CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214218Orig1s000

OTHER REVIEW(S)

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 25, 2022
To:	Opeyemi Udoka, DPT, CSM 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 214218
Applicant:	Hospira, Inc.

1 INTRODUCTION

On December 22, 2021, Hospira, Inc. submitted for the Agency's review a Class 2 Resubmission of their proposed 505 (b)(2) New Drug Application (NDA) 214218 for Pemetrexed Injection in response to an Agency Tentative Approval Letter dated February 23, 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 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 May 3, 2022, and May 2, 2022, respectively, 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 December 22, 2021, and received by DMPP and OPDP on May 13, 2022.
- Draft Pemetrexed Injection Prescribing Information (PI) received on December 22, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 13, 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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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:	April 21, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214218
Product Name and Strength:	Pemetrexed Injection, 100 mg/4 mL, 500 mg/20 mL, and 1 g/40 mL
Applicant/Sponsor Name:	Hospira, Inc.
OSE RCM #:	2020-858-4
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Acting Team Leader:	Janine Stewart, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on April 18, 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.

We also noted that Hospira made formatting changes to the container labels to increase the space surrounding the representative pharma code (FPO) to align with the actual pharma code size.[b] We found these proposed changes acceptable from a medication error perspective.

[a] Gao, T. Label and Labeling Review for Pemetrexed Injection (NDA 214218). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 Apr 5. RCM No.: 2020-858-3.

[b] Side-By-Side Comparison of Hospira's Previously Tentatively Approved Container Labeling (Previously Submitted) and Proposed Container Labeling. Lake Forest (IL): Hospira, Inc. 2022 Apr 18. Available from: \\CDSESUB1\evsprod\nda214218\0023\m1\us\side-by-side-comparison-containers.pdf.

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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)

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Date of This Review:	April 5, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214218
Product Name, Dosage Form, and Strength:	Pemetrexed Injection, 100 mg/4 mL, 500 mg/20 mL, and 1 g/40 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Hospira, Inc.
FDA Received Date:	February 4, 2021 and December 22, 2021
OSE RCM #:	2020-858-3
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 214218 is a 505(b)(2) NDA and the reference product is Alimta, NDA 021462.

Hospira previously submitted NDA 214218 on April 23, 2020, which received a Tentative Approval on February 23, 2021.[a]

Thus, Hospira submitted a Class 2 Resubmission on December 22, 2021. Hospira also stated that there are minor editorial changes to the PI with regarding to document version number and revision date[b], and that there are no further changes to the container labels and carton labeling as provided in the FDA Tentative Approval letter dated February 23, 2021.[a]

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] Woods, S. on behalf of Martha Donoghue. NDA 214218 Tentative Approval. Silver Spring (MD): FDA, CDER, OND, DOP2 (US); 2021 Feb 23.

[b] Pemetrexed Injection. 1.11.1 Summary of Changes. US NDA 214218. Lake Forest (IL): Hospira, Inc. 2021 Dec 22. Available from: \\CDSESUB1\evsprod\nda214218\0021\m1\us\summary-of-change.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 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 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)]".

4.2 RECOMMENDATIONS FOR HOSPIRA, INC.

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

B. General Comments (Container labels & Carton Labeling)

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

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pemetrexed Injection received on December 22, 2021 from Hospira, Inc., 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 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
Strength	100 mg/4 mL, 500 mg/20 mL, and 1 g/40 mL	100 mg/vial, 500 mg/vial

[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)
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 refrigerated at 2°C to 8°C (36°F to 46°F).	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Container Closure	6 mL, 20 mL, and 50 mL (b) (4) clear glass vials with (b) (4) l rubber stoppers and yellow (b) (4) Top	(b) (4) 14 mL and 50 mL 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]
NDA 210661 Pemetrexed for Injection	Apotex	100 mg/vial 500 mg/vial	NDA withdrawn on 10/25/2019	(b) (4)

[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.

(b) (4)

Table 3. Pemetrexed products				
Application	**Applicant**	**Strength**	**Regulatory Status**	**OSE Review**
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[p]
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[q] 2020-1442-1[r]
(b) (4)				
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[v] 2016-2183-1[w] 2016-2183-2[x]
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* *Subject of this review*	2020-858[y] 2020-858-1[z] 2020-858-2[aa] 2020-858-3

[p] 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.

