CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204824Orig1s000

<u>OTHER REVIEW(S)</u>

505(b)(2) ASSESSMENT

Application Information		
NDA # 204824/Original 1	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Otrexup™ Established/Proper Name: Methotrexate auto-injector, for subcutaneous injection Dosage Form: Pre-filled syringe to be administered subcutaneously Strengths: 10mg/0.4 mL, 15mg/0.4 mL, 20mg/0.4 mL, and 25mg/0.4 mL		
Applicant: Antares Pharma, Inc.		
Date of Receipt: December 14, 2012		
PDUFA Goal Date: October 14, 2013	Action Goal Date (if different): October 11, 2013	
RPM: Sadaf Nabavian/6-2777		
Proposed Indication(s): Rheumatoid Arthritis (RA) and polyarticular Juvenile Idiopathic Arthritis (pJIA)		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

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INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published Literature	The sponsor relied on literature to support the safety and efficacy of the new route of administration (subcutaneous) for the Rheumatoid Arthritis indication, as reflected in the Dosage and Administration section of the label (the subcutaneous route of administration is already an approved route for pJIA).
Hospira, NDA 11719 (MTX Injection) Dava, NDA 008085 (MTX Oral)	The listed products were referenced for the entire label except the Dosage Forms and Strengths section of the label. The listed products were referenced for Efficacy and Dosage information from the Indications, Dosage and Administration, Clinical Pharmacology, and Clinical sections of the label; and Safety information included in the Box Warning, Contraindications, Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Population, Nonclinical Toxicology, and Over-dosage Sections of the label.

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The sponsor used the BA/BE program to link their proposed product to the reference MTX (generic) injectable from Hospira administered either IM or SC, along with literature to support the safety with the SC administration. The following is what was conducted to bridge the proposed product to the reference products:

- 2 BA studies were conducted to bridge the proposed product to approved IM and Oral MTX Products.
    1. Study 1-Evaluated the relative BA of the SC administration as compared to IM/SC
    2. Study 2-Evaluated the relative BA of the SC administration as compared to oral reference and relative BA when administered into abdomen or thigh

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- The sponsor also relied on the literature for the efficacy and safety of the subcutaneous route of administration for the RA indication.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Methotrexate Injection	NDA 11719	Yes
Methotrexate Oral	NDA 008085	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been

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explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*
*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:
   a) Approved in a 505(b)(2) application?

      YES ☐ NO ☒

      *If "**YES**", please list which drug(s).*

      Name of drug(s) approved in a 505(b)(2) application:

   b) Approved by the DESI process?

      YES ☒ NO ☐

      *If "**YES**", please list which drug(s).*

      Name of drug(s) approved via the DESI process: DESI 008085 for the oncology indications for methotrexate (tablets and parenteral formulations). However, the oncology indications are not included as part of the indications that are to be approved for this product.

   c) Described in a final OTC drug monograph?

      YES ☐ NO ☒

      *If "**YES**", please list which drug(s).*

      Name of drug(s) described in a final OTC drug monograph:

   d) Discontinued from marketing?

      YES ☐ NO ☒

      *If "**YES**", please list which drug(s) and answer question d) i. below.*
      *If "**NO**", proceed to question #9.*

      Name of drug(s) discontinued from marketing:

      i) Were the products discontinued for reasons related to safety or effectiveness?

         YES ☐ NO ☒

         (Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

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This application provides for a new drug/device combination to be administered subcutaneously for indications for RA including JIA.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

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11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): NDA 11719, NDA 08085, ANDA 040632, A089341, A040632, A089342, A089343, A089340, A040263, A040716, A040768, A040767, A040385

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): None

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

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Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

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(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SADAF NABAVIAN
10/11/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**OTREXUP (methotrexate) injection for subcutaneous use**
Applicant	Antares Pharma, Incorporated
Application/Supplement Number	NDA 204824
Type of Application	Original application
Indication(s)	Treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and psoriasis
Established Pharmacologic Class[1]	Folate analog metabolic inhibitor
Office/Division	ODEII/DPARP
Division Project Manager	Sadaf Nabavian
Date FDA Received Application	December 14, 2012
Goal Date	October 14, 2013
Date PI Received by SEALD	October 4, 2013
SEALD Review Date	October 8, 2013
SEALD Labeling Reviewer	Debra Beitzell
SEALD Division Director	Laurie Burke

PI = prescribing information
[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Reference ID: 3386844

Highlights (HL)

GENERAL FORMAT

NO 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: *Correct width of right,left and top of page margins to be 1/2 inch.*

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *Without BW, HL exceeds 1/2 page. DPARP to grant waiver of 1/2 page HL limit in approval letter.*

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI

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Selected Requirements of Prescribing Information

• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *In the last line of the HL Limitation Statement, remove extra white space before the drug name, "OTREXUP."*

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

YES 12. All text must be **bolded**.

Comment:

YES 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." in *italics* and centered immediately beneath the heading.

Comment:

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES

24. Each contraindication is bulleted when there is more than one contraindication.
    Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS**".

Comment:

NO 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *In order to match the FPI, correct the following in the TOC: BW title, change "embryofetal" to "embryo-fetal" and remove hard return after "embryofetal" so that the title is presented as continuous wrapping text; subsection heading 1.3, change "Limitations" to "Limitation"; section 4, Contraindications, remove bulleted list of contraindications from the TOC (since these contraindications are not assigned subsection numbers, they should not be listed in the TOC); subsection heading 7.1, change "(NSAIDs)" to "Nonsteroidal Anti-Inflamatory Drugs"; and subsection heading 7.2, change "Proton Pump Inhibitor (PPI) Therapy" to "Proton Pump Inhibitors (PPIs)".*

Selected Requirements of Prescribing Information

NO 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment: *BW title in TOC must match FPI. Correct BW title as stated above in item 30.*

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse

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9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

NO 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: *Attach Patient Information and Instructions for Use to the end of the PI.*

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

YES 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

Selected Requirements of Prescribing Information

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

> *"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."*

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

> *"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."*

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

Reference ID: 3386844

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/s/

DEBRA C BEITZELL
10/08/2013

LAURIE B BURKE
10/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: September 10, 2013
From: Jacqueline Ryan, Combination Products Team Leader, GHDB, WO66, RM 2556
General Hospital Devices Branch, DAGID, ODE, CDRH

To: Sadaf Nabavian,, Senior Program Management, CDER, OMPT/CDER/OND/ODEII/DPARP

Subject: CDRH Consult NDA 204824, Prefilled Syringe and Autoinjector to deliver Methotrexate

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding NDA 204824The device constituent of this combination product consists of a prefilled syringe and auto injector to deliver methotrexate..

