CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214657Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 5/18/22

To: Idara Ojofeitimi, Regulatory Project Manager, Division of Oncology 2 (DO2)

From: Rachael Conklin, Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for PEMETREXED injection, for intravenous use

NDA: 214657

Background:
In response to DO2's consult request dated April 19, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and Patient Package Insert (PPI) for the original NDA submission for PEMETREXED injection, for intravenous use (Pemetrexed).

PI/PPI
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on May 3, 2022, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at rachael.conklin@fda.hhs.gov.

PI

Section	Statement from Draft (if applicable)	OPDP comments
8.4 Pediatric Use		OPDP notes that updates to this section have been made in the Alimta SCPI and we recommend that these revisions be made in this label as well.

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/s/

RACHAEL E CONKLIN
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 17, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214657
Product Name and Strength:	Pemetrexed Injection, 100 mg/4 mL, 500 mg/ 20 mL, and 1,000 mg/40 mL
Applicant/Sponsor Name:	Sandoz
OSE RCM #:	2020-1442-3
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on May 11, 2022 for Pemetrexed Injection. Division of Oncology 2 (DO2) requested that we review the revised container labels and carton labeling for Pemetrexed Injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Gao, T. Label and Labeling Review for Pemetrexed Injection (NDA 214657). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 May 3. RCM No.: 2020-1442-2.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 9, 2022
To:	Idara Ojofeitimi Regulatory Project Manager **Division of Oncology 2 (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rachael Conklin, MS, RN Team Leader **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	Pemetrexed Injection
Dosage Form and Route:	for intravenous use
Application Type/Number:	NDA 214657
Applicant:	Sandoz, Inc.

1 INTRODUCTION

On November 26, 2021, Sandoz, Inc. submitted for the Agency's review a Class 2 Resubmission of their proposed 505 (b)(2) New Drug Application (NDA) 214657 for Pemetrexed Injection in response to an Agency Tentative Approval Letter dated May 6, 2021. The reference listed drug (RLD) for this submission is ALIMTA (pemetrexed for injection), NDA 021462, held by Eli Lilly and Company, and the most recently approved labeling was on January 30, 2019. The proposed indications for Pemetrexed Injection are as follows:

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

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 2 (DO2) on April 19, 2022 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for Pemetrexed Injection.

2 MATERIAL REVIEWED

- Draft Pemetrexed Injection PPI received on November 26, 2021, and received by DMPP and OPDP on May 3, 2022.
- Draft Pemetrexed Injection Prescribing Information (PI) received on November 26, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 3, 2022.
- Approved ALIMTA (pemetrexed for injection) comparator labeling dated January 30, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

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RACHAEL E CONKLIN
05/10/2022 10:15:26 AM

LASHAWN M GRIFFITHS
05/10/2022 11:07:24 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 3, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214657
Product Name, Dosage Form, and Strength:	Pemetrexed Injection, 100 mg/4 mL, 500 mg/ 20 mL, and 1,000 mg/40 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Sandoz
FDA Received Date:	February 4, 2022 and March 23, 2022
OSE RCM #:	2020-1442-2
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Acting Team Leader:	Janine Stewart, PharmD

1 REASON FOR REVIEW

As part of the approval process for Pemetrexed Injection, the Division of Oncology 2 (DO2) requested that we review the proposed Pemetrexed Injection prescribing information (PI), patient package insert (PPI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

NDA 214657 is a 505(b)(2) NDA and the reference product is Alimta, NDA 021462.

Sandoz previously submitted NDA 214657 on July 7, 2020, which received a Tentative Approval on May 6, 2021.[a]

Thus, Sandoz submitted a Class 2 Resubmission on November 26, 2021 requesting Final Approval and Gratuitous Amendment.[b] Sandoz submitted container labels and carton labeling, on February 4, 2022.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

[a] Korsah, K. on behalf of Martha Donoghue. NDA 214657 Tentative Approval. Silver Spring (MD): FDA, CDER, OND, DOP2 (US); 2021 May 6.

