CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208746Orig1s000

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:	April 28, 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)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD 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 FOR INJECTION
Dosage Form and Route:	for intravenous use
Application Type/Number:	NDA 208746
Applicant:	Hospira, Inc., a Pfizer company

1 INTRODUCTION

On December 22, 2021, Hospira, Inc., a Pfizer Company submitted for the Agency's review a Class 2 Resubmission of their proposed 505 (b)(2) New Drug Application (NDA) 208746 for Pemetrexed for Injection in response to an Agency Tentative Approval Letter dated January 8, 2021. The reference listed drug (RLD) for this submission is ALIMTA (pemetrexed for injection), NDA 021462, held by Eli Lilly and Company, and most recently approved on January 30, 2019. The proposed indications for Pemetrexed for 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 February 23, 2022 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for Pemetrexed for Injection.

2 MATERIAL REVIEWED

- Draft Pemetrexed for Injection PPI received on December 22, 2021, and received by DMPP and OPDP on April 19, 2022.
- Draft Pemetrexed for 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 April 19, 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 208746
Product Name and Strength:	Pemetrexed for Injection, 100 mg/vial, 500 mg/vial, 1 g/vial
Applicant/Sponsor Name:	Hospira, Inc.
OSE RCM #:	2016-2183-3
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 20, 2022 for Pemetrexed for Injection. Division of Oncology 2 (DO2) requested that we review the revised container labels and carton labeling for Pemetrexed for 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.

[a] Gao, T. Label and Labeling Review for Pemetrexed for Injection (NDA 208746). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 Apr 6. RCM No.: 2016-2183-2.

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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:	April 6, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 208746
Product Name, Dosage Form, and Strength:	Pemetrexed for Injection, 100 mg/vial, 500 mg/vial, 1 g/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Hospira, Inc.
FDA Received Date:	December 22, 2021 and February 16, 2022
OSE RCM #:	2016-2183-2
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Acting Team Leader:	Janine Stewart, PharmD

1 REASON FOR REVIEW

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

1.1 REGULATORY HISTORY

NDA 208746 is a 505(b)(2) NDA and the reference product is Alimta, NDA 021462.

Hospira submitted NDA 208746 on September 15, 2016, which received a Complete Response on July 10, 2017 due to facility inspection issues.[a]

Hospira submitted NDA 208746 on July 10, 2020, which received a Tentative Approval on January 8, 2021.[b]

Thus, Hospira submitted a Class 2 Resubmission on December 22, 2021 and resubmitted the container labels and carton labeling with minor changes[c] on February 16, 2022.

2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

[a] Wilson, F. on behalf of Joseph Gootenberg. NDA 208746 Complete Response. Silver Spring (MD): FDA, CDER, OND, DOP2 (US); 2017 July 10.

[b] Highsmith, J. on behalf of Martha Donoghue. NDA 214218 Tentative Approval. Silver Spring (MD): FDA, CDER, OND, DOP2 (US); 2021 Jan 8.

[c] Side-By-Side Comparison of Hospira's Previously Tentatively Approved Container Labeling and Final Container Labeling. Lake Forest (IL): Hospira, Inc. 2022 Feb 16. Available from: \\CDSESUB1\evsprod\nda208746\0023\m1\us\container-labels-side-by-side.pdf.

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

*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 for Injection PI, PPI, container labels, and carton labeling and determined that the proposed PI, container labels, and carton labeling 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 for Injection PI, container labels, and carton labeling can be improved to ensure safe product use. We provide specific recommendations in Sections 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Dosage and Administration Section, 2.7 Preparation for Administration
    a. Revise the storage temperature to include the unit of measure after each number for clarity. For example, "[2°C to 8°C (36°F to 46°F)]".
2. How Supplied/Storage and Handling Section
    a. Revise the storage temperature to include the unit of measure after each number for clarity. For example, "[20°C to 25°C (68°F to 77°F)]".

4.2 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 statement “Caution: Cytotoxic agent” to “Warning: Hazardous Drug” to ensure consistency with the hazardous statement on the Prescribing Information.

B. Container Labels

    1. Revise the wording in the sentence “See accompany literature for storage of reconstituted and infusion solutions.” to “See prescribing information for storage reconstituted and infusion solutions.” for consistency.

C. Carton labeling

    1. Add the statement “for no more than 24 hours from the time of reconstitution.” at the end of the sentence “Store reconstituted and infusion solutions refrigerated at 2-8°C (36-46°F)” on the side panel. For example, “Store reconstituted and diluted solutions refrigerated at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution.”

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pemetrexed for Injection received on December 22, 2021 from Hospira, Inc., and the listed drug (LD).

