

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214121Orig1s000

OTHER REVIEW(S)

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:	July 28, 2020
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214121
Product Name and Strength:	Methotrexate Injection, 5 gram/50 mL (100 mg/mL)
Applicant/Sponsor Name:	Accord Healthcare Inc.
OSE RCM #:	2019-2205-1
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader (Acting):	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on July 22, 2020 for Methotrexate. Division of Oncology 2 (DO2) requested that we review the revised container label and carton labeling for Methotrexate (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container label and carton labeling is unacceptable from a medication error perspective. We have identified an additional recommendation to support the safe and effective use of this product.

3 RECOMMENDATIONS FOR ACCORD HEALTHCARE INC.

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

A. General Comments (Container labels & Carton Labeling)

^a Stewart J. Label and Labeling Review for Methotrexate (NDA 214121). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 30. RCM No.: 2019-2205

1. Revise the statement “Warning: See prescribing information.” to read “Warning: See prescribing information for boxed warnings, indications, and route of administration.”

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JANINE A STEWART
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07/29/2020 10:40:03 AM

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

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

Memorandum

Date: July 28, 2020

To: Kwadwo Korsah, PharmD, MS, Regulatory Project Manager
Division of Oncology 2 (DO2)

Stacy Shord, PharmD, Associate Director for Labeling, Office of Oncologic Diseases

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, PharmD, MBA, Team Leader, OPDP

Subject: OPDP Labeling Comments for METHOTREXATE injection

NDA: 214121

In response to DO2's consult request dated December 15, 2019, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for METHOTREXATE injection.

Labeling: OPDP's comments on the proposed PI are based on the draft PI available in Sharepoint on the morning of July 27, 2020, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labels submitted by the Applicant to the electronic document room on July 21, 2020, taking into account the Division of Medication Error Prevention and Analysis' review of the labels dated July 1, 2020, and we have no comments.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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LYNN M PANHOLZER
07/28/2020 09:25:10 AM

OOD Associate Director for Labeling Review

Product Title	METHOTREXATE injection, for intravenous use
Applicant	Accord
Application/Supplement Number	NDA 214121
Type of Application/Submission ¹	505(b)(2)
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Proposed Indication(s) (if applicable)	(b) (4) non-Hodgkin lymphoma, osteosarcoma, (b) (4)
Approved Indication(s) (if applicable)	Acute lymphoblastic leukemia, non-Hodgkin lymphoma, Burkitt lymphoma, and osteosarcoma
Date FDA Received Application	October 24, 2019
Review Classification (Priority/Standard)	Standard
Action Goal Date	August 24, 2020
Review Date	July 21, 2020
Reviewer	Stacy S Shord, Pharm.D.

Background: The applicant submitted a new drug application (NDA) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA). The Listed Drug (LD) is Methotrexate Injection, USP 25 mg/mL (Preservative Free) [NDA# 011719]. The labeling submitted with the application was not compliant with the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR).

On November 26, 2019, Accord submitted a revised labeling document that was updated to align with PLR and PLLR content and format.

On January 6, 2020, FDA issued a FILING COMMUNICATION – NO FILING REVIEW ISSUES IDENTIFIED which stated that the revised labeling (submitted on November 26, 2019) did not adequately conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. FDA identified the following examples of labeling issues:

- a. 21 CFR 201.56 states the labeling must be informative and accurate. Further, in accordance with 314.70 of this chapter, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading. Your proposed labeling, however, includes outdated information. For example, your proposed PI includes an outdated recommendation (b) (4). This does not accurately reflect current risk mitigation strategy surrounding the use of methotrexate in such patients.
- b. Your proposed PI does not conform to the PLLR, and is missing certain labeling information required by that rule. You should conduct a review and provide a summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication). If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Revise the labeling to incorporate the above information; including SPECIFIC POPULATIONS section, subsections 8.1 to 8.3; WARNINGS AND PRECAUTIONS section, entitled Embryo-Fetal Toxicity subsection; PATIENT COUNSELING INFORMATION; and Highlights.