[q] 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.

[r] 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.

(b) (4)

[v] 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.

[w] 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.

[x] 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.

[y] 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.

[z] 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.

[aa] 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.

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 Hospira, Inc.

- Container label received on February 4, 2021
- Carton labeling received on February 4, 2021
- Prescribing Information and Patient Package Insert (Image not shown) received on December 22, 2021, available from \\CDSESUB1\evsprod\nda214218\0021\m1\us\lab-1432-1-0-pkg-insert-clean.doc

G.2 Label and Labeling Images

Container labels

(b) (4)

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

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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 26, 2021
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214218
Product Name and Strength:	Pemetrexed Injection, 100 mg/4 mL, 500 mg/20 mL, and 1g/40 mL
Applicant/Sponsor Name:	Hospira Inc.
OSE RCM #:	2020-858-2
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels for the 100 mg/4 mL and the 500 mg/20 mL configurations received on January 12, 2021 for Pemetrexed. Division of Oncology 2 (DO2) requested that we review the revised container labels 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 memorandum.[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 Memorandum for Pemetrexed (NDA 214218). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 DEC 18. RCM No.: 2020-858-1.

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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:	December 18, 2020
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214218
Product Name, Dosage Form, and Strength:	Pemetrexed Injection, 100 mg/4 mL, 500 mg/20 mL, and 1g/40 mL
Applicant/Sponsor Name:	Hospira Inc.
OSE RCM #:	2020-858-1
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 December 7, 2020 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 revised carton labeling is acceptable from a medication error perspective. However, the revised container labels for the 100 mg/4 mL and the 500 mg/20 mL configurations are unacceptable from a medication error perspective. As proposed, the revised 100 mg/4 mL container label lacks important product information that appears on the side panel of the container labels for the other 2 configurations. The product information on the side panel of the revised 500 mg/20 mL container label appears cluttered. Contributing factors appear to be the lack of adequate white space and the change in the orientation of the side panel

[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.

information compared to the container labels we reviewed in the previous label and labeling review.[a] We provide recommendations in Section 3 below.

3 RECOMMENDATIONS FOR HOSPIRA INC.

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

A. The size of the reserved FPO space and unvarnished area is inconsistent between the container labels thereby allowing varying amounts of space and location for the "manufactured by" information.
    a. For the 100 mg/4 mL and the 500 mg/20 mL configurations, we recommend reducing the reserved FPO space and unvarnished area and relocating the "manufactured by" information to appear on the principal display panel (PDP).
    b. Then we recommend orienting the side panel text and linear barcode to appear vertically and thereby allow space for the product information to appear and the barcode to be readable (similar to how the information is presented on the container label for the 1 g/40 mL configuration).

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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:	October 20, 2020
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214218
Product Name, Dosage Form, and Strength:	Pemetrexed Injection, 100 mg/4 mL, 500 mg/20 mL, and 1g/40 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Hospira Inc.
FDA Received Date:	April 23, 2020
OSE RCM #:	2020-858
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 container labels, carton labeling, and Prescribing Information for areas of vulnerability that may lead to medication errors.

2 BACKGROUND

Hospira 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. 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. Hospira's proposed product differs from the RLD with respect to the dosage form (injection vs. for injection). Further, Hospira is not seeking an indication for 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 addition, Hospira is proposing 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 – N/A
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

Of the proposed PI, we reviewed Section 2 Dosage and Administration, Section 3 Dosage Forms and Strengths, Section 16 How Supplied/Storage and Handling, and Section 17 Patient Counseling Information. We note that Hospira is proposing a 1 g/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 do not anticipate the proposed Pemetrexed strength presentations will introduce any new risk of medication errors.

We also reviewed the proposed container labels and carton labeling. We provide recommendations in Section 5.1 to support the safe and effective use of the proposed product and to improve the clarity and readability of statements that appear on the proposed container labels, and carton labeling.

5 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed PI is acceptable from a medication error perspective. However, 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 and effective use of this product. Thus, we provide recommendations in Section 5.1 below.