[b] NDA 214657. Request for Final Approval. Reference Pemetrexed Injection, 25 mg/mL (100 mg/4 mL, 500 mg/20 mL, 1000 mg/40 mL). Princeton (NJ): Sandoz Inc. 2021 Nov 26. Available from: \\CDSESUB1\evsprod\nda214657\0025\m1\us\12-cover-letters\cover-letter.pdf

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Pemetrexed Injection PI and PPI and determined that the proposed PI can be improved for clarity.

If DO2 plans to revise the statement [redacted] (b) (4) to "hazardous drug" in Section 2.7 Preparation and Administration and 16 How Supplied/Storage and Handling, we recommend the container labels and carton labeling be updated with the statement "hazardous drug" to ensure consistency with the PI.

4 CONCLUSION & RECOMMENDATIONS

The proposed Pemetrexed Injection PPI is acceptable from a medication error perspective. The proposed Pemetrexed Injection PI, container label, and carton labeling can be improved for clarity. We provide specific recommendations in Sections 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Dosage and Administration, Section 2.7 Preparation for Administration
    a. Revise the storage temperature to include the unit of measure after each number for clarity. For example, "[2°C to 8°C (36°F to 46°F)]".
2. How Supplied/Storage and Handling
    a. Consider removing the statement [redacted] (b) (4) since this information is present in Section 2.7 Preparation for Administration.

4.2 RECOMMENDATIONS FOR SANDOZ

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. Revise the statement [redacted] (b) (4) to "Hazardous Drug" to ensure consistency with the hazardous statement on the Prescribing Information.
2. Revise the storage temperature to include the unit of measure after each number for clarity. For example, "15°C to 30°C (59°F to 86°F)".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pemetrexed Injection received on March 23, 2022 from Sandoz, and the listed drug (LD).

Table 2. Relevant Product Information for Pemetrexed Injection and the Listed Drug

Product Name	Pemetrexed Injection	Alimta[c] (NDA 021462)
Initial Approval Date	N/A	2/4/2004
Active Ingredient	Pemetrexed	Pemetrexed
Indication	Non-Squamous Non-Small Cell Lung Cancer • 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. Mesothelioma 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.	Non-Squamous Non-Small Cell Lung Cancer • 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. Mesothelioma 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.
Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	For Injection

[c] Alimta [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 Jan 30. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021462s053lbl.pdf.

Table 2. Relevant Product Information for Pemetrexed Injection and the Listed Drug		
Product Name	Pemetrexed Injection	Alimta[c] (NDA 021462)
Strength	100 mg/4 mL, 500 mg/ 20 mL, and 1,000 mg/40 mL	100 mg/vial, 500 mg/vial
Dose and Frequency	Non-squamous Non-Small Cell Lung Cancer 500 mg/m^2 intravenously over 10 minutes on Day 1 of each 21-day cycle. Mesothelioma 500 mg/m^2 intravenously over 10 minutes on Day 1 of each 21-day cycle.	Non-Squamous Non-Small Cell Lung Cancer 500 mg/m^2 intravenously over 10 minutes on Day 1 of each 21-day cycle. Mesothelioma 500 mg/m^2 intravenously over 10 minutes on Day 1 of each 21-day cycle.
How Supplied	Carton containing one single-dose vial	Carton containing one single-dose vial
Storage	(b) (4)	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Container Closure	4 mL, 20 mL, and 40 mL clear, colorless Typ (b) (4) glass vials, closed with (b) (4) rubber stoppers. The vials will be sealed with an aluminum (b) (4) cap with a light blue (b) (4) flip-off.	USP Type (b) (4) clear glass vials with gray (b) (4) rubber stoppers

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 3, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Pemetrexed. Our search identified numerous previous reviews (See Table 3), and we considered our previous recommendations to see if they are applicable for this current review.

Table 3. Pemetrexed products

Application	Applicant	Strength	Regulatory Status	OSE Review
NDA 021462 Alimta (pemetrexed) for Injection	Lilly	100 mg/vial 500 mg/vial	Approved 2/4/2004	None
NDA 209472 Pemfexy (pemetrexed) Injection	Eagle Pharmaceuticals	500 mg/20 mL	Approved 2/8/2020	2016-2997[d] 2016-2997-1[e] 2020-516[f]
NDA 208297 Pemetrexed for Injection	Dr. Reddy's	100 mg/vial 500 mg/vial 1 gram/vial	Tentative Approval on 5/14/2020	(b) (4)
NDA 208419 Pemetrexed Injection	Actavis	100 mg/4 mL 500 mg/20 mL 1 g/40 mL	Approved 8/21/2020	2017-156[l] 2018-211[m] 2018-211-1[n]

[d] Stewart, J. Label and Labeling Review for Pemfexy (Pemetrexed) Injection (NDA 209472). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Oct 25. RCM No.: 2016-2997.

