CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214408Orig1s000

OTHER REVIEW(S)

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:	July 15, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214408
Product Name and Strength:	Pemetrexed Injection, 100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL, and 1,000 mg/40 mL
Applicant/Sponsor Name:	Accord Healthcare Inc.
OSE RCM #:	2020-172-3
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

After receiving a tentative approval for NDA 214408 on May 17, 2022, the patent expired for the RLD, Alimta (NDA 021462) on May 24, 2022. Thus, the Applicant has submitted a Class 1 resubmission request for final approval of NDA 214408. We previously reviewed container labels and carton labeling received on May 3, 2022 (see Appendix A) that were revised in response to recommendations for Pemetrexed Injection that we made during a previous label and labeling review[a] and we found them acceptable. In the cover letter for this Class 1 resubmission for final approval received on May 19, 2022[b], the Applicant certifies they are not proposing any subsequent changes to the chemistry, manufacturing and controls, container labels, carton labeling, or prescribing information after the issuance of the tentative approval. Further, no labeling was submitted for review as part of this Class 1 resubmission.

2 CONCLUSION

We have no additional recommendations at this time.

[a] Gao, T. Label and Labeling Review for Pemetrexed Injection (NDA 214408). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 Apr 22. RCM No.: 2020-172-1.
[b] Re: NDA 214408 Cover Letter [Request for Final Approval]. Durham (NC): Accord Healthcare, Inc. 2022 MAY 19. Available from \\CDSESUB1\evsprod\nda214408\0017\m1\us\cover-letter-0017.pdf

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JANINE A STEWART
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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: 5/11/22

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

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

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

NDA: 214408

Background:
In response to DO2's consult request dated April 14, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and Patient Package Insert (PPI) for the original NDA submission for PEMETREXED injection, for intravenous use (Pemetrexed).

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

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

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

PI

Section	Statement from Draft (if applicable)	OPDP comments
8.4 Pediatric Use	"Adverse reactions observed in pediatric patients were similar to those observed in adults." (b) (4)	OPDP notes that updates to this section have been made in the Alimta SCPI and we recommend that these revisions be made in this label as well. In addition, we note that the statement that "Adverse reactions observed in pediatric patients were similar to those observed in adults," may imply that the safety profile of pemetrexed has been adequately defined in pediatric patients, despite the statement at the beginning of the section that safety has not been established in this population. Furthermore, we note that the pharmacokinetic information has been retained, even though the drug is not approved for use in pediatric patients. OPDP defers to the review division with regard to retaining this information in the pemetrexed labels.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 11, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214408
Product Name and Strength:	Pemetrexed Injection, 100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL, and 1,000 mg/40 mL
Applicant/Sponsor Name:	Accord Healthcare Inc.
OSE RCM #:	2020-172-2
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on May 3, 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.

[a] Gao, T. Label and Labeling Review for Pemetrexed Injection (NDA 214408). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 Apr 22. RCM No.: 2020-172-1.

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

PATIENT LABELING REVIEW

Date:	May 9, 2022
To:	Idara Ojofeitimi Regulatory Project Manager **Division of Oncology 2 (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, 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 214408
Applicant:	Accord Healthcare, Inc.

1 INTRODUCTION

On November 17, 2021, Accord Healthcare, Inc. submitted for the Agency's review a Class 2 Resubmission of their proposed 505(b)(2) New Drug Application (NDA) 214408 for Pemetrexed Injection in response to a Complete Response Letter dated November 23, 2020. The reference listed drug (RLD) for this submission is ALIMTA (pemetrexed for injection), NDA 021462, held by Eli Lilly and Company, and the most recently approved labeling was on January 30, 2019. The proposed indications for Pemetrexed Injection are as follows:

- locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC)
  - initial treatment in combination with pembrolizumab and platinum (b) (4) with no EGFR or ALK genomic tumor aberrations
  - initial treatment in combination with cisplatin
  - maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy as a single agent
  - after prior chemotherapy as a single agent
- mesothelioma in combination with cisplatin

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 2 (DO2) on April 14, 2022 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for Pemetrexed Injection.

2 MATERIAL REVIEWED

- Draft Pemetrexed Injection PPI received on November 17, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 3, 2022.
- Draft Pemetrexed Injection Prescribing Information (PI) received on November 17, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 3, 2022.
- Approved ALIMTA (pemetrexed for injection) comparator labeling dated January 30, 2019.

