CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215179Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: April 18, 2023

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

Barbara Scepura, Associate Director for Labeling, DO2

From: Kelle Caruso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

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

NDA: 215179

Background:
In response to DO2's consult request dated April 10, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and Patient Package Insert (PPI) for the original NDA submission for PEMETREXED INJECTION, for intravenous use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on April 11, 2023, and we do not have any comments at this time.

PPI:
A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on April 14, 2023.

Thank you for your consult. If you have any questions, please contact Kelle Caruso at 301-796-5044 or Kelle.Caruso@fda.hhs.gov.

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/s/

KELLE E CARUSO
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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:	April 14, 2023
To:	Idara Ojofeitimi, MS Chief, Project Management Staff **Division of Oncology 2 (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Ruth Mayrosh, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kelle Caruso, PharmD, BCPS 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 215179
Applicant:	Shilpa Medicare Limited

1 INTRODUCTION

On August 23, 2022, Shilpa Medicare Limited submitted for the Agency's review a Class 2 Resubmission of their proposed 505(b)(2) New Drug Application (NDA) 215179 for Pemetrexed Injection in response to a Complete Response (CR) letter issued by the Agency on April 14, 2022. 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 August 31, 2022. The proposed indications for Pemetrexed Injection are as follows:

- 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.

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 10, 2023, 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 August 24, 2022 and September 6, 2022, and received by DMPP and OPDP on April 11, 2023.
- Draft Pemetrexed Injection Prescribing Information (PI) received on August 24, 2022 and September 6, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 11, 2023.
- ALIMTA (pemetrexed for injection) comparator labeling dated August 31, 2022.

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/

JESSICA M CHUNG
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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:	October 20, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 215179
Product Name, Dosage Form, and Strength:	Pemetrexed Injection, 100 mg/10 mL, 500 mg/50 mL, 1,000 mg/100 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Shilpa Medicare Limited
FDA Received Date:	April 8, 2022 and September 6, 2022
TTT ID #:	2022-1360
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

Reference ID: 5064424

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 215179 is a 505(b)(2) NDA and the reference product is Alimta, NDA 021462.

See Table 1 below for regulatory history for NDA 215179 and DMEPA reviews completed.

Table 1. Regulatory history and DMEPA reviews

FDA Received Date	FDA Action	DMEPA Review
Shilpa submitted 505(b)(2) NDA 215179 that was received on August 27, 2020.	NDA 215179 received a Complete Response letter on June 24, 2021 due to product quality and facility inspection issues.[a]	2020-1806[b] 2020-1806-1[c] 2020-1806-2[d]
Shilpa submitted a Class 2 Resubmission that was received on October 14, 2021.	NDA 215179 received a Complete Response letter on October 14, 2021, which received a Complete Response on April 14, 2022 due to product quality issues.[e]	2020-1807-3[f]
Shilpa submitted a Class 2 Resubmission that was received on August 23, 2022.	Subject of this review	2022-1360 (subject of this review)

[a] Cohen, R. on behalf of Martha Donoghue. NDA 215179 Complete Response. Silver Spring (MD): FDA, CDER, OND, DOP2 (US); 2021 June 24.
[b] Stewart, J. Label and Labeling Review for Pemetrexed Injection (NDA 215179). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Feb 25. RCM No.: 2020-1806.
[c] Stewart J. Memorandum Review of Revised Label and Labeling for Pemetrexed Injection (NDA 215179). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 11. RCM No.: 2020-1806-1.
[d] Stewart, J. Memorandum Review of Revised Label and Labeling for Pemetrexed Injection (NDA 215179). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 May 21. RCM No.: 2020-1806-2.
[e] Ojofeitimi, I. on behalf of Martha Donoghue. NDA 215179 Complete Response. Silver Spring (MD): FDA, CDER, OND, DOP2 (US); 2022 Apr 14.
[f] Gao, T. Label and Labeling Review for Pemetrexed Injection (NDA 215179). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 Mar 24. RCM No.: 2020-1807-3.

Shilpa also submitted updated Pemetrexed Injection PI on September 6, 2022 and referred to the container labels and carton labeling submitted on April 8, 2022, stating that there are no changes to the Pemetrexed container labels and carton labeling.[g]

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Pemetrexed Injection PI and PPI and noted that Shilpa implemented all of our recommendations for the PI in the last review cycle.[f] Shilpa also further clarified that Pemetrexed Injection prepared in intravenous bag should be administered immediately and should not be stored.[h] The proposed Pemetrexed Injection PI is acceptable from a medication error perspective.