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

Product Name	Pemetrexed for Injection	Alimta[d] (NDA 021462)
Initial Approval Date	N/A	2/4/2004
Active Ingredient	Pemtrexed	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	For Injection	For Injection
Strength	100 mg/vial, 500 mg/vial, 1 g/vial	100 mg/vial, 500 mg/vial

[d] 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 for Injection and the Listed Drug		
Product Name	Pemetrexed for Injection	Alimta[d] (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 at 20-25°C (68-77°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	10 mL, 50 mL, and 100 mL USP Type (b) (4) clear glass vials with 20 mm (b) (4) rubber stoppers and Flip-Off Top	USP Type (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[e] 2016-2997-1[f] 2020-516[g]
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[m] 2018-211[n] 2018-211-1[o]
NDA 210661 Pemetrexed for Injection	Apotex	100 mg/vial 500 mg/vial	(b) (4)	(b) (4)
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[q]
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[r] 2020-1442-1[s]
(b) (4)				(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[w] 2020-858-1[x] 2020-858-2[y]
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* *Subject of this review*	2016-2183[z] 2016-2183-1[aa] 2016-2183-2[bb] 2016-2183-3

[e] 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.

[f] 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.

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

- Container labels received on February 16, 2022
- Carton labeling received on February 16, 2022

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[g] 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.

[h] (b) (4)

[i] (b) (4)

[j] (b) (4)

[k] (b) (4)

[l]

[m] 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.

[n] 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.

[o] 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.

[p] (b) (4)

[q] 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.

[r] 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.

[s] 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)

[w] 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.

[x] 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.

[y] 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.

[z] 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.

[aa] 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.

[bb] 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.

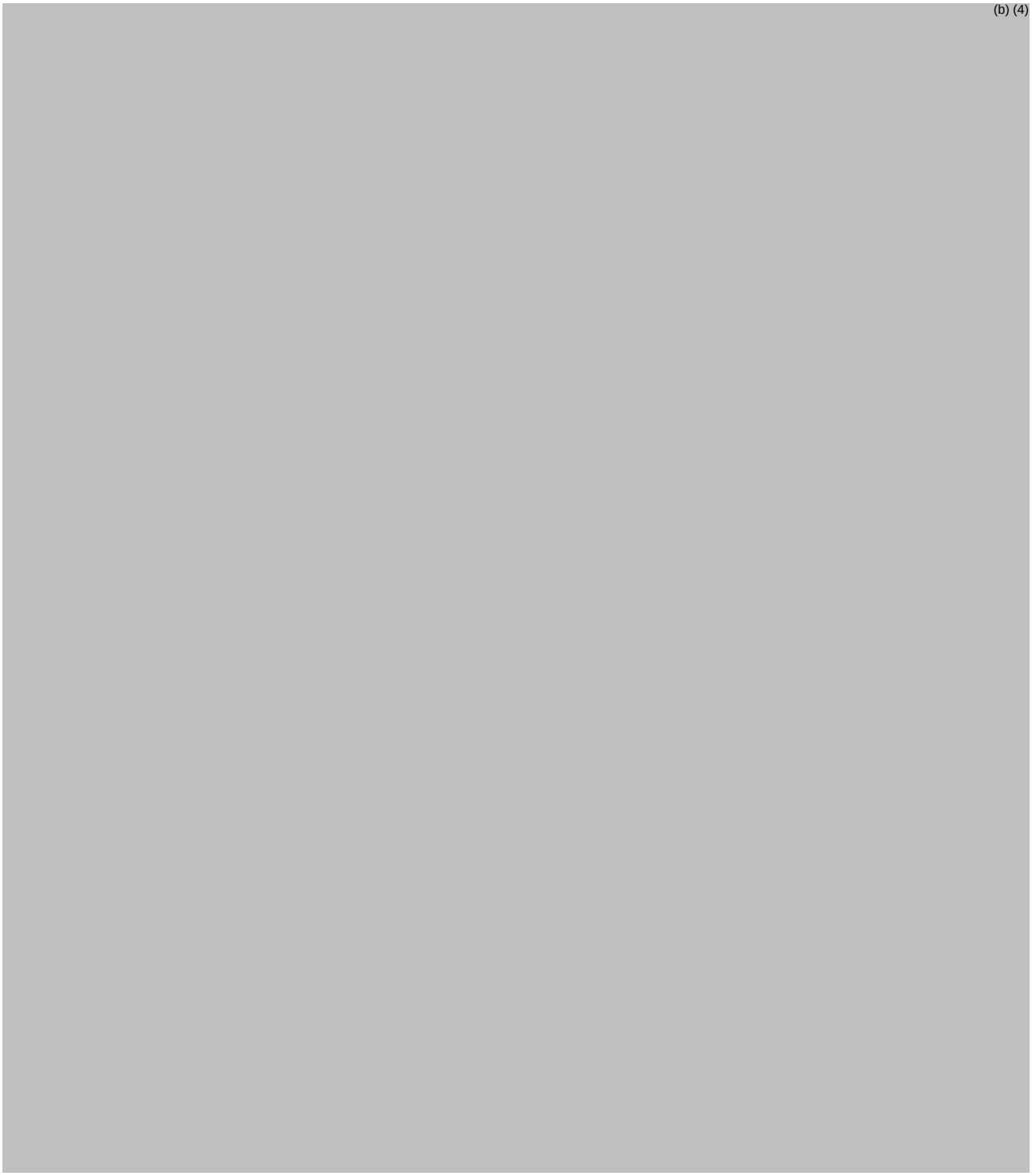
[cc] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Prescribing Information (Image not shown) received on December 22, 2021, available from \\CDSESUB1\evsprod\nda208746\0021\m1\us\lab-1264-1-0-pkg-insert-clean.doc