¹ Examples include: Original Biologics License Application (BLA), New Molecular Entity (NME) NDA, Original NDA, NDA Efficacy Supplement, 505(b)(2) New Drug Application (NDA), New Chemical Entity (NCE) NDA, NDA Prior Approval Labeling Supplement, NDA CBE-0 Labeling Supplement

- c. 21 CFR 201.57(c)(2)(iv) states that indications or uses must not be implied or suggested in other sections of the labeling if not included in INDICATIONS AND USAGE section. Omit information about a (b) (4) throughout the labeling, including in the BOXED WARNING, DOSAGE AND ADMINISTRATION section and SPECIFIC POPULATIONS section, and (b) (4) which are not listed in the INDICATIONS AND USAGE section, such as (b) (4) throughout the labeling including, but not limited to, the BOXED WARNING, CONTRAINDICATIONS section, WARNINGS AND PRECAUTIONS section, ADVERSE REACTIONS section, DRUG INTERACTIONS section, and SPECIFIC POPULATIONS section. When revising your PI to comply with FDA's regulations, you may assign a subsection to each indication (e.g., 1.1 Disease-A, 1.2 Disease-B) or present distinct indications using only bullets (e.g., "DRUG-X is indicated for:" followed by a bulleted list) immediately under the main section heading or within a subsection as recommended in the guidance document: Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry.
- d. (b) (4)
- e. 21 CFR 201.57(c)(2) states that each indication statement must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition; however, the indication statements in your current proposed PI do not meet this requirement. For example, the following statement is found in INDICATIONS AND USAGE section and does specify if methotrexate is indicated for the treatment, prevention, mitigation, cure or diagnosis of osteosarcoma: "
(b) (4)
"
- f. 21 CFR 201.57(c)(3)(i) states that the DOSAGE AND ADMINISTRATION section must state the recommended dose, as well as related information, including, as appropriate, the dosage range, dosages for each indication and subpopulation, the interval recommended between doses, the usual duration of use, etc; however, your proposed PI does not include the required dosing-related information for each indication. For example, a recommended dose is not provided for (b) (4). If you plan to retain indications for which your current PI does not include a recommended dose, provide a recommended dose and sufficient justification to support the recommended dose.
- g. 21 CFR 201.57(c)(6) states that the WARNINGS AND PRECAUTIONS section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). However, your PI does not clearly identify the warnings or precautions for your drug product. For example, your PI includes (b) (4). We recommend that each warning or precaution should be assigned its own subsection and that each subsection include a succinct description of the adverse reaction and outcome, known risk factors for the adverse reaction, mitigation strategies and how to treat or otherwise manage an adverse reaction as described in guidance document: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products- Content and Format.
- h. 21 CFR 201.57(c)(1) states that the boxed warning must briefly explain the risk and refer to more detailed information in the "Contraindications" or "Warnings and Precautions" section, accompanied by the identifying number for the section or subsection containing the detailed information. However, your proposed boxed warning includes information (b) (4). For example, the box contains information (b) (4), and thus should be amended to communicate a brief, concise summary of the information that is critical for the prescriber to consider. The information (b) (4) may better fit in other sections of the labeling.

- i. 21 CFR 201.57(c)(7) states that the ADVERSE REACTIONS section must describe the overall adverse reaction profile of the drug based on the entire safety database. However, the information as presented in your proposed labeling makes it difficult to understand the overall adverse drug reaction profile. You should revise this section as recommended in the guidance document Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products - Content and Format.
- j. 21 CFR 201.57(c)(8) states that the DRUG INTERACTIONS section must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice), and specific practical instructions for preventing or managing them; the mechanism(s) of the interaction(s), if known, must be briefly described. However, your proposed labeling does not provide mitigation strategies for each potential interaction. For example, your PI does not provide mitigation strategies when the drug is coadministered with salicylates, (b) (4) phenytoin, or sulfonamides. We recommend that this section of your PI include subsections that describe the different drug interactions. The drug interactions may be grouped by pharmacokinetic interactions, pharmacodynamic interactions, effects on adverse reactions, effects on clinical effectiveness, a combination of these factors, or other factors.