We reviewed the proposed Pemetrexed Injection container labels and carton labeling received on April 8, 2022 and noted that Shilpa implemented all of our recommendations in the last

[g] Amendment to Complete Response Resubmission – Labeling Pemetrexed Injection, 100mg/10mL, 500mg/50mL, 1g/100mL NDA# 215179; eCTD Sequence #0035. Mahabubnagar (Telangana, India): Shilpa Medicare Limited. 2022 Aug 24. Available from: \\CDSESUB1\EVSPROD\nda215179\0035\m1\us\cover-letter-0035-08-24-2022.pdf.
[h] Draft Pemetrexed Injection Prescribing Information with tracked changes. Mahabubnagar (Telangana, India): Shilpa Medicare Limited. 2022 Apr 8. Available from: \\CDSESUB1\EVSPROD\nda215179\0033\m1\us\draft-pack-insert-track-changes.docx

review cycle.[f] The proposed Pemetrexed Injection container labels and carton labeling are acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

The proposed Pemetrexed Injection PI, PPI, container labels and carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pemetrexed Injection received on September 6, 2022 from Shilpa Medicare Limited, and the listed drug (LD).

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

Product Name	Pemetrexed Injection	Alimta[i] (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 non-small cell lung cancer (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 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 non-small cell lung cancer (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 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

[i] Alimta [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2022 Aug 31. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/021462s055lbl.pdf.

Table 2. Relevant Product Information for Pemetrexed Injection and the Listed Drug		
Product Name	Pemetrexed Injection	Alimta[i] (NDA 021462)
Strength	100 mg/10 mL, 500 mg/50 mL, 1,000 mg/100 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	Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Container Closure	100 mg/10 mL: 10 mL type-I glass vial with light blue flip off top 500 mg/50 mL: 50 mL type-I glass vial with light blue flip off top 1,000 mg/100 mL: 100 type-I glass vial with light blue flip off top	USP Type (b) (4) clear glass vials with gray (b) (4) rubber stoppers

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 7, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, NDA 215179. Our search identified 4 previous reviews[j,k,l,m], and we considered our previous recommendations to see if they are applicable for this current review.

[j] Stewart, J. Label and Labeling Review for Pemetrexed Injection (NDA 215179). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Feb 25. RCM No.: 2020-1806.
[k] Stewart J. Memorandum Review of Revised Label and Labeling for Pemetrexed Injection (NDA 215179). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 11. RCM No.: 2020-1806-1.
[l] Stewart, J. Memorandum Review of Revised Label and Labeling for Pemetrexed Injection (NDA 215179). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 May 21. RCM No.: 2020-1806-2.
[m] Gao, T. Label and Labeling Review for Pemetrexed Injection (NDA 215179). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 Mar 24. RCM No.: 2020-1807-3.

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,[n] along with postmarket medication error data, we reviewed the following Pemetrexed Injection labels and labeling submitted by Shilpa Medicare Limited.

- Container label received on April 8, 2022
- Carton labeling received on April 8, 2022
- Prescribing Information and Patient Package Insert (Image not shown) received on September 6, 2022, available from \\CDSESUB1\EVSPROD\nda215179\0036\m1\us\draft-pack-insert-track-changes.docx

G.2 Label and Labeling Images

Container labels

(b) (4)

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

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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:	March 24, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 215179
Product Name, Dosage Form, and Strength:	Pemetrexed Injection, 100 mg/10 mL, 500 mg/50 mL, 1,000 mg/100 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Shilpa Medicare Limited
FDA Received Date:	March 4, 2022
OSE RCM #:	2020-1807-3
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Acting Team Leader:	Janine Stewart, PharmD

Reference ID: 4958001

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 214218 is a 505(b)(2) NDA and the reference product is Alimta, NDA 021462.

