CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210737Orig1s000
210737Orig2s000

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:	August 15, 2019
To:	Sally Seymour, MD Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Aman Sarai, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kyle Snyder, Pharm.D. Regulatory Review Officer **Division of Advertising and Promotion Review II** **Office of Prescription Drug Promotion (OPDP)** Laurie Buonaccorsi, Pharm.D. Regulatory Review Officer **Division of Advertising and Promotion Review II** **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	TRADENAME (methotrexate)
Dosage Form and Route:	injection, for subcutaneous use

Application Type/Number:	210737
Applicant:	Cumberland Pharmaceuticals Inc.

1 INTRODUCTION

On November 5, 2018, Cumberland Pharmaceuticals Inc. submitted for the Agency's review a 505(b)(2) New Drug Application for methotrexate for use in the treatment of severe, active rheumatoid arthritis (RA) and poluarticular juvenile idiopathic arthritis (PJIA) who are intoleratnt of or had an inadequate response to first-line therapy and symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy.The prefilled syringe will be available in doses ranging from 7.5 mg to 25 mg. The methotrexate injection NDA identified as a reference drug to provide support for safety and efficacy for this 505(b)(2) application is OTREXUP PFS NDA 22348.

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 Pulmonary, Allergy, and Rheumatology Products (DPARP) on January 17, 2019 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TRADENAME (methotrexate) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review was completed on March 4, 2019

2 MATERIAL REVIEWED

- Draft TRADENAME (methotrexate) PPI and IFU November 5, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 2, 2019.
- Draft TRADENAME (methotrexate) Prescribing Information (PI) received on November 5, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 2, 2019.
- Last approved OTREXUP PFS comparator labeling dated June 19, 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.

In our collaborative review of the PPI and IFU we:

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

4 CONCLUSIONS

The PPI and IFU are 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 and IFU 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 and IFU.

Please let us know if you have any questions.

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/s/

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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: August 13, 2019

To: Raj Nair, Clinical Reviewer
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Jessica Lee, Regulatory Project Manager, (DPARP)

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Kyle Snyder, Regulatory Review Officer, OPDP

CC: Matthew Falter, Team Leader, OPDP
Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for REDITREX (methotrexate) injection, for subcutaneous use

NDA: 210737

In response to DPARP's consult request dated January 17, 2019, OPDP has reviewed the proposed prescribing information (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for REDITREX (methotrexate) injection, for subcutaneous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPARP on August 2, 2019, and are provided below.

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

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 2, 2019, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at (240) 402-8792 or kyle.snyder@fda.hhs.gov; or Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

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

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/s/

KYLE SNYDER
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LAURIE J BUONACCORSI
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 9,2019
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 210737
Product Name and Strength:	Methotrexate injection, 7.5 mg/0.3 mL, 10 mg/0.4 mL, 12.5 mg/0.5 mL, 15 mg/0.6 mL, 17.5 mg/0.7 mL, 20 mg/0.8 mL, 22.5 mg/0.9 mL, 25 mg/mL
Applicant/Sponsor Name:	Cumberland Pharmaceuticals Inc.
FDA Received Date:	May 2, 2019
OSE RCM #:	2018-2446-1
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the revised prescribing information (PI), instructions for use (IFU), container label, and carton labeling for methotrexate 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 submitted revised PI, IFU, container label, and carton labeling, received on May 2, 2019 for methotrexate injection. The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Rychlik I. Label and Labeling Review for methotrexate injection (NDA 210737). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 04. RCM No.: 2018-2446.

APPENDIX A. LINK TO LABEL AND LABELING RECEIVED ON MAY 2, 2019

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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:	March 4, 2019
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 210737
Product Name **Strength:**	Methotrexate Injection, 7.5 mg/0.3 mL, 10 mg/0.4 mL, 12.5 mg/0.5 mL, 15 mg/0.6 mL, 17.5 mg/0.7 mL, 20 mg/0.8 mL, 22.5 mg/0.9 mL, 25 mg/mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Cumberland Pharmaceuticals Inc.
FDA Received Date:	November 5, 2018 and January 30, 2019
OSE RCM #:	2018-2446
DMEPA Safety Evaluator:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Sarah K. Vee, PharmD.

1. REASON FOR REVIEW

On November 5, 2018 Cumberland Pharmaceuticals Inc. submitted a 505 (b)(2) NDA for methotrexate injection (NDA 210737) in a single dose, prefilled syringe for Agency review. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested DMEPA evaluate the proposed Prescribing Information (PI), Instructions for Use (IFU), Carton and Container labeling for areas of vulnerability that could lead to medication errors.

1.2 BACKGROUND INFORMATION

The referenced listed drug (RLD) product for this application is Otrexup (NDA 204824). Otrexup (methotrexate) injection was approved in 2013 and is available in an autoinjector presentation. The prefilled syringe presentation of Otrexup was approved on May 31, 2017. DMEPA completed an Use Related Risk Analysis and Comparative Analysis review (OSE #2018-1304) for the proposed methotrexate injection on August 30, 2018 and agreed that a human factors validation study if not needed.