On January 27, 2020, Accord submitted a revised labeling document that was updated to address these labeling issues. This labeling document was subsequently reviewed by the multidisciplinary team.

This product differs from the LD, such that this drug product has a concentration of 100 mg/mL as compared to the LD of 25 mg/mL. Based on the risk of potentially fatal medication errors, FDA proposed to limit the indications associated with a high-dose dosing regimen. This proposal is consistent with Accord's rationale for the development of a product with a higher concentration, such that this product will provide practitioners with a convenient alternative to reduce hazardous waste disposal and cost for course of therapy.

Labeling Review:

The proposed labeling document was reviewed to help ensure that product information (PI):

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements²
- Is consistent with labeling guidance recommendations³ and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

The attached PI contains the working version of the product labeling sent to Accord on July 15, 2020 with my recommended edits and comments identified by my initial and includes comments and edits from other review team members. My labeling recommendations provided in this review (e.g., recommended edits and comments regarding parts of PI) should be considered preliminary and may not represent final recommendations for the product labeling.

² See [January 2006 Physician Labeling Rule](#); 21 CFR [201.56](#) and [201.57](#); and [December 2014 Pregnancy and Lactation Labeling Rule](#) (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR [201.56\(e\)](#) and [201.80](#).

³ See [PLR Requirements for PI](#) website for PLR labeling guidances.

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/s/

STACY S SHORD
07/21/2020 11:00:44 AM

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 30, 2020
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214121
Product Name, Dosage Form, and Strength:	Methotrexate Injection, 5 gram/50 mL (100 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Accord Healthcare Inc.
FDA Received Date:	October 24, 2019, January 27, 2020, and June 8, 2020
OSE RCM #:	2019-2205
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As part of the review process of this 505(b)(2) NDA for Methotrexate Injection, this review evaluates the proposed container labels, carton labeling, Prescribing Information (PI), and the Dear Healthcare Provider Letter for areas of vulnerability that could lead to medication errors.

2 BACKGROUND

Accord Healthcare is seeking approval of Methotrexate Injection, 5 g/50 mL (100 mg/mL) via the 505(b)(2) pathway. The Reference Listed Drug (RLD) is Methotrexate Injection, 1 g/40 mL (25 mg/mL). Accord's proposed product differs from the RLD with respect to concentration, and inactive ingredients, however the drugs are considered pharmaceutically equivalent.

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 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 – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Risk Mitigation Plan	F
Labels and Labeling	G

N/A=not applicable for this review

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

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The listed drug (LD) for the proposed Methotrexate Injection is Methotrexate (NDA 011719) approved in 1959. Methotrexate Injection has been marketed for over 40 years in various strengths (50 mg/2 mL, 100 mg/4 mL, 200 mg/8 mL, 250 mg/10 mL, and 1 g/40 mL) and all strengths are in the concentration of 25 mg/mL.

The preparation of high-dose methotrexate (12 g/m² and 15 mg/m²) infusions require large numbers of the currently marketed 1 g/40 mL (25 mg/mL) vials. Accord seeks approval for the proposed Methotrexate Injection 5 g/50 mL (100 mg/mL) as a convenient alternative because fewer vials of their proposed product would be required to prepare the same doses. However,

because Methotrexate Injection in the concentration of 25 mg/mL has been marketed since 1959 in various strengths, end users (pharmacist and nurses) are used to methotrexate injection in the concentration of 25 mg/mL and may mistakenly think the proposed 5 g/50 mL product is also a methotrexate in 25 mg/mL concentration. Additionally, the potential clinical impact from selection errors during dispensing (i.e. select the wrong Methotrexate vial from the pharmacy shelf) will also increase with the 5 g/50 mL vial because of the addition of the 100 mg/mL concentration. Thus, we are concerned that the proposed new 100 mg/mL concentration introduces the new risk of 4-fold overdose medication errors.