Shilpa submitted NDA 215179 on August 27, 2020, which received a Complete Response on June 24, 2021 due to product quality and facility inspection issues.[a]

Thus, Shilpa submitted a Class 2 Resubmission on October 14, 2021. Shilpa also submitted updated PI, container labels, and carton labeling on March 4, 2022 to include the currently proposed manufacturing site, Cadila Healthcare, on labels and labeling.[b]

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] Cohen, R. on behalf of Martha Donoghue. NDA 208746 Complete Response. Silver Spring (MD): FDA, CDER, OND, DOP2 (US); 2021 June 24.

[b] Pemetrexed Injection, 100mg/10mL, 500mg/50mL, 1g/100mL. NDA# 215179. Response to INFORMATION REQUEST. Mahabubnagar (Telangana, India): Shilpa Medicare Limited. 2022 Mar 4. Available from: \\CDSESUB1\evsprod\nda215179\0028\m1\us\response-fda-ir.pdf.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Pemextrexed Injection PI, container labels, and carton labeling and determined that they can be improved to ensure safe product use.

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

4 CONCLUSION & RECOMMENDATIONS

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

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

- Calculate the dose of Pemetrexed Injection and determine the volume of Pemetrexed Injection needed. Each vial contains an excess of Pemetrexed Injection to facilitate delivery of labeled amount.
- Withdraw the calculated dose of Pemetrexed Injection from the vial(s) and discard vial(s) with any unused portion.
- Transfer the calculated dose into an empty intravenous bag. Do NOT further dilute Pemetrexed Injection.
- Visually inspect for particulate matter and discoloration prior to administration. Discard if particulate matter or discoloration is observed.
- Administer Pemetrexed Injection undiluted, as an intravenous infusion over 10 minutes using an infusion pump.

b. Consider deleting (b) (4) since it (b) (4) and may lead to confusion.

c. Consider adding storage information for Pemetrexed Injection prepared in intravenous bag if not administered immediately.

2. Dosage Forms and Strengths

    a. Revise the strength statement for "1 g/100 mL" to "1,000 mg/100 mL" to be consistent with the strength statement for 1,000 mg/100 mL vial in Section 16 and the container labels and carton labeling.

3. How Supplied/Storage and Handling Section

    a. The strength should state the total amount followed by the total volume in each vial. For example, "Carton containing one single-dose vial, 100 mg/10 mL."

    b. Revise the strength statement of the 1000 mg/100 mL vial to read 1,000 with a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000" and to ensure consistency with the strength statement for 1,000 mg/100 mL vial in Section 3 and the container labels and carton labeling.

    c. Revise the storage statement "Store at 20–25°C (68-77°F); excursions permitted to 15-30°C (59-86°F)" to "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)" for clarity.

4.2 RECOMMENDATIONS FOR SHILPA MEDICARE LIMITED

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

A. General Comments (Container labels & Carton Labeling)

1. Revise the statement (b) (4) to "Hazardous Drug" to ensure consistency with the hazardous statement on the Prescribing Information.

2. Revise the storage statement "Store at 20–25°C (68-77°F); excursions permitted to 15-30°C (59-86°F)" to "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)" for clarity.

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 4, 2022 from Shilpa Medicare Limited, 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/10 mL, 500 mg/50 mL, 1,000 mg/100 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	Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Container Closure	**100 mg/10 mL:** 10 mL type-I glass vial with light blue flip off top **500 mg/50 mL:** 50 mL type-I glass vial with light blue flip off top **1,000 mg/100 mL:** 100 type-I glass vial with light blue flip off top	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.
[g] Townsend, O. Label and Labeling Review for Pemetrexed for Injection (NDA 208297). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Mar 3. RCM No.: 2015-2321.
[h] Thomas, S. Memorandum Review of Revised Label and Labeling for Pemetrexed for Injection (NDA 208297). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Apr 20. RCM No.: 2015-2321-1.
[i] Stewart, J. Label and Labeling Review for Pemetrexed for Injection (NDA 208297). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Apr 24. RCM No.: 2018-1297.
[j] Stewart, J. Memorandum Review of Revised Label and Labeling for Pemetrexed for Injection (NDA 208297). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 May 6. RCM No.: 2018-1297-1.
[k] Stewart, J. Memorandum Review of Revised Label and Labeling for Pemetrexed for Injection (NDA 208297). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 May 8. RCM No.: 2018-1297-2.
[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]
(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]
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*	2020-1442[w] 2020-1442-1[x]
NDA 215179 **Pemetrexed Injection**	Shilpa	100 mg/10 mL 500 mg/50 mL 1 g/100 mL	Complete Response on 6/24/2021 *11/17/2021 Class 2 Resubmission currently under review* *Subject of this review*	2020-1806[y] 2020-1806-1[z] 2020-1806-2[aa] 2020-1807-3

[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.

