

There are two nonclinical Pharm/Tox review- Drs. Anwar Goheer and Whitney Helms review dated 3/04/2021 and Drs. Emily Wearne and John Leighton dated 03/31/2021.

The Applicant conducted a toxicology study using their proposed formulation of pemetrexed in the presence or absence of impurities potentially present in this presentation at levels above the ICHQ3B limits, though the final formulation of Pemetrexed Injection does not include any impurities that require qualification. Overall, there were no clear toxicological differences between the pemetrexed active control and pemetrexed enriched with related impurities; pemetrexed-related findings were consistent with the described nonclinical findings for the listed drug.
The Applicant's proposed formulation of pemetrexed includes excipients not included in the listed drug and present at levels higher than levels described for other products included in the

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inactive ingredient database, specifically high levels of sodium thiosulfate (STS) and propylene glycol. STS is approved clinically for the treatment of cyanide poisoning and there are decades of clinical experience for its use in this as well as other indications at doses higher than those delivered at the proposed dose of pemetrexed. The safety of propylene glycol at the levels included in the currently proposed pemetrexed formulation is supported by extensive toxicological reviews propylene glycol conducted by US and other international government agencies including NTP-CERHR and the Agency for Toxic Substances and Disease Registry (ATSDR). Based on these data there are no safety concerns for the levels of either STS or PG in the currently proposed formulation.

The second memo by Drs Wearne and Leighton addresses the OPMA reviewer's concerns related to leachable and extractable levels. This memo concluded that the level of (b) (4) does not represent a significant risk from pharmacology/toxicology perspective.

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 studies have been conducted under the submitted NDA and no clinical issues need to be addressed related to this NDA. The clinical team recommends approval upon satisfactory review from other FDA disciplines.

7. Pediatric Research Equity Act Waiver

According to the memo by Kwadwo Korsah dated 3/17/2021, this application does NOT trigger PREA. The LD and this NDA have the same indication, dosing regimen, routes of administration and the same dosage form (injection).

8. Advisory Committee Meeting

Current submission did not go to an Advisory Committee Meeting.

9. Other Relevant Regulatory Issues

Per email by Mary Ann Holovac dated April 2, 2021, NDA 214657 is cleared for ******tentative approval****** action because the applicant provided a paragraph III patent certification to the unexpired patent on the relied upon listed drug.

10. Labeling

Labeling is aligned with the listed drug Alimta. DMEPA evaluated proposed Prescribing Information (PI), Patient Information, container labels and carton labeling for potential medical errors. DMEPA found PI, Patient Information, revised container labels and carton labeling are acceptable from a medication error perspective. Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP) reviewed the Patient Package Insert (PPI) and concluded that PPI is also acceptable with the recommended changes.

11. Risk Benefit Assessment

Please refer to NDA 021462 (Alimta)

12. Recommendations

The cross disciplinary team lead recommendation for NDA 214657 is **TENTATIVE APPROVAL.**

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/s/

BANU S ZOLNIK
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