3 REVIEW METHODS

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

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

accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

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

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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RACHAEL E CONKLIN
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BARBARA A FULLER
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LASHAWN M GRIFFITHS
05/10/2022 11:07:00 AM

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

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

Date of This Review:	April 22, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214408
Product Name, Dosage Form, and Strength:	Pemetrexed Injection, 100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL, and 1,000 mg/40 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Accord
FDA Received Date:	March 24, 2022
OSE RCM #:	2020-172-1
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), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

NDA 214408 is a 505(b)(2) NDA and the reference product is Alimta, NDA 021462.

Accord previously submitted NDA 214408 on January 27, 2020, which received a Complete Response on November 23, 2020 due to nonclinical and product quality issues.[a]

Thus, Accord submitted a Class 2 Resubmission on November 17, 2021, and resubmitted the container labels, carton labeling, and PI on March 24, 2022.[b]

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Review

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

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

[a] Ojofeitimi, I. on behalf of Harpreet Singh. NDA 214408 Complete Response. Silver Spring (MD): FDA, CDER, OND, DOP2 (US); 2020 Nov 23.

[b] Pemetrexed Injection, 25 mg/mL, 4 mL, 20 mL, 34 mL and 40 mL NDA Number: 214408; Sequence Number 0012. Information Request. Durham (NC): Accord Healthcare Inc. 2022 Mar 24. Available from: \\CDSESUB1\evsprod\nda214408\0012\m1\us\cover-letter-and-response-0012.pdf

APPEARS THIS WAY ON ORIGINAL

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

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

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

4 CONCLUSION & RECOMMENDATIONS

The proposed container label, and carton labeling can be improved to ensure safe product use. We provide specific recommendations in Section 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. Consider deleting the (b) (4) throughout Section 2.7 to reduce clutter and to improve readability.
    b. Revise the product name "(b) (4) (b) (4)" to use the USP monograph name (e.g., "0.9% Sodium Chloride Injection, USP (preservative-free)".
    c. Section 16 states to store Pemetrexed Injection in original carton to protect from light. Clarify whether the diluted product needs to be protected from light when stored under refrigerated conditions for 24 hours.
    d. 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. Dosage Forms and Strengths
    a. Consider revising the presentation of product information by adding a description of the dosage form per 21 CFR 201.57(c)(4)(ii) and to improve readability; for example, as follows:

    Injection: Pemetrexed Injection is a clear, colorless to pale yellow solution available in single-dose vials as follows:

    - 100 mg/4 mL (25 mg/mL)
    - 500 mg/20 mL 25 mg/mL)
    - 850 mg/34 mL (25 mg/mL)

- 1,000 mg/40 mL (25 mg/mL)

3. How Supplied/Storage and Handling Section

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

      Pemetrexed Injection is a clear, colourless to pale yellow solution supplied in single-dose vials at a 25 mg/mL concentration in the following strengths:

Strength	NDC number	Package
100 mg/4 mL	NDC 16729-522-**64**	Carton containing one (1) single-dose vial
500 mg/20 mL	NDC 16729-522-**05**	Carton containing one (1) single-dose vial
850 mg/34 mL	NDC 16729-522-**28**	Carton containing one (1) single-dose vial
1,000 mg/40 mL	NDC 16729-522-**35**	Carton containing one (1) single-dose vial

   b. Revise the storage statement "(b) (4)C;" to "Store at 20°C to 25°C;" and include Fahrenheit temperatures so that the sentence reads "Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F)".

4.2 RECOMMENDATIONS FOR ACCORD

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

A. General Comments (Container labels & Carton Labeling)

1. Revise strength statement of the 1000 mg/40 mL strength to include a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000". For example, "1,000 mg/40 mL".
2. 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.
3. Add the "Discard Unused Portion." after the package type term so that the statement reads "# mL Single Dose Vial. Discard Unused Portion." on the PDP.
4. Revise the statement "(b) (4)" to "Warning: Hazardous Drug" to ensure consistency with the hazardous statement on the Prescribing Information.

5. Revise the storage statement [redacted] to "Store at 20°C to 5°C;" and include Fahrenheit temperatures so that the sentence reads "Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F)".

6. Define the expiration date 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.

B. Container labels

1. Revise the usual dosage statement from "[redacted]." to ""Recommended Dosage: See prescribing information." to ensure consistency with the terminology used in the prescribing information.