[w] 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.

[x] 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.

[y] Stewart, J. Label and Labeling Review for Pemetrexed Injection (NDA 215179). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Feb 25. RCM No.: 2020-1806.

[z] Stewart J. Memorandum Review of Revised Label and Labeling for Pemetrexed Injection (NDA 215179). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 11. RCM No.: 2020-1806-1.

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 Shilpa Medicare Limited.

- Container labels received on March 4, 2022
- Carton labeling received on March 4, 2022
- Prescribing Information and Patient Package Insert (Image not shown) received on March 4, 2022, available from \\CDSESUB1\evsprod\nda215179\0028\m1\us\draft-labeling-text-word.docx

G.2 Label and Labeling Images

Container labels

[aa] Stewart, J. Memorandum Review of Revised Label and Labeling for Pemetrexed Injection (NDA 215179). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 May 21. RCM No.: 2020-1806-2.
[bb] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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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 Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	June 25, 2021
To:	Rebecca Cohen, RN, MPH, OCN Regulatory Health Project Manager **Division of Oncology III (DO3)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI)
Drug Name (established name):	Pemetrexed Injection
Dosage Form and Route:	For intravenous use
Application Type/Number:	NDA 215179
Applicant:	Shilpa Meidcare LTD

Reference ID: 4816997

1 INTRODUCTION

On August 27, 2020, Shipla Meidcare LTD submitted for the Agency's review an original New Drug Application (NDA-215179) for Pemetrexed Injection, for intravenous use, for the proposed indication of 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,
- 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. (1.1) Limitations of Use: pemetrexed injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer,
- in 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.

On October 6, 2020, the Division of Oncology III (DO3) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for Pemetrexed Injection, for intravenous use.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI for Pemetrexed Injection, for intravenous use.

2 CONCLUSIONS

Due to outstanding Chemistry, Manufacturing and Controls (CMS) deficiencies, DO3 issued a Complete Response (CR) letter on June 24, 2021. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

Reference ID: 4816997

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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: June 4, 2021

To: Rebecca Cohen, RN, MPH, OCN
CDR, U.S Public Health Service
Regulatory Health Project Manager
Division of Oncology 3
Office of Regulatory Operations – Oncologic Disease

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

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

NDA 215179

In response to Division of Oncology 3 (DO3)'s consult request dated October 6, 2020, OPDP has reviewed the proposed labeling (PI), patient package insert (PPI), and carton container labeling for PEMETREXED INJECTION, for intravenous use (Pemetrexed).

OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DO3 (Rebecca Cohen) on May 17, 2021 and have no comments. OPDP has reviewed the PPI and have no comment.

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room June 1, 2021, and we do not have any comments.

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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NAZIA FATIMA
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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:	May 21, 2021
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 215179
Product Name and Strength:	Pemetrexed Injection, 100 mg/10mL, 500 mg/50 mL, and 1,000 mg/100 mL
Applicant/Sponsor Name:	Shilpa Medicare Limited
OSE RCM #:	2020-1806-2
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 March 16, 2021 for Pemetrexed. Division of Oncology 2 (DO2) requested that we review the revised container labels and carton labeling for Pemetrexed (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.

[a] Stewart J. Label and Labeling Review for Pemetrexed (NDA 215179). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 11. RCM No.: 2020-1806-1.

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JANINE A STEWART
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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:	March 11, 2021
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 215179
Product Name and Strength:	Pemetrexed Injection, 100 mg/10mL, 500 mg/50 mL, and 1 g/100 mL
Applicant/Sponsor Name:	Shilpa Medicare Limited
OSE RCM #:	2020-1806-1
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised received on March 5, 2021 for Pemetrexed. Division of Oncology 2 (DO2) requested that we review the revised container labels and carton labeling for Pemetrexed (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 revised container labels and carton labeling are unacceptable from a medication error perspective. We provide additional recommendations in Section 3.