G.2 Label and Labeling Images

Container labels

(b) (4)



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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 14, 2020
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 208746
Product Name, Dosage Form, and Strength:	Pemetrexed for Injection, 100 mg/vial, 500 mg/vial, and 1 gram/vial
Applicant/Sponsor Name:	Hospira, Inc.
OSE RCM #:	2016-2183-2
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 December 11, 2020 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 208746). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 23. RCM No.: 2016-2183-1.

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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:	November 23, 2020
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 208746
Product Name, Dosage Form, and Strength:	Pemetrexed for Injection, 100 mg/vial, 500 mg/vial, and 1 gram/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Hospira, Inc.
FDA Received Date:	July 10, 2020
OSE RCM #:	2016-2183-1
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the review process of this Class 2 Resubmission for Pemetrexed Injection, this review evaluates the proposed container labels, carton labeling, and Prescribing Information for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Hospira originally submitted NDA 208746 for FDA's review on September 15, 2016. DMEPA completed a review of the proposed container labels, carton labeling, and Prescribing Information under OSE RCM# 2016-2183[a]. Subsequently, the Agency issued a CR letter on July 10, 2017[b] citing facility inspections deficiencies. The Agency decided to reserve comment on the proposed labeling until the application becomes adequate for review. Thus, DMEPA's container labels and carton labeling recommendations were not included in the CR letter.

On July 10, 2020, Hospira submitted a Class 2 Resubmission to respond to the July 10, 2017 CR letter. Final approval of this application is pending expiration of patents for the listed drug, Alimta, and is not expected to be finalized until May 2022.

2 MATERIALS REVIEWED

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

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

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

[a] Townsend, O. Label and Labeling Review for Pemetrexed Injection (Hospira – NDA 208746). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAR 01. RCM No.: 2016-2183.

[b] Wilson, F. Complete Response for NDA 208746. Silver Spring (MD): FDA, CDER, OND, DO2 (US); 2017 JUL 10. NDA 208746.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The listed drug for the proposed Pemetrexed for injection (NDA 208746) is Alimta (NDA 021462). Both products contain the same active moiety, pemetrexed, but differ in the salt form of the active ingredient. The active ingredient of the listed drug, Alimta, is pemetrexed disodium, but the active ingredient of the proposed product is pemetrexed ditromethamine. Despite the difference in active ingredients, both products provide the same amount of the active moiety, pemetrexed. The listed drug is currently marketed as 100 mg and 500 mg vial strengths. The Applicant is proposing 100 mg and 500 mg and 1 gram vial strengths. The three proposed vial strengths are visibly differentiated from one another by the use of color.

We also noted that the Principal Display Panel of the container labels is cluttered, which makes it difficult to locate important safety information. The container labels could be reformatted to provide clarity and increase readability.

To address these concerns, we have provided recommendations in Section 4 below.

4 CONCLUSION & RECOMMENDATIONS

The proposed prescribing information (PI), container labels, and carton labeling can be improved to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Dosage and Administration Section

a. 

b. As proposed, the information presented in Section 2.7 Preparation and Administration can be revised to eliminate redundancy and to improve clarity and readability. Further, we recommend presenting the preparation instructions in a tabular format; for example as follows:

2.7 Preparation for Administration

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

Determine the number of vials needed, then reconstitute and further dilute Pemetrexed for Injection as follows:

- Reconstitute each vial with 0.9% Sodium Chloride Injection, USP (preservative-free) AND further dilute prior to intravenous administration with 0.9% Sodium Chloride Injection, USP (preservative-free) as shown in Table 2.

(b) (4)

Table 2: Reconstitution and Further Dilution with 0.9% Sodium Chloride Injection, USP

	100 mg vial	500 mg vial	1 gram vial
Step 1 Reconstitute to achieve a 25 mg/mL[a] concentration	Reconstitute each 100-mg vial with 4.2 mL of 0.9% Sodium Chloride Injection, USP (preservative-free).	Reconstitute each 500-mg vial with 20 mL of 0.9% Sodium Chloride Injection, USP (preservative-free).	Reconstitute each 1-gram vial with 40 mL of 0.9% Sodium Chloride Injection, USP (preservative-free).
Step 2 Swirl and Inspect[b]	Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in color from colorless to yellow or green-yellow. FURTHER DILUTION IS REQUIRED prior to administration. Inspect reconstituted product visually for particulate matter and discoloration prior to further dilution. If particulate matter is observed, discard vial.		
Step 3	Withdraw the calculated dose of Pemetrexed for Injection from the		

Withdraw Calculated Dose	vial(s) and discard vial with any unused portion.
Step 4 Further Dilute[c]	Further dilute Pemetrexed for Injection with 0.9% Sodium Chloride Injection, USP (preservative-free) to achieve a total volume of 100 mL for intravenous infusion.