C. Carton labeling

1. To improve readability on the side panel, revise the recommended dosage statement from "[redacted]." to "Recommended Dosage: See prescribing information." to ensure consistency with the terminology used in the prescribing information. Also, relocate the recommended dosage statement to appear above the statement "Drug product solution must be diluted before administration:". For example:

> Recommended Dosage: See prescribing information.
>
> Drug product solution must be diluted before administration: Required dose/volume of drug product solution should be diluted to a total volume of 100 mL with 0.9% Sodium Chloride Injection (preservative free). See prescribing information.

2. Delete the statement [redacted]".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pemetrexed Injection received on March 24, 2022 from Accord, and the listed drug (LD).

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

Product Name	Pemetrexed Injection	Alimta[c] (NDA 021462)
Initial Approval Date	N/A	2/4/2004
Active Ingredient	Pemetrexed	Pemetrexed
Indication	Non-Squamous Non-Small Cell Lung Cancer • in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations. • in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC). • as a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. • as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy. Mesothelioma in combination with cisplatin, for the initial treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.	Non-Squamous Non-Small Cell Lung Cancer • In combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations. • in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC). • as a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. • as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy. Mesothelioma in combination with cisplatin, for the initial treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.
Route of Administration	Intravenous	Intravenous
Dosage Form	For Injection	For Injection

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

Table 2. Relevant Product Information for Pemetrexed Injection and the Listed Drug		
Product Name	Pemetrexed Injection	Alimta[c] (NDA 021462)
Strength	100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL, and 1,000 mg/40 mL	100 mg/vial, 500 mg/vial
Dose and Frequency	Non-squamous Non-Small Cell Lung Cancer 500 mg/m^2 intravenously over 10 minutes on Day 1 of each 21-day cycle. Mesothelioma 500 mg/m^2 intravenously over 10 minutes on Day 1 of each 21-day cycle.	Non-Squamous Non-Small Cell Lung Cancer 500 mg/m^2 intravenously over 10 minutes on Day 1 of each 21-day cycle. Mesothelioma 500 mg/m^2 intravenously over 10 minutes on Day 1 of each 21-day cycle.
How Supplied	Carton containing one single-dose vial	Carton containing one single-dose vial
Storage	Store (b) (4) (b) (4).	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Container Closure	100 mg/4 mL: 7 mL clear (b) (4) glass vial with royal blue flip off top 500 mg/20 mL: 20 mL clear (b) (4) glass vial with lavender flip off top 850 mg/34 mL: 50 mL clear (b) (4) glass vial with orange flip off top 1,000 mg/40 mL: 50 mL clear (b) (4) glass vial with red flip off top	USP (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	2015-2321[g] 2015-2321-1[h] 2018-1297[i] 2018-1297-1[j] 2018-1297-2[k]
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 208746 Pemetrexed for Injection	Hospira	100 mg/vial 500 mg/vial 1 gram/vial	Tentative Approval on 1/8/2021 *11/22/2021 Class 2 Resubmission currently under review*	2016-2183[o] 2016-2183-1[p] 2016-2183-2[q]

[d] Stewart, J. Label and Labeling Review for Pemfexy (Pemetrexed) Injection (NDA 209472). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Oct 25. RCM No.: 2016-2997.
[e] Stewart, J. Memorandum Review of Revised Label and Labeling for Pemfexy (Pemetrexed) Injection (NDA 209472). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Oct 2. RCM No.: 2016-2997-1.
[f] Stewart, J. Label and Labeling Review for Pemfexy (Pemetrexed) Injection (NDA 209472/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Apr 27. RCM No.: 2020-516.
[g] Townsend, O. Label and Labeling Review for Pemetrexed for Injection (NDA 208297). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Mar 3. RCM No.: 2015-2321.
[h] Thomas, S. Memorandum Review of Revised Label and Labeling for Pemetrexed for Injection (NDA 208297). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Apr 20. RCM No.: 2015-2321-1.
[i] Stewart, J. Label and Labeling Review for Pemetrexed for Injection (NDA 208297). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Apr 24. RCM No.: 2018-1297.
[j] Stewart, J. Memorandum Review of Revised Label and Labeling for Pemetrexed for Injection (NDA 208297). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 May 6. RCM No.: 2018-1297-1.
[k] Stewart, J. Memorandum Review of Revised Label and Labeling for Pemetrexed for Injection (NDA 208297). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 May 8. RCM No.: 2018-1297-2.
[l] Stewart, J. Label and Labeling Review for Pemetrexed Injection (NDA 208419). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Sept 11. RCM No.: 2017-156.
[m] Stewart, J. Label and Labeling Review for Pemetrexed Injection (NDA 208419). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 June 4. RCM No.: 2018-211.
[n] Stewart, J. Label and Labeling Review for Pemetrexed Injection (NDA 208419). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Apr 24. RCM No.: 2018-211-1.
[o] Townsend, Otto. Label and Labeling Review for Pemetrexed Injection (NDA 208746). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Mar 1. RCM No.: 2016-2183.
[p] Stewart, J. Label and Labeling Review for Pemetrexed for Injection (NDA 208746). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Nov 23. RCM No.: 2016-2183-1.
[q] Stewart, J. Memorandum Review of Revised Label and Labeling for Pemetrexed for Injection (NDA 208746). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Dec 14. RCM No.: 2016-2183-2.