[a] Stewart J. Label and Labeling Review for Pemetrexed (NDA 215179). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 25. RCM No.: 2020-1806.

Reference ID: 4760595

3 RECOMMENDATIONS FOR SHILPA MEDICARE LIMITED

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

A. Container Label and Carton Labeling

1. Consider revising the strength statement of the 1000 mg/ 100 mL vial presentation to read 1,000 with a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000".

B. Carton Labeling

1. Add a banner on uppermost portion of the principal display panel (PDP) that reads "Note Concentration"; using color, typography, contrast, and placement to promote the prominence of the statement to differentiate and emphasize the new concentration of the proposed pemetrexed injection from various other strengths of Pemetrexed Injection products in 25 mg/mL concentrations.

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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)

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

Date of This Review:	February 25, 2021
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 215179
Product Name, Dosage Form, and Strength:	Pemetrexed Injection, 100 mg/10mL, 500 mg/50 mL, and 1 g/100 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Shilpa Medicare Limited
FDA Received Date:	August 27, 2020, October 15, 2020, February 4, 2021
OSE RCM #:	2020-1806
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

Reference ID: 4752818

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), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 BACKGROUND

Shilpa Medicare Limited (Shilpa) is seeking approval of Pemetrexed Disodium Injection, 100 mg/10 mL, 500 mg/50 mL, and 1 g/100 mL via the 505(b)(2) pathway. 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. Shilpa Medicare Limited's proposed product differs from the RLD with respect to the dosage form (injection vs. for injection), concentration, and preparation prior to administration.

In the initial submission, the proposed product was described as a ready-to use formulation to be administered undiluted directly from the vials and discard any unused portion. Based on our interpretation of the information submitted, the proposed dosing would result in dose calculations that require multiple vials and in some cases may require the use of partial vials to achieve the calculated dose. We were concerned that the need to use multiple and partial vials of a ready-to-use formulation could lead to wrong dose medication errors. Thus, on February 1, 2021, we sent an Information Request to clarify the anticipated use of the proposed product. In their February 4, 2021 response, Shilpa clarified that they expect the calculated volume of their proposed product to be withdrawn from the vial(s) and placed into an empty IV bag to be administered undiluted and they submitted a revised PI, container labels and carton labeling[a].

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

[a] NDA 215179 Response to Information Request. India: Shilpa Medicare Limited. 2021 FEB 04. Available from: \\CDSESUB1\evsprod\nda215179\0009\m1\us\response-fda-ir.pdf

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
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

The listed drug (LD) for the proposed Pemetrexed Injection is Alimta (pemetrexed for injection) (NDA 021462) approved in 2004. Pemetrexed Injection has been marketed for over 16 years by various manufacturers in several strengths (100 mg/vial, 500 mg/vial, 100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL, and 1,000 mg/40 mL) which all yield a concentration of 25 mg/mL.

The preparation of pemetrexed infusions using currently marketed pemetrexed products requires further dilution in 0.9% Sodium Chloride or in 5% Dextrose to achieve a final volume of 100 mL before administration. Shilpa seeks approval of Pemetrexed Disodium Injection, 100 mg/10 mL, 500 mg/50 mL, and 1 g/100 mL via the 505(b)(2) pathway. Shilpa's proposed product differs from the RLD with respect to the concentration (10 mg/mL vs. 25 mg/mL) and the dosage form (injection vs. for injection). In addition, Shilpa's product is proposed as a formulation to be administered undiluted.

Because Pemetrexed Injection in the concentration of 25 mg/mL has been marketed since 2004 in various strengths, end users (pharmacist and nurses) are used to pemetrexed injection in the concentration of 25 mg/mL and may mistakenly think the proposed product with a concentration of 10 mg/mL is also a pemetrexed in 25 m/mL concentration. Although the potential clinical impact from selection errors during dispensing (i.e. select the wrong pemetrexed vial from the pharmacy shelf) are unlikely to result in overdose, we are concerned that the proposed new 10 mg/mL concentration introduces the new risk of confusion that may lead to medication errors.

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

5 CONCLUSION & RECOMMENDATIONS

Based on post-market experience, we are concerned about the risk associated with the introduction of the new 10 mg/mL concentration for Pemetrexed Injection to the marketplace that is familiar with a 25 mg/mL concentration. We conclude that the proposed PI , the container labels, and carton labeling for Pemetrexed Injection can be improved to increase the

clarity, readability, and the prominence of important information to promote the safe use of this product. Thus, we provide recommendations in Section 5.1 and Section 5.2.