2. Device Descriptions

The primary container closure for the drug product is a 1mL long Type 1 glass syringe (b) (4) with stainless steel 27 gauge ½ inch staked needle and soft needle shield. The syringe barrel with fixed needle shield is supplied as a sterile component and is not re-sterilized before use by the drug product manufacturer.

The **AJ** MTX is a spring powered needle-based injector of liquid drugs that facilitate self-injection or injection **by** a caregiver using an automated injection process... Injection is accomplished **by** pushing the device against the injection site - this retracts the needle guard to expose the needle that penetrates the user's skin to deliver the drug. When the needle has penetrated the user's skin to the required depth, the device "triggers" and the drug is delivered simultaneously using a single spring force. The user must hold the device firmly against the injection site for a short period of time to allow drug delivery to occur.
The **AJ** MTX is a single-shot, fixed dose, spring powered, disposable device, designed specifically for subcutaneous delivery of methotrexate, a drug used to treat rheumatoid arthritis. It is designed to accommodate a **1.0** ml, (b) (4)

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(b) (4) syringe, a **27** gauge **12.7** mm staked needle, and a rubber needle shield. Injection is accomplished **by** pushing the device against the injection site with the needle guard firmly held against the injection site.

Figure 7: Representative Schematic of the Autoinjector

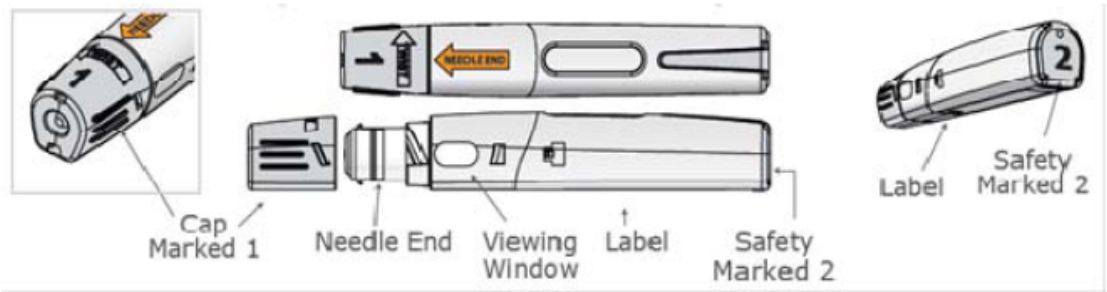
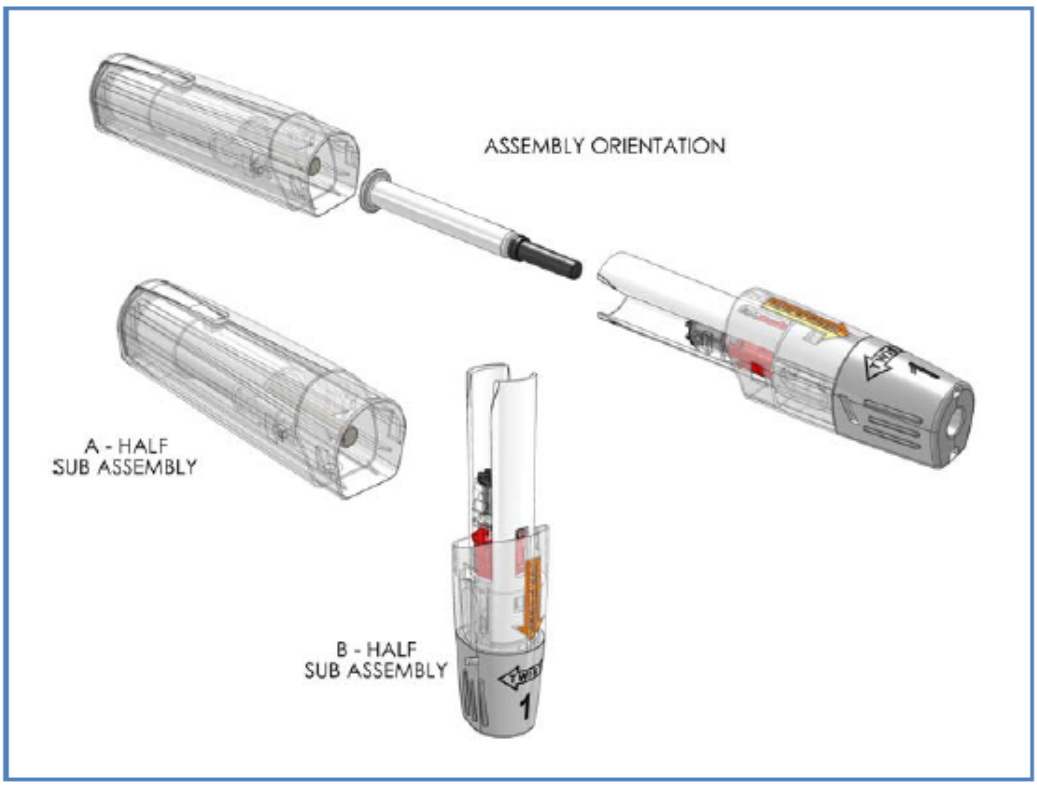


Figure 8: Representative Model Autoinjector Assembly



The **AJ** MTX incorporates passive sharps protection into its design. The needle guard serves to conceal the needle before injection, determines the injection needle depth and triggers the device to accomplish the injection. The needle guard also serves as the safety shield upon completion of the injection. The needle guard is held in the fully extended position **by** the return spring and is free to retract partially and return to its fully extended position until the device has been fired. Upon firing and removal from the injection site, the needle guard extends and is then locked in the extended position, preventing user exposure to the needle a second time.
The design of the sharps protection features of the device takes into consideration the

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recommendations listed in Section **5** of FDA's guidance document *Medical Devices with Sharps Injury Prevention Features* for needle shield type devices

Table 2: Materials of Construction - Medi-Jet MTX – A-half Assembly Components		
Part	**Skin Contact**	**Material**
Housing – Rear (A-half)	Yes	(b) (4)
Latch	No	
Ram	No	
Trigger	No	
Main Spring	No	
Safety	Yes	

Table 3: Materials of Construction - Medi-Jet MTX – B-half Assembly Components		
Part	**Skin Contact**	**Material**
Needle Guard	Yes	(b) (4)
Sleeve	No	
Lock Ring	No	
Bushing	No	
Safety Cap	Yes	
Return Spring	No	
Housing – Front (B-half)	Yes	

.