(b) (4)

[a] Do not use calcium containing solutions for reconstitution.

[b] If not used immediately, store reconstituted, preservative-free product under refrigerated conditions [2-8°C (36-46°F)] for no longer than 24 hours from the time of reconstitution. Discard vial after 24 hours.

[c] If not used immediately, store diluted, reconstituted product under refrigerated conditions [2-8°C (36-46°F)] for no more than 24 hours from the time of reconstitution. Discard after 24 hours.

4.2 RECOMMENDATIONS FOR HOSPIRA, INC.

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

A. General Comments (Container labels & Carton Labeling)

1. The product strength should be expressed in terms of the total amount of drug per vial. Change the strength statement so that it indicates the amount of drug in each vial.
   For example, "XXX mg/vial" or "XXX mg per vial" or "XXX gram/vial" or "XXX gram per vial".

2. 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.

3. Revise the "(b) (4)" statements on the principal display panel (PDP) to read "For Intravenous Infusion after dilution". We recommend this condensed statement to reduce clutter on the PDP and to minimize the risk of administering the drug as an intravenous bolus.

4. Relocate the statement "Discard Unused Portion" (b) (4) and place it immediately after the package type term statement so it reads "Single-dose vial. Discard unused portion." This statement can be relocated where space permits; such as to the lower portion of the PDP. See example in B.1. below.

5. To highlight the storage statement, add the heading, "Storage:" in bolded font to read, "Storage: Store (b) (4) at 20° - 25°C (68° - 77°F)…".

6. 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

7. Assigning National Drug Codes (NDC) with sequential drug product codes (middle digits) for different strengths of the same drug product does not adequately distinguish the products, and has led to selecting and dispensing of the wrong strength. To better differentiate National Drug Codes, we recommend changing the product codes (e.g., 1060, 1061, and 1062) so that they are not sequential. If for some reason the middle digits cannot be revised, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type. For example: XXXX-XXXX-XX.

B. Container Labels

1. The Principal Display Panel (PDP) is cluttered making it difficult to locate important safety information. To increase the prominence of the established name, dosage form, and strength; and to reduce clutter on the PDP, we recommend that you relocate [redacted] (b) (4) to side panel. This would provide adequate white space between the important safety information, such as example PDP layout below (example to help demonstrate our recommendation only, not to font/size/color/artwork):

Rx only NDC ####-####-##
Pemetrexed for Injection
100 mg/vial
Lyophilized
For Intravenous Infusion after dilution
Single-dose vial. Discard unused portion
Caution: cytotoxic Agent

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

2. If space permits, add reconstitution instructions and the resultant concentration (25 mg/mL). These instructions will inform persons responsible for preparing the product what type and volume of diluent should be used for reconstitution, and the amount of drug contained in each milliliter once reconstituted.

3. If space permits, add storage information for the prepared Pemetrexed solution after reconstitution and dilution: "Store reconstituted and infusion solutions refrigerated at 2° - 8°C (36° - 46°F)"

C. Carton Labeling

1. To ensure consistency with the Prescribing Information, revise the statement, "(b) (4)" to read "Recommended Dosage: See prescribing information."

2. Revise the statement "(b) (4) ....." to read "To Dilute: Dilute required volume of drug to a total (b) (4) of 100 mL with 0.9% Sodium Chloride Injection, USP (preservative -free)...". We recommend this simplified statement to reduce clutter on the side panel.

3. Revise the statement "(b) (4) " to read "Store reconstituted and infusion solutions refrigerated at 2° - 8°C (36° - 46°F)".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pemetrexed received on July 10, 2020 from Hospira, Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Pemetrexed and the Listed Drug		
Product Name	Pemetrexed	Alimta
Initial Approval Date	N/A	02/04/2004
Active Ingredient	Pemetrexed ditromethamine	Pemetrexed disodium
Indication	Non-Small Cell Lung Cancer and Mesothelioma	Non-Small Cell Lung Cancer and Mesothelioma
Route of Administration	Intravenous	Intravenous
Dosage Form	For Injection	For Injection
Strength	100 mg, 500 mg and 1 gm	100 mg and 500 mg
Dose and Frequency	Same as Listed Drug	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/m2 intravenously over 10 minutes on Day 1 of each 21-day cycle.
How Supplied	Single-dose vials individually packaged in individual cartons	Single-dose vials individually packaged in individual cartons
Storage	Store at 20°C -25°C (68°F - 77°F) [see USP Controlled Room Temperature].	Store at 25°C (77°F); excursions permitted to 15°C -30°C (59°F -86°F) [see USP Controlled Room Temperature].