[e] Stewart, J. Memorandum Review of Revised Label and Labeling for Pemfexy (Pemetrexed) Injection (NDA 209472). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Oct 2. RCM No.: 2016-2997-1.

[f] Stewart, J. Label and Labeling Review for Pemfexy (Pemetrexed) Injection (NDA 209472/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Apr 27. RCM No.: 2020-516.

(b) (4)

[l] Stewart, J. Label and Labeling Review for Pemetrexed Injection (NDA 208419). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Sept 11. RCM No.: 2017-156.

[m] Stewart, J. Label and Labeling Review for Pemetrexed Injection (NDA 208419). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 June 4. RCM No.: 2018-211.

[n] Stewart, J. Label and Labeling Review for Pemetrexed Injection (NDA 208419). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Apr 24. RCM No.: 2018-211-1.

Table 3. Pemetrexed products				
Application	**Applicant**	**Strength**	**Regulatory Status**	**OSE Review**
NDA 208746 Pemetrexed for Injection	Hospira	100 mg/vial 500 mg/vial 1 gram/vial	Tentative Approval on 1/8/2021 *11/22/2021 Class 2 Resubmission currently under review*	2016-2183[o] 2016-2183-1[p] 2016-2183-2[q]
NDA 210661 Pemetrexed for Injection	Apotex	100 mg/vial 500 mg/vial	(b) (4)	
NDA 214218 Pemetrexed Injection	Hospira	100 mg/4 mL 500 mg/20 mL 1 g/40 mL	Tentative Approval on 2/23/2021 *12/22/2021 Class 2 Resubmission currently under review*	2020-858[s] 2020-858-1[t] 2020-858-2[u]
NDA 214408 Pemetrexed Injection	Accord	100 mg/4 mL 500 mg/20 mL 850 mg/34 mL 1,000 g/40 mL	Complete Response on 11/23/2020 *11/17/2021 Class 2 Resubmission currently under review*	2020-172[v]
(b) (4)				
NDA 214657 Pemetrexed Injection	Sandoz	100 mg/4 mL 500 mg/20 mL 1,000 g/40 mL	Tentative Approval on 5/6/2021 *12/22/2021 Class 2 Resubmission currently under review* *Subject of this review*	2020-1442[z] 2020-1442-1[aa] 2020-1442-2

[o] Townsend, Otto. Label and Labeling Review for Pemetrexed Injection (NDA 208746). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Mar 1. RCM No.: 2016-2183.

[p] Stewart, J. Label and Labeling Review for Pemetrexed for Injection (NDA 208746). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Nov 23. RCM No.: 2016-2183-1.

[q] Stewart, J. Memorandum Review of Revised Label and Labeling for Pemetrexed for Injection (NDA 208746). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Dec 14. RCM No.: 2016-2183-2.

(b) (4)

[s] Stewart, J. Label and Labeling Review for Pemetrexed Injection (NDA 214218). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Oct 20. RCM No.: 2020-858.

[t] Stewart, J. Memorandum Review of Revised Label and Labeling for Pemetrexed Injection (NDA 214218). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Dec 18. RCM No.: 2020-858-1.

[u] Stewart, J. Memorandum Review of Revised Label and Labeling for Pemetrexed Injection (NDA 214218). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Jan 26. RCM No.: 2020-858-2.

[v] Stewart, J. Label and Labeling Review for Pemetrexed Injection (NDA 214408). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 June 19. RCM No.: 2020-172.

(b) (4)

[z] Stewart, J. Label and Labeling Review for Pemetrexed Injection (NDA 214657). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Dec 10. RCM No.: 2020-1442.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[bb] along with postmarket medication error data, we reviewed the following Pemetrexed Injection labels and labeling submitted by Sandoz.