3. Documents Reviewed

MAF (b) (4) Revision 03, November 14, 2012

4. CDRH Review and Comments

GHDB's review of MAF (b) (4) includes of a review of Device Performance and Biocompatibility. Human Factors data are reviewed separately by DAGRID Human Factors Team

Device Performance Testing Overview
The following standards and guidance documents were used in the development and testing of the device:
* **ISO 11608-1:2000(E)** - Pen injectors for medical use - Part **1:** Pen injectors - Requirements and test methods - Section 7.4 preconditioning **by** free fall.
* **FDA** Guidance for Industry and **FDA** Staff - Medical Devices with Sharps Injury Prevention Features - August **9, 2005.** This guidance was used as a reference when determining the product testing and sample size requirements.
* **ASTM F1980:1992** Accelerated aging of sterile medical device packaging. This

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standard was used to determine the accelerated aging conditions.
* **IEC 60068-2-27:1987** - Basic environmental testing procedures Part 2: Tests - Test **EA** and guidance: (b) (4).
* **IEC 60068-2-30:2005** - Basic environmental testing procedures Part 2: Tests - Test DB: (b) (4)
* **IEC 60068-2-64:1993** - Environmental testing - Part 2: Test methods test FH: (b) (4) and guidance.
* **JEC 60721-3-7:2002** - Classification of environmental conditions - Part **3-7:** Classification of groups of environmental parameters and their severities - Portable and non-stationary use - (class (b) (4)**).**

Design verification tests performed are listed below.

• Delivered Volume - verified that the device could consistently deliver the specified amount of fluid from the pre-filled syringes.
• Ejection Time - determined the time that it takes to expel the specified volume from the assembly.
• Exposed Needle Length - determined the distance that the needle extends beyond the needle guard, once the needle guard has been fully retracted. Collar (Needle Guard)
• Lockout Override Force - measures the amount of force necessary to override the lockout feature (i.e. passive sharps feature).
• Needle to Needle Guard Distance - verified that the distance between the tip of the needle and the outmost edge of the needle guard meet the specifications ensuring that the needle is fully enclosed in the needle guard even when assembled using the longest possible syringe.
• Activation Force (Trigger Force) - determined the force required to activate (trigger) the finished device.
• Safety Cap Removal Torque - verified that the torque required to remove the safety cap is within the specification. The safety cap must be able to stay on during normal transport and storage, but still allow for easy removal by the end user.
• Safety Removal Force - verified that the force required to remove the safety is within the specification. The safety must be able to stay on during normal transport and storage, but still allow for easy removal by the end user.
• Safety Override Test - verified that the force required to override the safety is within the specification. The safety must be able to resist accidental triggering during normal usage.
Ram / Latch Push out Force - determined the force required to push the ram out of the latch. The ram / latch interface affects the ability of the device to trigger consistently and the push-out force provides a quantitative measurement of that consistency.
Device Integrity - assessed the amount of force required to overcome the mechanical features which keep the A-half and B-half sub-assemblies attached to each other.
Device Function - verified that the device functions properly with normal usage.
Device Drop Test - verified that the device functions properly after being dropped from a height of 1000 mm, on each of three axes.
Spring Relaxation - assessed the main spring to determine what percentage of load loss could be expected over the shelf-life of the product.
Biocompatibility Testing - verified skin-contacting materials met appropriate biocompatibility criteria.
Cool Temperature Performance - verified that the finished device functions properly after storage at 4°C.

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Warm Temperature Performance - verified that the finished device functions properly after storage at 40°C.
Cold Temperature Storage - verified that the device functions properly after the subassemblies
have been subjected to cold storage conditions (-40°C).
Hot Temperature Storage - verified that the device functions properly after the subassemblies
have been subjected to hot storage conditions (70°C @ 50% RH).
Environmental Cycling - verified that the device functions properly after the subassemblies
have been subjected to conditions of high humidity when combined with cyclic temperature changes.
Device Vacuum Test - verified that the device functions properly after being subjected to vacuum conditions.
Device Vibration Test - verified that the device functions properly after being subjected to vibration conditions.
Device Shock Test - verified that the device functions properly after being subjected to mechanical shock conditions.
Shelf-life Testing - verified that the device functions properly after being subjected to an accelerated shelf-life aging protocol
.

Reviewer's Comment:
Test reports and methods were reviewed. All test items met criteria. ISO 11608-1 testing and other critical functional or attribute testing are described below.

ISO 11608-1 Testing Summary

Delivered Volume/ Dose Accuracy

The dose accuracy requirements (section 7.4) of ISO 11608-1:2012(E) Pen-injectors for medical use — Part 1: Pen-injectors - Requirements and test methods were used as the basis for the test design and acceptance criteria. Sample sizes were chosen for 95% confidence and 97% reliability.

Table 5: Delivered (Expelled) Volume Test Results

N	Spec (ml)	Results				
		Avg (ml)	Range (ml)	Std Dev (ml)	$\bar{X}$-ks (ml)	Pass/Fail
30	(b) (4)					Pass

All samples met dose accuracy criteria

Environmental Pre- Conditioning/ Cycling Testing

Cool Temperature Performance

Reference ID: 3371365

Table 22: Cool Temperature Performance Test Results

Device Function	N	Spec (ml)	Results				
			Avg (ml)	Range (ml)	Std Dev (ml)	$\bar{X}$-ks (ml)	Pass/Fail
Delivery Volume	30					(b) (4)	Pass
Successful Needle Shield Removal	30	100%	-	-	-	-	Pass
Successful Device Triggering	30	100%	-	-	-	-	Pass
Successful Needle Guard Lockout	30	100%	-	-	-	-	Pass

All samples passed.