5.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Dosage and Administration Section

a. 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 volume of Pemetrexed Injection needed.
2) Withdraw the calculated dose of Pemetrexed Injection from the vial(s) and discard vial with any unused portion.
3) Transfer the required dose to an empty infusion bag. Do not further dilute Pemetrexed Injection.
4) Visually inspect for particulate matter and discoloration prior to administration. Discard if particulate matter or discoloration is observed.
5) Administer pemetrexed as an intravenous infusion over 10 minutes.

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, the concentration, and to improve readability; for example, as follows:

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

- 100 mg/10 mL (10 mg/mL)
- 500 mg/50 mL (10 mg/mL)
- 1 g/100 mL (10 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, colorless to pale yellow or greenish-yellow solution in a USP type-I glass vial with a rubber stopper and aluminium cap.

Strength/Fill volume	NDC number	Pack style
100 mg/10 mL	NDC 63759-3048-1	Carton containing one (1) single-dose vial
500 mg/50 mL	NDC 63759-3049-1	Carton containing one (1) single-dose vial
1 g/1000 mL	NDC 63759-3050-1	Carton containing one (1) single-dose vial

Storage and Handling

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from light.

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

5.2 RECOMMENDATIONS FOR SHILPA MEDICARE LIMITED

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

A. General Comments (Container labels & Carton Labeling)

1. 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.

2. Consider revising the statement (b) (4) to read: "For intravenous infusion only". We recommend this to minimize the risk of administering the drug as an injection.

3. Revise the statement (b) (4) to use positive language. E.g., "Administer Undiluted." We recommend this revision due to post-marketing reports that negative statements (e.g. do not) may have the opposite of the intended meaning because the word "not" can be overlooked and the warning may be misinterpreted as an affirmative action.

4. To ensure consistency with the Prescribing Information, revise the statement on the side panel, [redacted] (b) (4) See package insert…" to read "Recommended Dosage: See prescribing information ".
5. Combine the statements "Discard unused portion" and "Single Dose Vial" to appear together on the PDP as "Single dose vial. Discard unused portion." and to appear under the "For intravenous Infusion …" statement.

B. Container Labels

1. As proposed, the container labels feature an [redacted] (b) (4). This feature is inconsistent with the intended use of the product because [redacted] (b) (4)

[redacted] (b) (4)

2. Revise the presentation of the concentration "(10 mg/mL)" to present the statement with highlights, shadow effect, boxing, or other methods to emphasize the new concentration to end users.

C. Carton Labeling

1. Add a banner on uppermost portion of the principal display panel (PDP) that reads "Note Concentration"; using color, typography, contrast, and placement to promote the prominence of the statement to differentiate and emphasize the new concentration of the proposed pemetrexed injection from various other strengths of Pemetrexed Injection products in 25 mg/mL concentrations.
    a. Revise the presentation of the concentration "(10 mg/mL)" to present the statement with highlights, shadow effect, boxing, or other methods to point out this the new concentration to end users.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pemetrexed received on October 15, 2020 from Shilpa Medicare Limited, and the listed drug (LD).

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

Reference ID: 4752818

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/10 mL 500 mg/50 mL 1,000 mg/100 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	Type-I (b) (4) glass vials with 20mm dark grey (b) (4) rubber stoppers and 20 mm light blue aluminum seals	USP Type (b) (4) clear glass vials with gray (b) (4) rubber stoppers

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 22, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Pemetrexed. Our search identified 3 previous reviews[b,c,d] 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,[e] along with postmarket medication error data, we reviewed the following Pemetrexed labels and labeling submitted by Shilpa Medicare Limited.

- Container label received on February 4, 2021
- Carton labeling received on February 4, 2021
- Prescribing Information (Image not shown) received on February 4, 2021, available from \\CDSESUB1\evsprod\nda215179\0009\m1\us\draft-labeling-text-word.docx

[b] Stewart, J. Label and Labeling Review for Pemetrexed Injection (NDA 214657). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 DEC 10 RCM No.: 2020-858.

[c] 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.

[d] 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.

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

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JANINE A STEWART
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