5.1 RECOMMENDATIONS FOR HOSPIRA INC.

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

A. General Comments (Container labels & Carton Labeling)

1. Revise the storage statement [redacted] (b) (4) to read "Store refrigerated at 2°C to 8°C (36°F to 46°F)." We recommend this for consistency with the storage statement in the PI.

2. Consider revising the statements [redacted] (b) (4) and [redacted] (b) (4) to read "For Intravenous Infusion After Dilution". We recommend this condensed statement to minimize the risk of administering the drug as an intravenous bolus.

3. Revise the "Single Dose Vial" statement on the principal display panel (PDP) to read "Single Dose Vial - Discard Unused Portion" to minimize the risk of the entire contents of the vial being given as a single dose.

4. 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.

5. 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

A. Container Labels

1. As proposed, the "For Intravenous use…" and the "Caution: …" statements on the 100 mg/ 4 mL container label crowd the principal display panel (PDP) and compete for prominence with the established name and the strength statement.
   a. Reduce the font size of the "For Intravenous use…" and the "Caution: …" statements.
   b. Center the strength statement (100 mg/4mlL) and relocate the concentration statement (25 mg/mL) to appear below the strength statement.

2. To the side panel, add the statement that reads "Recommended Dosage: See prescribing information" per 21 CFR 201.55

3. Add "Use 0.9% Sodium Chloride Injection, USP (preservative free) when diluting Pemetrexed Injection" to the container label to help avoid errors associated with using a wrong solution for dilution.
   a. If space permits on the container label, add the statement similar to "To Dilute: Dilute the required volume of drug with 0.9% Sodium Chloride Injection, USP (preservative free) to a total volume of 100 mL."

C. Carton Labeling

1. Revise the [redacted] (b) (4) statement to read "Recommended Dosage: See prescribing information." for consistent terminology with the Prescribing Information (PI).

2. Revise the "To Dilute: …" statement on the side panel to read similar to "To Dilute: Dilute the required volume of drug with 0.9% Sodium Chloride Injection, USP (preservative free) to a total volume of 100 mL.". We recommend this to support the safe and effective use of the product.

3. To eliminate redundancy on the PDP, remove the [redacted] (b) (4) statement that appears in the top right corner of the PDP.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pemetrexed received on April 23, 2020 from Hospira 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 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 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.	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.
Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	For Injection
Strength	100 mg/4 mL 500 mg/20 mL 1 g/40 mL	100 mg and 500 mg
Dose and Frequency	Combination Use with Cisplatin 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 refrigerated at 2°-8°C (36°-46°F).	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Container Closure	6 mL, 20 mL, and 50 mL (b) (4) clear glass vials with (b) (4) rubber stoppers	(b) (4) 50 mL clear glass vials with gray (b) (4) rubber stoppers

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,[a] along with postmarket medication error data, we reviewed the following Pemetrexed labels and labeling submitted by Hospira Inc..

- Container label received on April 23, 2020
- Carton labeling received on April 23, 2020
- Prescribing Information (Image not shown) received on April 23, 2020, available from \\cdsesub1\evsprod\nda214218\0001\m1\us\lab-1432-0-1-uspi.doc

G.2 Label and Labeling Images

Container Labels

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

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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: October 19, 2020

To: Stacie Woods
Regulatory Health Project Manager
Division of Oncology (DO2)

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

CC: Brian Tran, Team Leader, OPDP

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

NDA: 214218

In response to DO2's consult request, dated April 24, 2020, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) and carton and container labeling for the original NDA submission for PEMETREXED FOR INJECTION, for intravenous use (pemetrexed).

OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DO2 on October 5, 2020. OPDP does not have any comments on the draft PI.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on October 16,2020.

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on April 23, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Nazia Fatima at 240-402-5041 or Nazia.Fatima@fda.hhs.gov.

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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:	October 16, 2020
To:	Stacie Woods, PharmD 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 214218
Applicant:	Hospira Inc.

1 INTRODUCTION

On April 23, 2020, Hospira Inc., submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 214218 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 April 24, 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 April 23, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 5, 2020.
- Draft PEMETREXED INJECTION Prescribing Information (PI) received on April 23, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 5, 2020.
- 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.

Please let us know if you have any questions.

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/s/

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