Warm Temperature Performance

Table 23: Warm Temperature Performance Test Results

Device Function	N	Spec (ml)	Results				
			Avg (ml)	Range (ml)	Std Dev (ml)	$\bar{X}$-ks (ml)	Pass/Fail
Delivery Volume	30					(b) (4)	Pass
Successful Needle Shield Removal	30	100%	-	-	-	-	Pass
Successful Device Triggering	30	100%	-	-	-	-	Pass
Successful Needle Guard Lockout	30	100%	-	-	-	-	Pass

All samples passed.

Cold Temperature Storage

Table 24: Cold Temperature Storage Test Results

Device Function	N	Spec (ml)	Results				
			Avg (ml)	Range (ml)	Std Dev (ml)	$\bar{X}$-ks (ml)	Pass/Fail
Delivery Volume	30					(b) (4)	Pass
Successful Needle Shield Removal	30	100%	-	-	-	-	Pass
Successful Device Triggering	30	100%	-	-	-	-	Pass
Successful Needle Guard Lockout	30	100%	-	-	-	-	Pass

All samples passed.

Hot Temperature Storage

Reference ID: 3371365

Table 25: Hot Temperature Storage Test Results

Device Function	N	Spec (ml)	Results				
			Avg (ml)	Range (ml)	Std Dev (ml)	$\bar{X}$-ks (ml)	Pass/Fail
Delivery Volume	30					(b) (4)	Pass
Successful Needle Shield Removal	30	100%	-	-	-	-	Pass
Successful Device Triggering	30	100%	-	-	-	-	Pass
Successful Needle Guard Lockout	30	100%	-	-	-	-	Pass

All samples passed.

Environmental Cycling

Table 26: Cyclical Damp Heat Test Results

Device Function	N	Spec (ml)	Results				
			Avg (ml)	Range (ml)	Std Dev (ml)	$\bar{X}$-ks (ml)	Pass/Fail
Delivery Volume	30					(b) (4)	Pass
Successful Needle Shield Removal	30	100%	-	-	-	-	Pass
Successful Device Triggering	30	100%	-	-	-	-	Pass
Successful Needle Guard Lockout	30	100%	-	-	-	-	Pass

All samples passed.

Drop Testing

Table 17: Device Drop Test Results (Delivered Volume)

Device Function	N	Spec (ml)	Results				
			Avg (ml)	Range (ml)	Std Dev (ml)	$\bar{X}$-ks (ml)	Pass/ Fail
Delivery Volume	90					(b) (4)	Pass
Successful Needle Shield Removal	90	100%	-	-	-	-	Pass
Successful Device Triggering	90	100%	-	-	-	-	Pass
Successful Needle Guard Lockout	90	100%	-	-	-	-	Pass
No Visible Damage to Syringe	90	100%	-	-	-	-	Pass
No Visible Damage to Device	90	100%	-	-	-	-	Pass

All samples passed.

Exposed Needle Length

Reference ID: 3371365

Table 7: Exposed Needle Length Test Results

N	Spec (mm)	Results				
		Avg (mm)	Range (mm)	Std Dev (mm)	$\bar{X}$-ks (mm)	Pass/Fail
30	≥2.5	5.0	4.8 – 5.2	0.1	4.7	Pass

All samples passed.

Ejection Time

Table 6: Ejection Time Test Results

N	Spec (sec)	Results				
		Avg (sec)	Range (sec)	Std Dev (sec)	$\bar{X}$+ks (sec)	Pass/Fail
30	(b) (4)					Pass

All samples passed.

Biocompatibility Testing

Testing was performed on skin-contacting components (front housing, rear housing, safety, safety cap and needle guard) of the device according to ISO 10993 for limited contact with intact skin.

Reviewer's Comment:
L929 MEM Cytotoxicity testing, Intracutaneous Reactivity and Sensitization(Kligman Maximization) test
results were all acceptable.

Shelf Life Testing

Testing was performed to verify that the device functions after being subjected to accelerated aging to simulate 4 years of real-time aging. Specifications were that the delivered volume should be (b) (4) and no devices should have failures of needle shield stripping, device triggering, or needle guard lockout. Thirty devices were tested and all passed.

Sharps Injury Protection Feature Testing

Sharps Injury Prevention study utilized a single-center, prospective, observational design to evaluate the sharps injury prevention features of the Medi-Jet MTX Device. Evaluation of the sharps feature was performed by obtaining data as to whether or not the sharps injury prevention feature was activated, and once activated that the prevention feature could not be deactivated, and remained protective through disposal of the device. The study was intended to simulate actual use and to allow the gathering and analysis of data that records the performance of the device sharps protection. Evaluators were used as surrogates and observers assessed and recorded the sharps protection device performance and the adherence of the evaluators with the relevant Instructions For Use (IFU). The study took place at a single investigational center with 14 evaluators evaluating the 518 study devices (37 devices per evaluator).This sample size is consistent with the recommendation from FDA's guidance.

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The sharps prevention feature was activated in all 518 devices deployed. The successful sharps prevention activation rate was between 99.3 and 100.0 percent, with 95% confidence. Because the lower bound of the two-sided 95% exact binomial confidence interval is greater than 99.3%, the successful sharps prevention activation rate was greater than 99.0% (p-value = 0.0222).

5. Master File Contact Information

Master File Holder:
Antares Pharma, Incorporated
13755 First Avenue North, Suite 100
Minneapolis, MN 55441
Phone: 763.475.7700
Fax: 763.476.1009

Contact:
Julius Sund, Vice President Manufacturing and Engineering - Parenteral Products Division
Phone: 763.475.7718
E-mail: isund(@antarespharma.com

6. CDRH Recommendations

CDRH General Hospital Devices Branch does not have any concerns regarding MAF (b) (4).

Digital Signature Concurrence Table	
Reviewer Sign-Off Jacqueline Ryan	
Branch Chief Sign-Off Richard Chapman	

Reference ID: 3371365

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/s/

SADAF NABAVIAN
09/10/2013

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:	September 05, 2013
To:	Badrul Chowdhury, MD, PhD 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)** Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, RN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Roberta Szydlo, RPh, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	Otrexup (methotrexate)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 204824
Applicant:	Antares Pharma, Inc.