Table 2. Relevant Product Information for Pemetrexed and the Listed Drug		
Product Name	Pemetrexed	Alimta
Container Closure	Type (b) (4) 10 mL, 50 mL, and 100 mL Clear Glass Vials with gray (b) (4) rubber closures and 20 mm aluminum seals and flip-off tops	USP Type (b) (4) 50 mL clear glass vials with gray (b) (4) rubber stoppers

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 20, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Pemetrexed. Our search identified 4 previous reviews[c,d,e,f,g,h,i] for other 505(b)(2) Pemetrexed for Injection applications, and we considered our previous recommendations to see if they are applicable for this current review.

[c] (b) (4) .

[d] (b) (4)

[e] (b) (4)

[f] Townsend, O. Label and Labeling Review for Pemetrexed for Injection. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017Mar01. RCM No.: 2016-2183.

[g] Stewart, J. Label and Labeling Review for Pemetrexed Injection Concentrate. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017Sep11. RCM No.: 2017-156.

[h] Stewart, J. Label and Labeling Review for Pemetrexed Injection. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017Oct25. RCM No.: 2016-2997.

[i] (b) (4)

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 Hospira, Inc..

- Container label received on July 10, 2020
- Carton labeling received on July 10, 2020
- Prescribing Information (Image not shown) received on July 10, 2020, available from \\CDSESUB1\evsprod\nda208746\0014\m1\us\draft-labeling-text.doc

G.2 Label and Labeling Images

[e] 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

PATIENT LABELING REVIEW

Date:	November 16, 2020
To:	Jana L. Highsmith 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)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD 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 FOR INJECTION
Dosage Form and Route:	for intravenous use
Application Type/Number:	NDA 208746
Applicant:	Hospira, Inc., a Pfizer company

1 INTRODUCTION

On July 10, 2020, Hospira, Inc., a Pfizer Company submitted for the Agency's review a Class 2 Resubmission of their proposed 505 (b)(2) New Drug Application (NDA) 208746 for Pemetrexed for Injection in response to an Agency Complete Response Letter dated July 10, 2017. The reference listed drug (RLD) for this submission is ALIMTA (pemetrexed for injection), NDA 021462, held by Eli Lilly and Company, and most recently approved on January 30, 2019. The proposed indications for Pemetrexed for 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 August 19, 2020 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for Pemetrexed for Injection.

2 MATERIAL REVIEWED

- Draft Pemetrexed for Injection PPI received on July 10, 2020, and received by DMPP and OPDP on November 10, 2020.
- Draft Pemetrexed for Injection Prescribing Information (PI) received on July 10, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 10, 2020.
- 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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LASHAWN M GRIFFITHS
11/16/2020 12:29:38 PM

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

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

Memorandum

Date: November 13, 2020

To: Jana L. Highsmith
Regulatory Health Project Manager
Division of Oncology 2
Division of Regulatory Operations for Office of Oncologic Diseases

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

Subject: **PEMETREXED FOR INJECTION, for intravenous use**
NDA 208746

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

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Office of Prescription Drug Promotion (OPDP) has reviewed the draft prescribing information (PI) for PEMETREXED FOR INJECTION, for intravenous use (pemetrexed) as requested by Division of Oncology Products (DOP2) in a consult dated August 19, 2020. OPDP's review of the proposed PI is based on the draft PI titled, "USPI_annotated_From_ToSponsor11102020" send by electronic mail on November 10, 2020 to OPDP (Nazia Fatima) from DO2 (Jana Highsmith). OPDP does not have any comments on the PI.

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

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

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/s/

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

REVIEW DEFERRAL MEMORANDUM

Date:	June 17, 2017
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
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:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI)
Drug Name (established name):	PEMETREXED
Dosage Form and Route:	for injection, for intravenous use
Application Type/Number:	NDA 208746
Applicant:	Hospira, Inc., a Pfizer company

1 INTRODUCTION

On September 15, 2016, Hospira, Inc., a Pfizer company submitted for the Agency's review a New Drug Application (NDA) 208746 for PEMETREXED for injection in accordance with Section 505 (b)(2) of the Federal Food, Drugs and Cosmetic Act. The reference listed drug (RLD) for this submission is ALIMTA (pemetrexed for injection), NDA 021462, held by Eli Lilly and Company, and approved February 4, 2004. The proposed indications for PEMETREXED for injection are as follows:

- locally advanced or metastatic nonsquamous non-small cell lung cancer
  - initial treatment in combination with cisplatin
  - maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy
  - after prior chemotherapy as a single agent
- mesothelioma in combination with cisplatin.

On November 16, 2016, the Division of Oncology Products 2 (DOP2) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for PEMETREXED for injection.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI for PEMETREXED for injection.

2 CONCLUSIONS

Due to outstanding deficiencies, DOP2 plans to issue a Complete Response (CR) letter. 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.