- Container labels received on February 4, 2022
- Carton labeling received on February 4, 2022
- Prescribing Information and Patient Package Insert (Image not shown) received on March 23, 2022, available from \\CDSESUB1\evsprod\nda214657\0027\m1\us\114-labeling\final\package\prescribing-information-word.doc.

G.2 Label and Labeling Images[cc]

Container labels

(b) (4)

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[aa] Stewart, J. Memorandum Review of Revised Label and Labeling for Pemetrexed Injection (NDA 214657). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Jan 28. RCM No.: 2020-1442-1.

[bb] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

[cc] Final Vial – Carton Labels. Princeton (NJ): Sandoz Inc. 2022 Feb 4. Available from \\CDSESUB1\evsprod\nda214657\0026\m1\us\114-labeling\final\carton-or-container\final-vial-carton-labels.pdf.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 19, 2021

To: Kwadwo Korsah
Regulatory Health Project Manager
Division of Oncology 2 (DO2)

From: Nazia Fatima, PharmD, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **PEMETREXED injection, for intravenous use**
NDA 214657

Office of Prescription Drug Promotion comments on proposed prescribing information (PI) and Carton\Container Labeling

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Office of Prescription Drug Promotion (OPDP) has reviewed the draft prescribing information (PI) for PEMETREXED injection, for intravenous use (Pemetrexed) as requested by Division of Oncology 2 (DO2) on August 21, 2021.

OPDP has reviewed the proposed draft PI and draft carton\container labeling and has no comments. Combined OPDP and Division of Medical Policy Programs (DMPP) comments on the proposed Patient Package Insert (PPI) were provided under a separate cover.

If you have any questions, please feel free to contact, Nazia Fatima at 240-402-5041 or Nazia.Fatima@fda.hhs.gov. OPDP appreciates the opportunity to provide comments on this PI. Thank you!

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/s/

NAZIA FATIMA
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 16, 2021
To:	Kwadwo Korsah, PharmD, MS Regulatory Project Manager **Division of Oncology II (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nazia Fatima, PharmD, MBA, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	PEMETREXED INJECTION
Dosage Form and Route:	for intravenous use
Application Type/Number:	NDA 214657
Applicant:	Sandoz Inc.

1 INTRODUCTION

On July 7, 2020, Sandoz Inc., submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 214657 for PEMETREXED INJECTION for intravenous use. The Applicant references ALIMTA (pemetrexed injection) for intravenous use, NDA 021462 held by Eli Lilly and Co., as the Reference Listed Drug (RLD).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology II (DO2) on August 21, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for PEMETREXED INJECTION for intravenous use.

2 MATERIAL REVIEWED

- Draft PEMETREXED INJECTION PPI received on July 7, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 5, 2021.
- Draft PEMETREXED INJECTION Prescribing Information (PI) received on July 7, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 5, 2021.
- Approved ALTIMA (pemetrexed for injection) labeling dated January 30, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 28, 2021
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214657
Product Name and Strength:	Pemetrexed Injection, 100 mg/4 mL, 500 mg/20 mL, and 1,000 mg/40 mL
Applicant/Sponsor Name:	Sandoz Inc.
OSE RCM #:	2020-1442-1
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on January 13, 2021 for Pemetrexed Injection. Division of Oncology 2 (DO2) requested that we review the revised container labels and carton labeling for Pemetrexed Injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Stewart, J. Label and Labeling Review for Pemetrexed Injection (NDA 214657). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 DEC 10. RCM No.: 2020-1442.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	December 10, 2020
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214657
Product Name, Dosage Form, and Strength:	Pemetrexed Injection, 100 mg/4 mL, 500 mg/20 mL, and 1,000 mg/40 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Sandoz Inc.
FDA Received Date:	July 7, 2020 and October 6, 2020
OSE RCM #:	2020-1442
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the review of this 505(b)(2) submission for Pemetrexed Injection, DO2 requested that we review the proposed Prescribing Information (PI), Patient Information, container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 BACKGROUND

The Reference Listed Drug (RLD) is Alimta (pemetrexed disodium) for Injection (NDA 021462) which is supplied as a lyophilized powder in 100 mg/vial and 500 mg/vial packaging configurations. Sandoz Inc. is seeking approval of Pemetrexed Disodium Injection, 100 mg/4 mL, 500 mg/20 mL, and 1,000 mg/40 mL via the 505(b)(2) pathway. Sandoz's proposed product differs from the RLD with respect to the dosage form (injection vs. for injection). In addition, Sandoz is seeking approval of 1 additional strength presentation (1,000 mg/40 mL).