1 INTRODUCTION

On December 14, 2012, Antares Pharma, Inc submitted for the Agency's review a New Drug Application for Otrexup (methotrexate) indicated for the treatment of rheumatoid arthritis, including juvenile rheumatoid arthritis, and moderate to severe psoriasis.

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 16, 2013 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for Otrexup (methotrexate), injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and DMEPA deferred to DMPP to provide IFU review comments.

2 MATERIAL REVIEWED

- Draft Otrexup (methotrexate) PPI received on December 14, 2012 and IFU received on June 7, 2013, and received by DMPP January 7, 2013 and July 12, 2013 respectively.
- Draft Otrexup (methotrexate) PPI received on December 14, 2012, and IFU received on June 7, 2013, and received by OPDP on January 16, 2013, and July 12, 2013, respectively.
- Draft Otrexup (methotrexate) Prescribing Information (PI) received on December 14, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on August 22, 2013.
- Draft Otrexup (methotrexate) Prescribing Information (PI) received on December 14, 2012, revised by the Review Division throughout the review cycle, and received by OPDP on August 22, 2013.

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. In our review of the PPI and IFU the target reading level is at or below an 8th grade 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 have reformatted the PPI and IFU document using the Verdana font, size 11 when possible.

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are 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 meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

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/

SHARON W WILLIAMS
09/05/2013

ROBERTA T SZYDLO
09/05/2013

ROBIN E DUER
09/05/2013

LASHAWN M GRIFFITHS
09/05/2013

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

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

Memorandum

Date: September 3, 2013

To: Sadaf Nabavian, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Roberta Szydlo, Regulatory Review Officer (Rheumatology)
Puja Shah, Regulatory Review Officer (Dermatology)
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Acting Group Leader, OPDP
Adora Ndu, Acting Group Leader, OPDP
Lynn Panholzer, Regulatory Review Officer, OPDP

Subject: NDA 204824
OPDP labeling comments for OTREXUP (methotrexate) injection, for subcutaneous use

---

In response to DPARP's consult request dated January 16, 2013, OPDP has reviewed the draft labeling (Package Insert [PI] and Carton/Container labeling) for OTREXUP (methotrexate) injection, for subcutaneous use (Otrexup) and offers the following comments. OPDP's comments regarding the proposed patient labeling (Patient Package Insert [PPI] and Instructions for Use [IFU]) will be incorporated into a collaborative review by the Division of Medical Policy Programs (DMPP) and OPDP and will be provided under separate cover.

OPDP's comments on the PI are provided directly below and are based on the proposed draft marked-up labeling titled "Otrexup_MTX-PLR-converted-uspi_DPARP-SEALD-ONDQA-CP_21Aug13b_CA.doc" that was provided via email from DPARP on August 21, 2013. We note that the Clinical Review dated August 20, 2013, indicates that DPARP intends to keep the differences between the labeling for Otrexup and other methotrexate drug products minimized because the originators will need to update their labeling in the future, after which time the labeling for Otrexup will need to be revised. OPDP has elected to conduct a comprehensive review of the PI for Otrexup in its entirety.

Reference ID: 3366821

OPDP has reviewed the proposed carton and container labeling submitted by the applicant on June 7, 2013, and located in the EDR (eCTD Sequence Number 0012). We offer the following comment:

- The proposed carton and container labeling for the demonstrator states, "NOT FDA CLEARED OR APPROVED." We note that similar language is not presented on the trainer device for another recently approved drug, Auvi-Q. Is this disclaimer appropriate to include?

OPDP appreciates the opportunity to provide comments on the proposed labeling.

If you have any questions, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

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

Reference ID: 3366821

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/s/

ROBERTA T SZYDLO
09/03/2013

PUJA J SHAH
09/03/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling, Packaging, and Human Factors Study Review

Date:	July 23, 2013
Reviewer:	Teresa McMillan, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Lubna Merchant, PharmD, M.S. Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh. Division of Medication Error Prevention and Analysis
Drug Name(s):	Otrexup (Methotrexate) Injection
Strengths:	10 mg/0.4 mL, 15 mg/0.4 mL, 20 mg/0.4 mL, 25 mg/0.4 mL
Application Type/Number:	NDA 204824
Applicant/Sponsor:	Antares Pharma
OSE RCM #:	2013-120 and 2013-997

*** This document contains proprietary and confidential information that should not be released to the public.***

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Reference ID: 3347268

1 INTRODUCTION

This review evaluates the Human Factors and Clinical Use Study Report, container labels, carton labeling, insert labeling and Instructions for use submitted on December 14, 2012, by Antares Pharma, for NDA 204824, Otrexup (Methotrexate Injection).

1.1 PRODUCT INFORMATION

The following product information is provided in the December 14, 2012 submission.

- Active Ingredient: Methotrexate
- Indication of Use: Rheumatoid Arthritis including polyarticular-course juvenile rheumatoid arthritis and severe psoriasis
- Route of Administration: Subcutaneous
- Dosage Form: Injection
- Strength: 10 mg/0.4 mL, 15 mg/0.4 mL, 20 mg/0.4 mL, 25 mg/0.4 mL
- Dose and Frequency: 10 mg to 25 mg subcutaneously once weekly. May be adjusted in 5 mg increments every (b) (4) to achieve optimal clinical response. Max dose- titrate to effect.
- How Supplied: Single-use disposable (b) (4), an autoinjector device delivery system
- Storage: Store at 20°C to 25°C (68 °F to 77 °F); excursions permitted to 15°C to 30°C (59 °F to 86 °F)

This product is integrated with the device. The Applicant refers to the device component as (b) (4) in the Prescribing Information and the Instructions for Use as well as on the labels and labeling. After seeking clarification from the Applicant, we learned that the Applicant does not intend on using (b) (4) and only wish to pursue the root name Otrexup. The Applicant submitted revised labels and labeling which omitted the use of (b) (4) on June 7, 2013.

2 MEDICATION ERROR RISK ASSESSMENT OF DEVICE AND THE LABELS AND LABELING

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database and literature for Methotrexate medication error reports (See Appendix A for description of FAERS database). We also reviewed the Otrexup (methotrexate) HF Study and Clinical Use Study Report results, labels and package insert labeling submitted by the Applicant.