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/s/

SHARON R MILLS
06/17/2017

BARBARA A FULLER
06/17/2017

LASHAWN M GRIFFITHS
06/18/2017

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:	March 1, 2017
Requesting Office or Division:	Division of Oncology Product 2 (DOP2)
Application Type and Number:	NDA 208746
Product Name and Strength:	Pemetrexed for Injection, 100 mg, 500 mg, and 1 gm
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Hospira, Inc.
Submission Date:	September 15, 2016
OSE RCM #:	2016-2183
DMEPA Primary Reviewer:	Otto L. Townsend, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As part of the NDA review of this 5050(b)(2) submission for Pemetrexed for Injection, DOP2 requested that we review the proposed container labels, carton labeling, and Prescribing Information for areas of vulnerability that may lead to medication errors.

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 Label and Labeling 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
FDA Adverse Event Reporting System (FAERS)*	E
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The listed drug for the proposed Pemetrexed for injection (NDA 208746) is Alimta (NDA 021462). Both products contain the same active moiety, pemetrexed, but differ in the salt form of the active ingredient. The active ingredient of the listed drug, Alimta, is pemetrexed disodium, but the active ingredient of the proposed product is pemetrexed ditromethamine. Despite the difference in active ingredients, both products provide the same amount of the active moiety, pemetrexed. The listed drug is currently marketed as 100 mg and 500 mg vial strengths. The Applicant is proposing 100 mg and 500 mg and 1 gram vial strengths. The three proposed vial strengths are visibly differentiated from one another by the use of color. Also, the Applicant uses the same color scheme for the the 100 mg and 500 mg vial strengths that is used for the listed drug (orange for 100 mg and blue for 500 mg).

There are currently four tentatively approved Abbreviated New Drug Applications for Pemetrexed for injection products. In addition to the submission that is the subject of this review, Hospira also has a tentatively approved ANDA (ANDA 202111) for pemetrexed. The other applications are held by Accord (ANDA 203485), APP Pharmaceuticals (ANDA 090384),

and Teva (ANDA 090352). Final approval of these applications is pending expiration of patents for the listed drug, Alimta, and is not expected to be finalized until May 2022.

Our search of FAERS did not identify any cases that described medications errors that could be applicable to the labels and labeling of this proposed pemetrexed product. Our search of the Institute for Safe Medication Practices (ISMP) newsletters did not identify any articles that described medication errors associated with the labeling of the listed drug, Alimta, but it did yield one article that reported ISMP's plan to add pemetrexed to its List of Confused Drug Names because of its risk of confusion with pralatrexate. ISMP also recommends the use of tall man lettering to differentiate these two products. These names are not included in the FDA's list of name pairs that may be prone to look-alike confusion[a].

In our search of AIMS and the L: / drive, we found two past reviews of pemetrexed ditromethamine that were completed by DMEPA. We reviewed the recommendations in those reviews to determine if they should be included in this review.

During our review, we were notified of DOP2's plan to harmonize Prescribing Information (PI) for all injectable pemetrexed products including the listed drug, Alimta, and those submitted under 505(b)(2) applications. DOP2 plans to make substantial changes to the PI for the listed drug, Alimta, which Eli Lilly has agreed to consider and subsequently submit to the Agency as a prior approval labeling supplement. With this plan in mind, we noted issues with the proposed PI for this NDA. In Section 2 (Dosage and Administration), the Applicant proposed the use of symbols that the ISMP considers error-prone[b]. For example, they used the symbol, <, which is intended to mean less than, but may be misinterpreted as more than. The Applicant also did not include the unit of measurement following the first value in the temperature range (see recommendations).

(b) (4)

We also noted that the Principal Display Panel of the container labels is cluttered, which makes it difficult to locate important safety information. The container labels could be reformatted to provide clarity and increase readability. The PDP contains redundant statements "1 x 100 mg" and "Single-use Vial", but this appears to be Hospira's trade dress and is seen on many existing Hospira products (e.g. Epirubicin HCl Injection, USP; Gemcitabine for Injection, USP; etc.). Thus, we do not object to these redundant statements.

[a] FDA Name Differentiation Project. 2013.[cited 2017 JAN 11]. Available from http://www.fda.gov/Drugs/DrugSafety/MedicationErrors/ucm164587.htm

To address these concerns, we have provided recommendations in Section 4 below.

Additionally, we noted the use of the package type term, “single use vial”, on the container labels and carton labeling as well as the PI. We defer to Office of Pharmaceutical Quality (OPQ) for the determination of the appropriate package type term on labels and labeling.