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C– N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F– N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We conducted a risk assessment the proposed PI, container labels, and carton labeling. We note that Sandoz is proposing a 1,000 mg/40 mL vial presentation which offers a different vial presentation than that of the RLD, Alimta, which is supplied as 100 mg/vial and 500 mg/vial. The proposed presentation yields a 25 mg/mL concentration which is consistent across both the proposed and the RLD product lines. Therefore, we find the additional proposed Pemetrexed strength presentation acceptable from a medication error perspective.

Our review of materials found that the proposed Pemetrexed PI, container labels, and carton labeling may be improved to promote safe use of this product. Thus, we provide related recommendations below in Section 5.

5 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Pemetrexed PI, container label, and carton labeling can be improved to promote the safe use of the product. We provide recommendations for DO2 in Section 5.1 and recommendations for Sandoz Inc. in Section 5.2 below.

5.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Dosage and Administration Section

a. We recommend listing numbers greater than or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000" (e.g., change 1000 to 1,000).

b. Consider revising Section 2.7 Preparation and Administration for improved clarity and readability as follows:

Pemetrexed injection is a (b) (4) drug. Follow applicable special handling and disposal procedures.[1]

1) Calculate the dose of Pemetrexed Injection and determine the number of vials needed.
2) Withdraw the calculated dose of Pemetrexed Injection from the vial(s) and discard vial with any unused portion.
3) Further dilute Pemetrexed Injection with 0.9% Sodium Chloride Injection, USP (preservative-free) to achieve a total volume of 100 mL for intravenous infusion.
4) Visually inspect for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard if particulate matter or discoloration is observed.
5) Administer pemetrexed as an intravenous infusion over 10 minutes.
6) If not used immediately, store diluted product under refrigerated conditions [2-8°C (36-46°F)] for no more than 24 hours from the time of dilution. Discard after 24 hours.

2. Dosage Forms and Strengths Section

a. Consider revising the presentation of information in Section 3: Dosage Forms and Strengths to include the description of the dosage form and to improve readability; for example, as follows:

Injection: Pemetrexed Injection is a clear, colorless to yellow or green-yellow solution available in sterile single-dose vials:

- 100 mg/4 mL (25 mg/mL)
- 500 mg/20 mL (25 mg/mL)
- 1,000 mg/40 mL (25 mg/mL)

3. How Supplied/Storage and Handling Section

    a. Consider revising the presentation of information in Section 16: How Supplied/Storage and Handling to improve readability; for example, as follows:

How Supplied

Pemetrexed Injection is supplied as a clear, colourless to yellow or green-yellow sterile solution in a clear glass vial with a grey rubber stopper, aluminium cap, and a light blue flip-off cap.

Strength/Fill volume	NDC number	Pack style
100 mg/4 mL	NDC 0781-3518-76	Carton containing one (1) single-dose vial
500 mg/20 mL	NDC 0781-3519-90	Carton containing one (1) single-dose vial
1,000 mg/40 mL	NDC 0781-3520-91	Carton containing one (1) single-dose vial

Storage and Handling

Store at (b) (4) Protect from light.

Pemetrexed injection is a (b) (4) drug. Follow applicable special handling and disposal procedures.

5.2 RECOMMENDATIONS FOR SANDOZ INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton labeling)

1. As proposed, the text on the container labels and on all panels of the carton labeling appears in small font size that may be difficult for users to read. Increase the font size of the product information to improve the readability of the information.

2. The established name lacks prominence while the strength and concentration statements within the color blocks appear with the greatest prominence on the carton labels and container labeling. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

a. Ensure the product name and strength are presented with the greatest prominence where they appear on the principal display panels, as well as on the top flap panel of the carton labeling.

3. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

4. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.1 The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

   [1]The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

5. Per 21 CFR 201.55, add the statement "Recommended Dosage: See prescribing information." to appear on the side panel.

6. To ensure consistency with the Prescribing Information, revise the statement on the back panel, (b) (4) to read "See prescribing information for…".