We shared our concerns with DO2 and the Division sent the following Information Request (IR) to Accord:

“FDA has concerns regarding the risk of possible lethal overdose of your product due to concentration differences with other products already on the market. In order to address this concern, submit a plan to address the risk of potential overdose. The plan could include limiting to only indications that are treated with high dose methotrexate (e.g. ALL, osteosarcoma), a detailed plan for differential packaging that highlights the higher concentration, plan for communication with pharmacies and plan for monitoring for any medication errors.”

Because Accord stated the proposed Methotrexate Injection 5 g/50 mL (100 mg/mL) as a convenient alternative for high-dose methotrexate preparation and the proposed vial is a single-dose vial (not multiple-dose vial), it is reasonable to request Accord to limit the indication of this proposed product to only those indications where a high dose is recommended. However, because reviewing the PI for a product's indication is not a routine practice at the dispensing phase of the medication use process, we discussed with the review team that limiting the indication is unlikely to prevent product selection errors between the proposed Methotrexate 5 g/50 mL (100 mg/mL) and other Methotrexate products of various strengths in 25 mg/mL.

In response to the IR, Accord submitted a risk management plan^a for our review. Their proposed risk mitigation plan included:

- a communication plan with healthcare professionals (HCPs)
- a plan for differential packaging that highlights the higher concentration
- a plan for monitoring for any medication errors

Our review of Accord's IR response finds the proposed Dear Healthcare Provider (DHCP) Letter may be improved to better inform HCP of the new 100 mg/mL concentration Methotrexate Injection and to provide specific recommendations to help prevent wrong selection medication errors between the proposed Methotrexate 5 g/50 mL (100 mg/mL) and other Methotrexate

^a Re: NDA 214121 Response to Information Request. Durham (NC): Accord Healthcare, Inc. 2020 JUN 08. Available from: <\\cdsesub1\evsprod\nda214121\0009\m1\us\response-to-information-request-0009.pdf>

products of various strengths in 25 mg/mL. Accord's "plan for differential packaging" contained the same proposed container label and carton labeling as the ones in the October 24, 2019 submission, which we provide recommendation in section 5.2. Accord's "monitoring plan" appears to be routine pharmacovigilance activities for marketed drug products, but we recommend augmenting monitoring activities specifically for medication errors associated with the proposed Methotrexate 5 g/50 mL (100 mg/mL).

Our review of materials found that the proposed Methotrexate PI, container labels, carton labeling, DHCP letter, and monitoring plan for medication errors may be improved to promote safe use of this product. Thus, we provide related recommendations below in Section 5.

5 CONCLUSION & RECOMMENDATIONS

Although institutions may employ best practices such as independent double checks for oncology products and segregated storage for high risk products, based on post-market experience, we are concerned about the residual risk associated with the introduction of the new 100 mg/mL concentration for Methotrexate Injection to the marketplace that is familiar and used to 25 mg/mL concentration.

We recommend DO2 consider this residual risk as a part of this NDA review. While labeling strategies may help to mitigate the risk of medication errors, they do not eliminate the residual risk associated with introducing a new concentration for Methotrexate Injection that is 4 times the currently available concentration. If DO2 considers the residual risk acceptable, we provide mitigation strategies to minimize these risks in Sections 5.1 and 5.2 below.

5.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information (PI)

1. General

- a. As presented, the strength expression is incomplete. Revise the strength expression to include the total strength per total volume followed by the concentration in parentheses, i.e., 5 g/50 mL (100 mg/mL), where it appears in the PI.