Table 3. Pemetrexed products				
Application	**Applicant**	**Strength**	**Regulatory Status**	**OSE Review**
NDA 210661 Pemetrexed for Injection	Apotex	100 mg/vial 500 mg/vial	NDA withdrawn on 10/25/2019	2017-1140[r]
NDA 214218 Pemetrexed Injection	Hospira	100 mg/4 mL 500 mg/20 mL 1 g/40 mL	Tentative Approval on 2/23/2021 *12/22/2021 Class 2 Resubmission currently under review*	2020-858[s] 2020-858-1[t] 2020-858-2[u]
NDA 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[v] 2020-1442-1[w]
(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* *Subject of this review*	2020-172[aa] 2020-172-1

[r] Stewart, J. Label and Labeling Review for Pemetrexed for Injection (NDA 210661). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Dec 8. RCM No.: 2017-1140.

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

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

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

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

[w] 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)

[aa] 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.

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 Accord.

- Container label and carton labeling received on March 24, 2022[cc]
- Prescribing Information and Patient Package Insert (Image not shown) received on March 24, 2022, available from \\CDSESUB1\evsprod\nda214408\0012\m1\us\final-labeling-text-word-0012.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.
[cc] 1.14.2.1 Final carton or container labels. Durham (NC): Accord Healthcare Inc. 2022 Mar 24. Available from: \\CDSESUB1\evsprod\nda214408\0012\m1\us\final-carton-container-labels-0012.pdf.

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

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

Date of This Review:	June 19, 2020
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214408
Product Name, Dosage Form, and Strength:	Pemetrexed Injection, 100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL, and 1,000 mg/40 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Accord Healthcare Inc.
FDA Received Date:	January 27, 2020
OSE RCM #:	2020-172
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader (Acting):	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

Accord Healthcare is seeking approval of Pemetrexed Injection, 100 mg/4 mL, 500 mg/20 mL, 850 mg/34 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. Accord's proposed product differs from the RLD with respect to the dosage form (injection vs. for injection). In addition, Accord is proposing 2 additional strength presentations (850 mg/34 mL and 1,000 mg/40 mL). However, the products are considered pharmaceutically equivalent and all of the configurations yield the same concentration of 25 mg/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

We reviewed the materials submitted and provide recommendations in Section 5 to improve the clarity and readability of statements that appear on the proposed PI, container labels, and carton labeling.

We note that Accord is proposing 2 additional vial presentations (850 mg/34 mL and 1,000 mg/40 mL) which offer different vial presentations than that of the RLD, Alimta, which is supplied as 100 mg/vial and 500 mg/vial. From a medication error perspective, we find the introduction of these 2 additional presentations acceptable because the Applicant is not introducing a vial containing a different concentration.

5 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed PI , the container labels, and carton labeling for Pemetrexed Injection can be improved to increase the clarity, readability, and the prominence of important information to promote the safe use of this product. Thus, we provide recommendations in Section 5.1 and Section 5.2.