The two products are identical in their indications of use, dosage forms, dosing regimens and routes of administration. However, we note, that the RLD product (b) (4) whereas the Cumberland product maintains a 25mg/mL concentration with changes to the proposed pre-filled syringe fill volumes to achieve dose strength (see Appendix A).

2. MATERIALS REVIEWED

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

Table 1. Materials Considered for this 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
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS 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 PI, IFU, carton and container labels for NDA 210737 to determine if they are acceptable from a medication error perspective. A risk assessment was completed to identify deficiencies that may lead to medication errors.

We identified areas in the labeling that can be improved to increase readability and prominence of important information and further mitigate the risk of medication error. Specifically, we note that the PI omits specific dose volume units-of-measure (i.e. mL) after each dose designation. This may cause reader confusion, inadvertently leading to medication errors such as overdose and/or under-dose for patients. Furthermore, Section 2, 3, and 16 can be revised to contain all appropriate information to facilitate the identification of the dosage form, strengths and administration information is presented in a clear, concise manner. Moreover, strength-dependent labeling colors in the IFU (Figure C) needs to be aligned with that of the carton and containers for consistency across labels and labeling.

We acknowledge that this is a 505(b)(2) application; however, we note that Section 2: Dosage and Administration is text heavy. To increase readability and to highlight important dose and administration information, product information pertaining to dosage form, warnings and precautions, clinical pharmacology, contraindications, product handling and treatment outcomes maybe moved to the appropriate subsections in the PI. We defer to clinical to decide the appropriateness of the information presented in Section 2. For added readability, dosage and administration information can be presented in a bullet format.

Additional recommendations for the Applicant's carton labeling and container labels may be found below in Section 4.2.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI, IFU, labels and labeling can be improved to promote the safe use of the product. We provide recommendations to the Division in Section 4.1 and to [redacted] (b) (4) in Section 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)
   1. Highlights: Dosage and Administration
      a. To increase readability and highlight important dose and administration information, consider reducing text heavy presentation of the dosage and administration information in the highlights as follows and include a statement to alert the reader to additional important information within the full prescribing information. For example:
         - *Reditrex is for once-weekly subcutaneous injection only.*
         - *Administer RediTrex in the abdomen or the thigh.*

         [redacted] (b) (4)

         Recommended starting dose of RediTrex:
         - *Adult Rheumatoid Arthritis: 7.5 mg once weekly.*

- *Polyarticular Juvenile Idiopathic Arthritis: 10 mg/m^2 once weekly.*
- *Psoriasis: 10 to 25 mg once weekly; recommended not to exceed 30 mg/week.*

See Full Prescribing Information for complete dosage and administration information.

2. Highlights: Dosage Forms and Strengths
    a. To facilitate the identification of the dosage form and strengths, include the product concentration and expression of dose volume per syringe. For example:

    Injection: 25 mg/mL methotrexate solution in a single-dose, pre-filled syringe available in the following strengths: 7.5 mg/0.3 mL, 10 mg/0.4 mL, 12.5 mg/0.5 mL, 15 mg/0.6 mL, 17.5 mg/0.7 mL, 20 mg/0.8 mL, 22.5 mg/0.9 mL, 25 mg/mL

3. Dosage Forms and Strengths
    a. To help facilitate the identification of the dosage form, consider including descriptive product information about the solution color (e.g. clear solution) as part of the product description.
    b. To facilitate the identification of the dosage form and strengths, include the product concentration and expression of dose volume per syringe. For example:

    Injection: 25 mg/mL methotrexate solution in a single-dose, pre-filled syringe available in the following strengths: 7.5 mg/0.3 mL, 10 mg/0.4 mL, 12.5 mg/0.5 mL, 15 mg/0.6 mL, 17.5 mg/0.7 mL, 20 mg/0.8 mL, 22.5 mg/0.9 mL, 25 mg/mL

4.2 RECOMMENDATIONS FOR CUMBERLAND PHARMACEUTICALS INC.

We recommend the following be implemented prior to approval of this NDA 210737:

A. General Comments:

1. The proposed proprietary name, RediTrex, was found unacceptable by the Agency on November 28, 2018; however, it is currently presented throughout product labels and labeling. Submit updated labels and labeling inclusive of an approved proprietary name when available.

B. Instructions for Use

1. Align the color representation of the 10 mg/0.4mL sample label in Figure C with the same color utilized on the carton labeling and container labels to maintain consistency in product strength representation throughout all labels and labeling.

C. Prescribing Information (PI).

1. To avoid a ten-fold misinterpretation of strength or dose, as referenced in ISMP's List of Error-Prone Abbreviations, Symbols and Dose Designations, remove all trailing zeros throughout the PI.

2. To help maintain readability, ensure consistent use of bolding for product strengths and storage/handling information (i.e. un-bold storage information to align with presentation of cytotoxic handling statement or vice versa).

D. Container labels & Carton Labeling

1. There is inadequate differentiation between the background colors used for the strength expression statements between the 10 mg/0.4 mL versus 22.5 mg/0.9 mL labels (b) (4) and the 7.5 mg/0.3 mL versus 20 mg/0.8 mL labels (b) (4) Consider the use of different colors or some other means to provide adequate differentiation between the carton labeling and container labels of these strengths.