2. Dosage and Administration Section

- a. Revise section 2 to modernize and streamline the language so the recommended dosage for each indication can be easily located. As currently presented, for example, section "(b) (4)", the recommended dosage is (b) (4) which cannot be easily located.
- b. Spell out "IV" with its intended meaning as "intravenous" or "intravenously" in sentences throughout Section 2 of the PI.

3. Dosage Forms and Strengths Section

- a. Consider revising the presentation of information in Section 3: *Dosage Forms and Strengths* to provide a complete description of the dosage form; for example, as follows:

Injection: 5 g/50 mL (100 mg/mL), clear orange-yellow, isotonic, preservative-free solution in a single-dose vial.

4. How Supplied/Storage and Handling Section

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

How Supplied

Methotrexate Injection is a clear, orange-yellow, isotonic, sterile, preservative preservative-free solution supplied in a carton containing 1 single-dose vial.

- 5 g/50 mL (100 mg/mL) NDC 16729-516-11

Storage

Store at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature]; excursions permitted to 15° to 30°C (59° to 86°F).
PROTECT FROM LIGHT.

B. Dear Healthcare Provider (DHCP)Letter

1. Revise the DHCP letter to

- a. Include a short introduction of the available Methotrexate Injection products, various strengths all in 25 mg/mL concentration.
- b. Introduce your Methotrexate 5 g/50 mL (100 mg/mL) product.
- c. Describe the container label and carton labeling statements in place to point out the new concentration 100 mg/mL so HCP will know what to check for while dispensing.
- d. Include specific recommendations for the pharmacy, such as the different storage options to prevent wrong selection medication errors between Methotrexate 5 g/50 mL (100 mg/mL) and other Methotrexate Injection products in various strengths of 25 mg/mL concentration.

C. Monitoring Plan for Medication Errors

1. We recommend a Postmarketing Requirement (PMR), where following review of the proposed Methotrexate Injection, 5 g/50 mL (100 mg/mL), if approved, Accord will monitor medication errors associated with the Methotrexate Injection due to the new 100 mg/mL concentration (e.g., dosing errors, selection errors, etc.) for 3 years, will review any medication error reports, and submit a

summary (preferable in a PDF file) as well as line by line of the detail case narratives (preferable in an Excel file) to the Agency every 6 months.

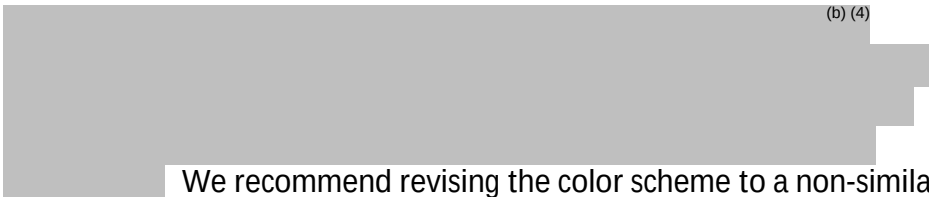
D. ISMP Newsletter

1. If approved, DMEPA plans to publish a newsletter article in an ISMP Newsletter as another way to reach out and inform healthcare providers of the introduction of a 100 mg/mL new concentration Methotrexate Injection product.

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. To differentiate and emphasize the new concentration of the proposed Methotrexate Injection, 5 g/50 mL (100 mg/mL), from various other strengths of Methotrexate Injection products in 25 mg/mL concentrations:
 - a.  (b) (4)
We recommend revising the color scheme to a non-similar color to Accord's currently marketed Methotrexate products and use a non-white background. For example, consider a dark orange on a faint yellow background, or other color combinations so differentiate the proposed Methotrexate Injection, 5 g/50 mL (100 mg/mL).
 - b. Revise the presentation of the concentration "(100 mg/mL)" to present the statement with highlights, shadow effect, boxing, or other methods to point out this the new concentration to end users.
2. To improve readability of important information by allowing for more  (b) (4) space on the PDP, relocate the "Rx Only" statement from the PDP to the side panel.
3. Combine the statements "Single Dose Vial" and "Discard unused portion" to appear together on the PDP as "Single dose vial. Discard unused portion".
 - a. Delete the statement "Discard unused portion" that appears on the side panel.
4. To ensure consistency with the Prescribing information, revise the statement " (b) (4)" to read "Warning: See prescribing information." We also recommending presenting the statement in sentence case instead of all upper-case letters to improve readability.
5. 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. Carton Labeling