4 CONCLUSION & RECOMMENDATIONS

The proposed Prescribing Information (PI), container labels, and carton labeling for Pemetrexed for injection can be improved to promote the safe use of the product. Our recommendations are applicable to the proposed PI that was submitted on September 15, 2016. We note that these recommendations may not be applicable if the harmonization effort moves forward.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. In Section 2 (Dosage and Administration),
    a. To prevent misinterpretation of the symbols such as, < and ≥, spell out the words. For example, change < to read, “less than”.

    b. To provide clarity and to promote the safe use of the proposed Pemetrexed for injection, in Section 2.6, revise the statement

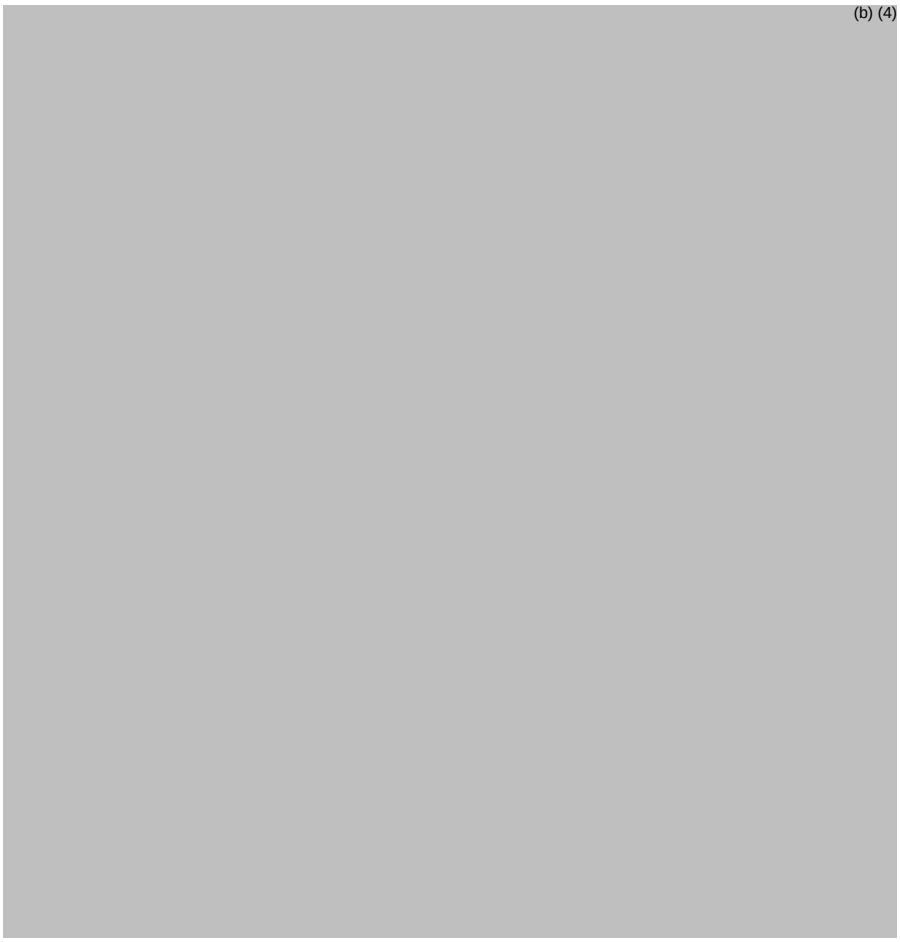
    [redacted (b) (4)]”

    To read

    “[redacted (b) (4)]”

c. To minimize potential confusion during reconstitution and dilution of Pemetrexed for Injection, consider incorporating a table in Section 2 (Dosage and Administration) to help the preparer determine how to appropriately reconstitute and further dilute Pemetrexed for Injection:

Table XX. Reconstitution and Dilution



2. In Section (b) (4) (Storage and Handling), change the storage statements to include the unit of measurement after each temperature value. For example, change the statement, "Store (b) (4) at 20-25°C (68-77°F)..." to read, "Store (b) (4) at 20°C - 25°C (68°F - 77°F)…".

4.2 RECOMMENDATIONS FOR HOSPIRA

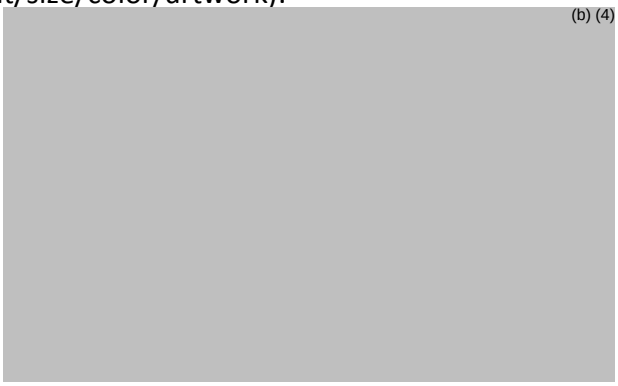
We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container Labels and Carton Labeling)

1. The product strength should be expressed in terms of the total amount of drug per vial. Change the strength statement so that it indicates the amount of drug in each vial.
   For example, "XXX mg/vial" or "XXX mg per vial" or "XXX gram/vial" or "XXX gram per vial".
2. Assigning National Drug Codes (NDC) with sequential drug product codes (middle digits) for different strengths of the same drug product do not adequately distinguish the products (e.g., 100 mg – 0409-1060-01 versus 500 mg – 0409-1061-01). To better differentiate National Drug Codes, we recommend changing the product codes (middle digits) so that they are not sequential.