7. Revise and relocate the (b) (4) statement that appears on the top right corner of the PDP to read "Single-Dose vial. Discard unused portion." and to appear under the "For intravenous Infusion …" statement.

8. For the 1,000 mg/40 mL strength: We recommend listing numbers greater than or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000" (e.g., change 1000 to 1,000).

9. The cautionary statement [redacted] lacks prominence. Revise the statement to appear with greater prominence in red font color.
10. To eliminate the redundancy, delete the statement [redacted]" which appears on the back panel.

B. Container Labels

1. Ensure the barcode is surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).

C. Carton Labeling

1. The proprietary name, established name, and strength of the product are displayed in a vertical orientation. This may reduce readability when the carton is stored upright in a drug storage area. Consider rotating the proprietary name, established name and strength from a vertical orientation to a horizontal to improve user readability.
2. For the 1,000 mg/40 mL strength: The storage information lacks prominence Move the "Storage: …" statement on the back panel so the text it appears with greater prominence in its own section of the back panel.
3. Relocate the statement on the back panel, "For intravenous infusion…" to appear above the "Dilution:…" statement.
4. Revise the [redacted] statement that appears on the back panel to read "Single-Dose vial. Discard unused portion." We recommend this to minimize the risk of the entire contents of the vial being given as a sigle dose.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pemetrexed received on October 6, 2020 from Sandoz Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Pemetrexed and the Listed Drug		
Product Name	Pemetrexed	Alimta (NDA 021462)
Initial Approval Date	N/A	02/04/2004
Active Ingredient	Pemetrexed disodium	Pemetrexed disodium
Indication	Non-Squamous Non-Small Cell Lung Cancer • 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.	Non-Squamous Non-Small Cell Lung Cancer • 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.

Table 2. Relevant Product Information for Pemetrexed and the Listed Drug		
	Mesothelioma indicated, 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.	Mesothelioma indicated, 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.
Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	For Injection
Strength	100 mg/4 mL 500 mg/20 mL 1,000 mg/40 mL	100 mg and 500 mg
Dose and Frequency	Combination Use with Pembrolizumab and/or Platinum Chemotherapy for Nonsquamous Non-Small Cell Lung Cancer or Malignant Pleural Mesothelioma: 500 mg/m^2 intravenously over 10 minutes on Day 1 of each 21-day cycle. Single-Agent Use as Maintenance Following First-Line Therapy, or as a Second-Line Therapy: 500 mg/m^2 intravenously over 10 minutes on Day 1 of each 21-day cycle.	Combination Use with Pembrolizumab and/or Platinum Chemotherapy for Nonsquamous Non-Small Cell Lung Cancer or Malignant Pleural Mesothelioma: 500 mg/m^2 intravenously over 10 minutes on Day 1 of each 21-day cycle. Single-Agent Use as Maintenance Following First-Line Therapy, or as a Second-Line Therapy: 500 mg/m^2 intravenously over 10 minutes on Day 1 of each 21-day cycle.
How Supplied	Single-dose vials individually packaged in cartons	Single-dose vials individually packaged in individual cartons
Storage	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Container Closure	(b) (4) glass vials with (b) (4) rubber stoppers and (b) (4) aluminum seals	USP Typ (b) (4) clear glass vials with gray (b) (4) rubber stoppers

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 20, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Pemetrexed. Our search identified 2 previous reviews[a,b] for other 505(b)(2) Pemetrexed Injection applications, and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Pemetrexed labels and labeling submitted by Sandoz Inc..

- Container label received on July 7, 2020
- Carton labeling received on July 7, 2020
- Prescribing Information (Image not shown) received on October 6, 2020, available from \\CDSESUB1\evsprod\nda214657\0008\m1\us\114-labeling\draft\labeling\package-insert-word.doc
- Patient Information received on July 7, 2020, available from \\CDSESUB1\evsprod\nda214657\0001\m1\us\114-labeling\draft\labeling\patient-information.pdf

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[a] Stewart, J. Label and Labeling Review for Pemetrexed Injection (NDA 214218). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 20 RCM No.: 2020-858.

[b] Stewart, J. Label and Labeling Review for Pemetrexed (NDA 214408). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 19 RCM No.: 2020-172.

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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