2.1 FAERS SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 1. We excluded duplicate cases, medication errors involving the tablet formulation, cases that listed methotrexate as a concomitant medication, intentional overdose, adverse events unrelated to a medication error, and wrong dose errors involving the tablet formulation. Following exclusions four methotrexate medication

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error cases remained. Two involve the dispensing of a preserved formulation of methotrexate rather that the intended preservative free formulation and two describe wrong routes of administration (e.g., intravenous ordered for oral route to save money and subcutaneous injection instead of intramuscular injection).

Table 1: FAERS Search Strategy For Medication Errors with Methotrexate Injection	
Date	No date limitations-Search ran on January 16, 2013
Drug Names	*METHOTREXATE (b) (4) *(active ingredient)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues (HLT) Product Label Issues (HLT) Product Quality Issues (NEC) [HLT]

2.2 Literature Search for Medication Error Cases

We searched the ISMP publications on January 16, 2013 for additional medication error cases and actions concerning Methotrexate and none were identified.

2.3 Labels and Labeling Deficiencies

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels, carton labeling, insert labeling, and Instructions for Use submitted on June 7, 2013. The images of the container labels, carton labeling, and instructions for use are shown in Appendices B, C, and D. There is no image of the insert labeling.

This product is the first methotrexate formulation for subcutaneous use. Methotrexate is currently marketed as oral tablets and injection (i.e. intravenous, intrathecal, intramuscular, intra-arterial). Otrexup is administered at the same dose (10 mg to 25 mg) as the currently marketed methotrexate products but varies with respect to frequency of administration. Otrexup is only give once weekly whereas the marketed products can be given daily or once weekly. The route of administration does appear on the labels and labeling of Otrexup. Although the statement is not overly prominent, it is permissible because the label is small and already crowded with information. Moreover, the device design does not afford administration by another route. Since Otrexup is only given once weekly we can consider inclusion of the frequency of administration "once weekly" on the principle display panel of the device label if space permits and carton labeling.

Otrexup will be marketed in four strengths. The carton labeling for the four proposed strengths are not adequately differentiated from each other. This is problematic because the lack of label differentiation can lead to selection errors of the wrong strength.

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

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The IFU does not include instructions for disposal of this product, yet the How Supplied/Storage and Handling section of the insert labeling advises users to consider procedures for proper handling and disposal of cytotoxic drugs and references published handling and disposal guidelines. Additionally, the patient counseling information section of the insert labeling advises users to be informed of proper disposal after use. It is important to provide patients with clear instructions on disposal of this cytotoxic medication.

The Applicant also proposes to present the IFU on the device label. Participants in the human factors study commented that the device label could be improved by making text bigger and that the instructions on the device label panels should state steps 1, 2, and 3 and not A, B, C. However, the size of the text cannot be increased due to the label size. Also, no revisions were made by the Applicant in regards to the instructional steps and no rationale was provided. Because this label was tested in the Human Factors Study discussed in section 2.4 and no failures were attributed to these comments we are not recommending any changes to the layout of the device label.

2.4 HUMAN FACTORS STUDY

The Human Factors study submitted on December 14, 2012 assessed the usability of the autoinjector and its instructions for use. The study design is described in Appendix E. Two failures and thirty-one close calls were observed with the critical tasks in this study.

The failures involve (1) the inability to deliver a complete injection as a result of the device being held at the injection site for less than one second and (2) the participant pointed the needle end of the device towards the hand. The Applicant did not recommend any modifications to the IFU because the failures occurred due a test artifact and an uncooperative participant. However, we have concerns regarding these two failures for the following reasons and provide recommendations to the IFU in section 4.1 Comments to the Applicant to help mitigate these failures:

- One participant was startled by the click at the start of the injection and removed the device prior to completion. The resettable demonstrator device used during training did not have an audible click. A commercial device which included an audible click was used for the remainder of the training to help mitigate this failure. Although there were no additional failures of this type reported as a result of using two different devices, one participant did not hold the device for the required 3 seconds per the IFU due to thinking the click meant to remove the device. The Applicant did not consider this a failure because the dose is delivered within (b) (4) and the participant held for 1-2 seconds. The Applicant also states the demonstrator device for market has a softer click than the commercial device. The training device and the commercial device should be the same in all aspects to help mitigate any confusion regarding the operation of the device.
- With respect to the second failure in which the needle end of the device was pointed towards the hand, the participant did not read the IFU and stated that her actions would not be equivalent to use in a “real world” scenario. The IFU contains a diagram which identifies the different parts of the device. However,

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there is no statement in the IFU which references this device and instructs the user that this is what the Otrexup device looks like.

The majority of the close calls observed with the critical tasks was consistent between all trained and untrained groups and consisted of the following:

- held the device for 1-2 seconds or less than 3 seconds (n=11)

  Participants reported experiencing this close call for the following reasons: not reading the IFU and relying on previous training, forgot to count to three, felt rushed or excited, believed the injection was complete because the viewing window was red and the device wasn't leaking, and thought the click represented the end of the injection.

- injected with inadequate force to fully retract the needle shield (n=10)

  Participants reported experiencing this close call for the following reasons: not applying sufficient force for no apparent reason, thought the device contained a button, thought the click was heard and no additional force was needed, and felt nervous.

- confusion regarding the location and removal of the safety cap (n=5)

  Participants reported experiencing this close call for the following reasons: forgot to remove the safety, thought the safety was a button, and completely removing safety because it isn't fixed to the device.

The remaining close calls consisted of the following: forgot to check the window before the injection, injected within two inches of the navel, and looked for a button to operate device. The participant who injected within two inches from the navel noted the symbol used in the diagram around the navel is confusing and thought it meant to inject in this area. The Applicant did not modify the IFU to help mitigate any of the close calls because these issues were rectified by participants reading the IFU and correcting the potential errors on their own, calling the 1-800 number for assistance, and although the IFU instructs users to hold the device at the site of injection for 3 seconds the drug is delivered in (b) (4) and therefore participants received the full dose.