B. Container Labels

1. The Principal Display Panel (PDP) is cluttered making it difficult to locate important safety information. To increase the prominence of the established name, dosage form, and strength; and to reduce clutter on the PDP, we recommend that you relocate the (b) (4) to side panel. This would provide adequate white space between the important safety information, such as example PDP layout below (example to help demonstrate our recommendation only, not to font/size/color/artwork):



2. Change the storage statements to include the unit of measurement after each temperature value. For example, change the statement, "Store (b) (4) at 20-25°C (68-77°F)..." to read, "Store (b) (4) at 20°C - 25°C (68°F - 77°F)…".

3. Relocate the statement "Discard Unused Portion" (b) (4), and place it immediately after the package type term statement.

C. Carton Labeling

1. (b) (4)

2. To highlight the Dosage statement, add the heading, "(b) (4) Dosage:" in bolded font and change the (b) (4) dosage statement from "(b) (4) " to read, "See Prescribing Information".
   For example: "(b) (4) **Dosage:** See Prescribing Information"

3. To highlight the storage statement, add the heading, "Storage:" in bolded font. In addition, include the unit of measurement after each temperature value.
   For example, change the statement, "Store (b) (4) at 20-25°C (68-77°F)..." to read, "**Storage:** Store (b) (4) at 20°C - 25°C (68°F - 77°)…".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pemetrexed that Hospira submitted on September 15, 2016 and the listed drug (LD).

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

Product Name	**Pemetrexed**	**Alimta**
Initial Approval Date	N/A	02/04/2004
Active Ingredient	Pemetrexed ditromethamine	Pemetrexed disodium
Indication	Non-Small Cell Lung Cancer and Mesothelioma	Non-Small Cell Lung Cancer and Mesothelioma
Route of Administration	Intravenous	Intravenous
Dosage Form	For Injection	For Injection
Strength	100 mg, 500 mg and 1 gm	100 mg and 500 mg
Dose and Frequency	Same as Listed Drug	**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/m2 intravenously over 10 minutes on Day 1 of each 21-day cycle.
How Supplied	Single-use vials individually packaged in individual cartons	Single-use vials individually packaged in individual cartons
Storage	Store at 20°C -25°C (68°F - 77°F) [see USP Controlled Room Temperature].	Store at 25°C (77°F); excursions permitted to 15°C - 30°C (59°F -86°F) [see USP Controlled Room Temperature].

Table 2. Relevant Product Information for Pemetrexed and the Listed Drug		
Product Name	**Pemetrexed**	**Alimta**
Container Closure	Type (b) (4) 10 mL, 50 mL, and 100 mL Clear Glass Vials with gray (b) (4) rubber closures and 20 mm aluminum seals and flip-off tops	USP Type (b) (4) 50 mL clear glass vials with gray (b) (4) rubber stoppers

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

Since this is a 505(b)(2) submission, on January 3, 2017, we searched the L:drive and AIMS using the terms, "Pemetrexed" and "Alimta" to identify reviews previously performed by DMEPA that might inform our review.

B.2 Results

Our search identified two previous reviews[c,d]. The previous reviews were for a proposed product by (b) (4). We reviewed recommendations contained in those reviews to determine if any were applicable to this review.

[c] (b) (4)

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On January 3, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, and Nursing
Search Strategy and Terms	Match Any of the Words: Alimta, pemetrexed

D.2 Results

Our search of ISMP newsletters did not identify any articles that described medication errors associated with the labeling of the listed drug, Alimta. However, our search did identify one article[e] from 2010 that announced ISMP's plans to update its List of Confused Drug Names[f] to include the names pemetrexed and pralatrexate due to their potential for confusion.

[e] ISMP Updates its list of drug name pairs with tall man letters. ISMP Med Saf Alert Acute Care. 2010; 15(23):1-3.

[f] ISMP's List of Confused Drug Names [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2017 JAN 10]. Available from http://www.ismp.org/tools/confuseddrugnames.pdf.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on January 3, 2017 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[g]

Table 3: FAERS Search Strategy	
Initial FDA Receive Dates	**12/1/15* through 12/31/16**
Product Name	**Alimta**
Product Active Ingredient	**Pemetrexed; Pemetrexed disodium**
Event (MedDRA Terms)	*Medication errors* SMQ (narrow)

* Our last search was performed on December 3, 2015

E.2 Results

Our search retrieved 2 cases, but after further evaluation, we didn't identify any medication error cases that were relevant for this review and could be addressed by labels and labeling revisions.

E.3 List of FAERS Case Numbers

N/A

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX G. LABELS AND LABELING

[g] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[h] along with postmarket medication error data, we reviewed the following Pemetrexed labels and labeling submitted by Hospira on September 15, 2016.

- Container labels
- Carton labeling
- Prescribing Information

G.2 Label and Labeling Images

(b) (4)

[redacted]

[h] 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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