2. The National Drug Code (NDC) number is currently denoted by a placeholder, submit the proposed NDC number for Agency review for all carton and container labels. We note, as currently presented in the PI, the product code in the NDC number across all strengths (-0355-) is the same. This can lead to selection errors by pharmacists who rely on the middle portion of the NDC as a manual check. Therefore, ensure that the middle 4 digits (XXXX) are different between the strengths.

3. 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. Increase the prominence and readability of important route of administration information.

a. Relocate the statement, "For Subcutaneous Use Only" to its own line, to ensure readability maintain an adequate amount of whitespace around the approved route statement and increase the statement's font to make it more prominent.

C. Carton Labeling

1. Relocate the approved route of administration, from the back-side panel, to a central location on the primary display panel (PDP). Maintain an adequate amount of whitespace around the approved route statement to ensure readability and increase the affirmative statement's font to make it more prominent.

2. Revise the safety warning statement, [redacted] (b) (4) to read "The syringe is for one single dose only" and relocate to the PDP. The statement should be placed immediately below the route of administration statement so that there is no intervening matter between the two administration warnings. This will ensure that the warnings are in the same viewing angle and field and therefore less likely to be overlooked.

3. To increase readability and ensure proper storage and handling of the product, relocate and bold the storage warning, "Protect from light", to follow the temperature storage information on the back-side display panel. This will ensure that the warnings are in the same viewing angle and field and therefore less likely to be overlooked.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for NDA 210737 received on November 5, 2018 from Cumberland Pharmaceuticals Inc., and the listed drug (LD).

Table 2. Relevant Product Information for NDA 210737 methotrexate injection and the Listed Drug

Product Name	**Methotrexate injection**	**Otrexup[a]**
Application Type and Number	NDA 210737	NDA 204824
Initial Approval Date	N/A (pending)	2013
Active Ingredient	methotrexate	
Indication	Methotrexate Injection is indicated for the treatment of the following indications: • Severe, active rheumatoid arthritis (RA) and polyarticular juvenile idiopathic arthritis (pJIA), who are intolerant of or had an inadequate response to first-line therapy • Symptomatic control of severe, recalcitrant, and disabling psoriasis in adults who are not adequately responsive to other forms of therapy	
Route of Administration	Subcutaneously injection. Administer in the abdomen or thigh.	
Dosage Form	Injection	
Strength	7.5 mg/0.3 mL, 10 mg/0.4 mL, 12.5 mg/0.5 mL, 15 mg/0.6 mL, 17.5 mg/0.7 mL, 20 mg/0.8 mL, 22.5 mg/0.9 mL, 25 mg/mL	10 mg/0.4 mL, 12.5 mg/0.4 mL, 15 mg/0.4 mL, 17.5 mg/0.4 mL, 20mg/0.4 mL, 22.5 mg/0.4 mL, 25 mg/0.4 mL
Dose and Frequency	Inject once weekly. Starting doses of methotrexate: • RA: 7.5 mg once weekly • pJIA: 10 mg/m^2 once weekly • Psoriasis: 10 to 25 mg once weekly • Adjust dose gradually to achieve an optimal response	
How Supplied	Cartons containing: • 4 single-dose, pre-filled syringes	Cartons containing: • 4 single-dose, pre-filled syringes or auto-injector (LD)
Storage	Store between 20˚C to 25˚C (68˚F to 77˚F); excursions permitted to 15˚C to 30˚C (59˚F to 86˚F). Protect from light.	

[a] Otrexup [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 JAN 03. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204824s008lbl.pdf.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 3, 2019, we searched the Document Archiving, Reporting and Regulatory Tracking System (DARRTS) for previous DMEPA reviews relevant to our review for NDA 210737. Our search identified one previous review[b] and we considered our previous recommendations to see if they are applicable for this current review.

[b] Barlow, M. Comparative Analysis and Use-Related Risk Analysis Review for methotrexate injection (NDA 210737). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 30 AUG 2018. RCM No.: 2018-1304.

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,[c] along with postmarket medication error data, we reviewed the following NDA 210737 labels and labeling submitted by Cumberland Pharmaceuticals Inc.

- Container label received on November 5, 2018
- Blister label received on November 5, 2018
- Carton labeling received on November 5, 2018
- Instructions for Use received on January 30, 2019
- Medication Guide received on November 5, 2018
- Prescribing Information (Image not shown) received on November 5, 2018

G.2 Label and Labeling Images

Prescribing Information (Image not shown)

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Instructions for Use (Image not shown)

\\cdsesub1\evsprod\nda210737\0013\m1\us\114-label\1141-draft-label\instruction-for-use-reditrex-word.docx

Carton labeling and Blister labels (Image not shown)

\\cdsesub1\evsprod\nda210737\0008\m1\us\114-label\1141-draft-label\draft-carton-contain-label.pdf

Container labels

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

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SARAH K VEE
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