1. Add a banner on upper left corner of the principal display panel (PDP) that reads “New Concentration”; using color, typography, contrast, and placement to promote the prominence of the statement to differentiate and emphasize the new concentration of the proposed methotrexate injection, 5 g/50 mL (100 mg/mL), from various other strengths of Methotrexate Injection products in 25 mg/mL concentrations.
2. Remove the “Preservative Free” statement from the PDP since this statement already appears on the side panels to improve readability of important information by allowing for more (b) (4) space on the PDP.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

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

Table 2. Relevant Product Information for Methotrexate and the Listed Drug		
Product Name	Methotrexate Injection	Methotrexate Injection ^b [Preservative-Free] Hospira, Inc. NDA 011719
Initial Approval Date	N/A	August 10, 1959
Active Ingredient	methotrexate	methotrexate
Indication	(b) (4) Non-Hodgkin's Lymphoma, Osteosarcoma	Neoplastic diseases, Psoriasis, and Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis
Route of Administration	Intravenous (b) (4)	Intramuscular, Intravenous, Intra-arterial, and Intrathecal
Dosage Form	Injection	Injection
Strength	5 gram/50 mL (100 mg/mL)	1 gram/40 mL (25 mg/mL)
Dose and Frequency	Due to complexity and length of the Dosage and Administration section in the proposed PI for this product, please refer to Appendix G for details on dose and frequency for this product.	Due to complexity and length of the Dosage and Administration section in the PI for this product, please refer to most recently approved PI for details on dose and frequency for this product.
How Supplied	Single-dose vial: 5 g/50 mL (100 mg/mL)	Single dose vial: 1 g/40 mL (25 mg/mL)
Storage	Store at controlled room temperature, 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature]; excursions permitted to 15° to 30°C (59° to 86°F). PROTECT FROM LIGHT.	Store at controlled room temperature, 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature]; excursions permitted to 15° to 30°C (59° to 86°F). PROTECT FROM LIGHT.

^b Methotrexate Injection [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2018 MAY 07. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/011719s125lbl.pdf

Container Closure	50 mL clear glass vial USP (b) (4) with a 20 mm (b) (4) rubber stopper	
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APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 4, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Methotrexate Injection. Our search identified 1 previous reviews^c, and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX F. RISK MITIGATION PLAN

Risk Mitigation Plan received on June 8, 2020, available from
<\\cdsesub1\evsprod\nda214121\0009\m1\us\response-to-information-request-0009.pdf>

^c Townsend, O. Label and Labeling Review for Methotrexate Injection (NDA 011719/S-122). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 JUL 28. RCM No.: 2015-1338.

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,^d along with postmarket medication error data, we reviewed the following Methotrexate labels and labeling submitted by Accord Healthcare Inc..

- Container label received on October 24, 2019
- Carton labeling received on October 24, 2019
- Prescribing Information (Image not shown) received on January 27, 2020, available from <\\cdsesub1\evsprod\nda214121\0003\m1\us\draft-labeling-text-word.doc>
- Dear Healthcare Provider Letter (Image not shown) received on June 8, 2020

G.2 Label and Labeling Images

Container Label

(b) (4)



^d Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton Labeling

(b) (4)



This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JANINE A STEWART
06/30/2020 05:18:52 PM

CHI-MING TU
07/01/2020 08:47:41 AM