We note that the IFU includes instructions or diagrams for each close call noted and based on the participant's responses the close calls may have occurred due to the user. Thus, we provide comments in Section 4.1 Comments to the Applicant to further improve the IFU to help mitigate these close calls. We are not recommending the human factors study be repeated because the revisions to the IFU are minor and do not require validation.

We also conclude the proposed IFU changes alone may not fully address all close calls identified. Although no device misfires or incomplete injections were identified, we are particularly concerned with the number of close calls identified for the inadequate use of force and holding the device for 1-2 seconds. Postmarketing experience with similar autoinjectors has attributed inadequate force and not holding the device for the allotted time for administration as reasons for device misfires and incomplete injections. The testing device used in this study did not contain a needle or placebo solution. Therefore, an incomplete injection would not have been identified. Additionally, the click at the start

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of the injection was noted twice as the cause for prematurely removing the device. Modifications to the device such as revising the click to occur post injection rather than at the start of the injection may be warranted to further improve the usability of the device. We defer to CDRH to validate these aspects (delivery of the medication in (b) (4) and the amount of force needed to retract the needle shield) of the device design and they may have additional recommendations to help further optimize the device design.

2.5 CLINICAL USE STUDY

This actual use study was conducted to assess the usability of the autoinjector after standardized training by site personnel and review of written instructions. The study design is described in Appendix F. The applicant reports all participants injected the product correctly, there were no device malfunctions, and most participants' found the instruction for use and device easy to use. However, there was no decay time between training and self-injection and therefore the study did not capture how a user would perform under "real world" use. This product is given once weekly so it is conceivable that a significant time may pass from the time a patient receives instructions on the use of the product and when they receive their medication. Therefore, this study cannot be used to validate this device.

3 CONCLUSIONS

The Human Factors Study confirmed that users may encounter difficulties while administering this product. Thus, DMEPA concludes that the proposed label and labeling can be improved to increase the prominence of important information on the label to promote the safe use of the product. We provide recommendations in section 4.

4 RECOMMENDATIONS

Based on the close calls observed in the Human Factors review, DMEPA recommends the following be implemented prior to approval of this NDA:

4.1 COMMENTS TO THE DIVISION

A. General Comments

We conclude that changes to the labels and labeling alone may not fully address all close calls identified. Modifications to the device such as revising the click to occur post injection rather than at the start of the injection may be warranted to further improve the usability of the device. We defer to the Center for Devices and Radiological Health to validate these aspects (delivery of the medication in (b) (4) and the amount of force needed to retract the needle shield) of the device design and they may have additional recommendations to help further optimize the device design.

4.2 COMMENTS TO THE APPLICANT

A. General Comments

Ensure that the training device and the commercial device operate the same in all aspects.

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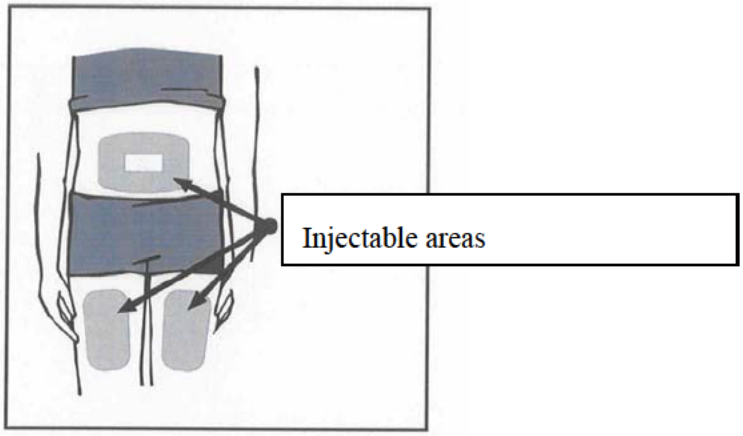
B. Instructions For Use

1. Label the illustration that displays the Otrexup autoinjector as Figure XXX.

2. After "Wash your hands well with soap and warm water" under the "Prepare For Use" heading state the following:

   Figure XXX. Shows what the Otrexup autoinjector looks like.

3. In Figure (b) (4) Remove the (b) (4) add arrows that point to and identify the abdomen and thigh areas to be injected. Also, maintain the (b) (4) statement. See example below:



4. Revise step 3, "Administration" to the following bulleted instructions:

   - Place needle end of Otrexup against thigh or abdomen (b) (4) at 90˚. Firmly push until you hear a click.
   - Hold for **3 seconds** (slowly count 1, 2, 3) (b) (4). (See Figure F)

5. The IFU does not contain instructions for disposal of this product. Add a section at the end of the IFU with instructions for disposal of this product.

C. Device Container Label and Carton Labeling [All labels and labeling]

1. Remove or decrease the size of the graphic which appears above the proprietary name. As presented, it detracts from important information such as the proprietary and established names as well as the strength.

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D. Carton Labeling [All labeling]

1. The carton labeling for the four strengths are not adequately differentiated from each other. The trade dress colors used for the label are similar across strengths thereby minimizing the strength differentiation. To prevent selection errors, revise this label to provide additional means of visual differentiation such as boxing to further differentiate the four available strengths. In addition, increase the font size of the strength presentation so that it is prominently displayed on the label.
2. Increase the font size of the "For subcutaneous use only" statement to increase its prominence.
3. Add a "Once weekly" statement after the route of administration statement on the principal display panel to denote the frequency of administration for this subcutaneous formulation of methotrexate.

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

Reference ID: 3347268

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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

Reference ID: 3347268

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TERESA S MCMILLAN
07/25/2013

LUBNA A MERCHANT
07/26/2013

CAROL A HOLQUIST
07/26/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: July 10, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID

THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID

CC: Molly Story, Human Factors and Accessible Medical Technology Specialist, DAGID

TO: Peter Starke, Medical Officer, CDER/OND/ODEII/DPARP
Sadaf Nabavian, Regulatory Project Manager, CDER/OND/ODEII/DPARP

SUBJECT: NDA 204824
Applicant: Antares Pharma
Drug: Methotrexate (b) (4)
Device: Autoinjector
Intended Use: for treatment of Rheumatoid Arthritis, including Juvenile Rheumatoid Arthritis, and moderate to severe psoriasis
CDRH CTS Tracking: ICC1300169/CON138401

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ron Kaye, Human Factors and Device Use-Safety Team Leader

CDRH Human Factors Review

Overview and Recommendations

The Division of Pulmonary, Allergy, and Rheumatoid Products, Office of Drug Evaluation II, Office of New Drugs, Center for Drug Evaluation and Research requested a Human Factors consultative review of the NDA 204824 submitted by Antares Pharma for their Methotrexate (b) (4) autoinjector.