5.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Dosage Forms and Strengths Section

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

   Injection: Pemetrexed Injection is a clear, colorless to (b) (4) or (b) (4) solution available in (b) (4) single-dose vials:

   - 100 mg/4 mL (25 mg/mL)
   - 500 mg/20 mL 25 mg/mL)
   - 850 mg/34 mL (25 mg/mL)
   - 1,000 mg/40 mL (25 mg/mL)

2. How Supplied/Storage and Handling Section

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

   <u>How Supplied</u>

   Pemetrexed Injection is a clear, colourless to pale yellow solution supplied in single-dose vials at a 25 mg/mL concentration in the following package strengths:

Strength/ (b) (4)	NDC number (b) (4)

100 mg/4 mL	NDC 16729-522-**64**	Carton containing one (1) single-dose vial
500 mg/20 mL	NDC 16729-522-**05**	Carton containing one (1) single-dose vial
850 mg/34 mL	NDC 16729-522-**28**	Carton containing one (1) single-dose vial
1,000 mg/40 mL	NDC 16729-522-**35**	Carton containing one (1) single-dose vial

Storage and Handling
Store a (b) (4)°C to 25°C ((b) (4)°F to 77°F). Protect from light.

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

5.2 RECOMMENDATIONS FOR ACCORD HEALTHCARE INC.

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

A. General Comments (Container labels & Carton Labeling)

1. As currently presented, the product code in the NDC number (middle 3 digits) is the same for all 4 strengths (-522-). The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Using the identical product code for injectable products containing the same concentration of drug but different total volumes is not an effective differentiating feature. Therefore, revise the product code in the NDC numbers to ensure that the middle 3 digits are different between the strengths.
2. 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.
3. Revise the (b) (4) statement on the PDP to read "Single Dose Vial. Discard Unused Portion".
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.

B. Container Labels

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

C. Carton Labeling

1. Revise the "([redacted] (b) (4) statements to read "Recommended Dosage: See prescribing information." for consistent terminology with the Prescribing Information and to reduce clutter on the side panel.
2. Revise the statement "[redacted] (b) (4)..." to read "To Dilute: Required volume of drug should be diluted...". We recommend this simplified statement to reduce clutter on the side panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pemetrexed received on January 27, 2020 from Accord Healthcare Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Pemetrexed and the Listed Drug		
Product Name	Pemetrexed	Alimta (NDA 021462)
Initial Approval Date	N/A	02/04/2004
Active Ingredient	Pemetrexed disodium	Pemetrexed disodium
Indication	Non-Squamous Non-Small Cell Lung Cancer • In combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations. • in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC). • as a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. • as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy.	Non-Squamous Non-Small Cell Lung Cancer • In combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations. • in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC). • as a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. • as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy.

Table 2. Relevant Product Information for Pemetrexed and the Listed Drug		
	Mesothelioma indicated, in combination with cisplatin, for the initial treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.	Mesothelioma indicated, in combination with cisplatin, for the initial treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.
Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	For Injection
Strength	100 mg/4 mL 500 mg/20 mL 850 mg/34 mL 1,000 mg/40 mL	100 mg and 500 mg
Dose and Frequency	Combination Use with Pembrolizumab and/or Platinum Chemotherapy for Nonsquamous Non-Small Cell Lung Cancer or Malignant Pleural Mesothelioma: 500 mg/m^2 intravenously over 10 minutes on Day 1 of each 21-day cycle. Single-Agent Use as Maintenance Following First-Line Therapy, or as a Second-Line Therapy: 500 mg/m^2 intravenously over 10 minutes on Day 1 of each 21-day cycle.	Combination Use with Pembrolizumab and/or Platinum Chemotherapy for Nonsquamous Non-Small Cell Lung Cancer or Malignant Pleural Mesothelioma: 500 mg/m^2 intravenously over 10 minutes on Day 1 of each 21-day cycle. Single-Agent Use as Maintenance Following First-Line Therapy, or as a Second-Line Therapy: 500 mg/m^2 intravenously over 10 minutes on Day 1 of each 21-day cycle.
How Supplied	Single-dose vials individually packaged in cartons	Single-dose vials individually packaged in individual cartons
Storage	Store at (b)(4)°-25°C ((b)(4)°-77°F). Protect from light.	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Table 2. Relevant Product Information for Pemetrexed and the Listed Drug		
Container Closure	5 mL, 30 mL, and 50 mL (b) (4) colorless glass vials with rubber stoppers, aluminum metallic caps, and (b) (4) discs.	USP (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 Accord Healthcare Inc..

- Container label received on January 27, 2020
- Carton labeling received on January 27, 2020
- Prescribing Information (Image not shown) received on January 27, 2020, available from \\cdsesub1\evsprod\nda214408\0001\m1\us\draft-labeling-text-word.doc

G.2 Label and Labeling Images

(b) (4)

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

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