Antares has conducted a human factors validation study with at least 15 participants representing each of the three major groups: healthcare providers, caregivers, and patients with moderate and severe Rheumatoid Arthritis. Representative training provided on day 1 included several practice injections and an unassisted simulated injection using the autoinjector and injection pad. The training decay was seven days. The testing of first at-home injection was conducted on day 8. All participants had access to the instructions for use (IFU), on-device instructions, and a 1-800 customer support number. Based on use-related risk analysis and formative studies, the 10 critical tasks were identified for successful dose delivery. The study showed 48 of 50 users completed successful injection. The results identified two failures that were determined to be study artifacts, and several non-safety use errors and operational difficulties, which the user was able to resolve and completed their injection.

The reviewer did not identify any concern associated with the study results. The study was well executed and the resulting data were found acceptable. The reviewer concluded that the user interface is optimized, and does not require any additional modifications.

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CDRH Human Factors Review

Combination Product Device Information

Submission Number: NDA 204824
Applicant: Antares Pharma
Drug Constituent: Methotrexate (b) (4)
Device Constituent: Autoinjector
Intended Use: for treatment of Rheumatoid Arthritis, including Juvenile Rheumatoid Arthritis, and moderate to severe psoriasis
Review Materials:
\\CDSESUB1\EVSPROD\NDA204824\204824.enx

CDRH Human Factors Involvement History

Date	Involvements
12/1/2011	CDRH HF was requested to review the human factors/usability study protocol. This review identified three minor deficiencies regarding representative study participants, use of IFU during study, and participant debriefing.
4/19/2012	CDRH HF was requested to review and pre-submission (pre-IDE # 120225) where Antares submitted results of the validation study, and requested CDRH's response regarding the acceptability of the data submitted for the validation study. Since CDRH does not generally review testing data under a pre-IDE submission, this reviewer recommends that at this meeting, CDRH requests that Antares submit the test report as part of the IND through CDER, and CDRH will provide a comprehensive review.
7/10/2013	CDRH HF was requested to review the NDA submission that included an actual human use study, and human factors/usability validation study. The actual human use study did not provide useful human factors/usability data therefore, this review focused on the results of validation study. This review found the human factors/usability study acceptable. The reviewer does not have any further concerns regarding the human factors component of the submission.

Summary of Review Materials and Reviewer Discussion

Antares has conducted a human factors validation study with at least 15 participants representing each of the three major groups: healthcare providers, caregivers, and patients with moderate and severe Rheumatoid Arthritis. To address FDA's comments regarding ensuring that participants represented intended patient user group i.e. moderate to severe RA, Antares stated that study was designed to screen participants to ensure that all participants met or exceeded the expected level of hand function impairment of intended users. 33 participants representing RA and caregivers received training representative of training that a patient and caregiver would receive from a healthcare provider. This training provided on day 1 included several practice injections and an unassisted simulated injection using the autoinjector and injection pad. The training decay was seven days. The testing of first at-home injection was conducted on day 8. All participants had access to the instructions for use (IFU), on-device instructions, and a 1-800 customer support number.

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Based on use-related risk analysis and formative studies, the following tasks were identified as critical for successful dose delivery:

1. Inspect contents of syringe.
2. Locate the appropriate injection site.
3. Twist the cap (marked 1) counter clockwise to remove.
4. Remove the safety (marked 2) completely from the device.
5. Grip the device in hand.
6. Place Needle End of device perpendicular to and directly against the injection site.
7. Firmly push the Needle End of the device into the injection site until the needle shield is fully retracted (note: user retraction of the Needle End of the device fully is necessary for the triggering and lock-out functions of the device to operate).
8. Hold the device at the injection site for 3 seconds after hearing a click (the click occurs after fully retracting the Needle End of the device [i.e., Needle End does not move further while still pushing down]). The device delivers the entire 0.4 mL injection volume in (b) (4) holding the device on the injection site for at least (b) (4) ensures that the entire dose is delivered; the choice of three seconds in the Instructions for Use is to assure compliance.
9. Remove the device from the injection site.
10. Visually confirm that the viewing window is occluded.

Antares indicated that while it is possible for a participant to experience an unsuccessful task perform, they can still perform a successful injection. These results will be categorized as non-safety related use errors or operational difficulties. For example, if a participant holds the device in place properly for only (b) (4) seconds, the user will deliver a full dose but will not have followed the IFU accurately.

The study results showed that 81/83 trials (i.e., simulated injections) were successful (34 simulated injections by patients (each patient performed two unassisted injections, one during training, and one after a 7-day training decay), 32 simulated injections by lay caregivers each patient performed two unassisted injections, one during training, and one after a 7-day training decay, and 17 injections by professional caregivers). There were two failures (one patient during training, and one healthcare provider during testing). These failures were:

- 1 patient (Patient #3) delivered an incomplete injection in the first trial, because she held the device at the injection site for less than one second. The user indicated being startled by the sound of the click. However, this result was determined to be a study artifact. The user received additional training from moderator, and tried with a second device and was able to deliver a successful injection and to complete all injection tasks as described in the instructions for use.
- 1 professional caregiver (Nurse # 13) failed to deliver a successful injection after she pointed the needle end of the device toward her own hand, instead of toward the Study Moderator's abdomen. The user indicated that she behaved differently than she would in

Reference ID: 3343319

real life situation, and this result was also determined to be a test artifact. The user was given a second device, and after reading the IFU, she delivered a successful injection.

All three user groups experienced non-safety use errors and operational difficulties in holding the device at the injection site for at least 3 second, and not pushing the device against the skin with adequate force. The hold time at the injection site errors and difficulties did not result in incomplete injections because the participant either saw the red indicator or heard the device click. The force used to push the device against the skin errors and difficulties were resolved once the participant realized that they had not delivered a complete dose by visual inspection, or by indicating that they did not hear the click and the viewing window was not red, and with additional force, they were able to complete the injection.

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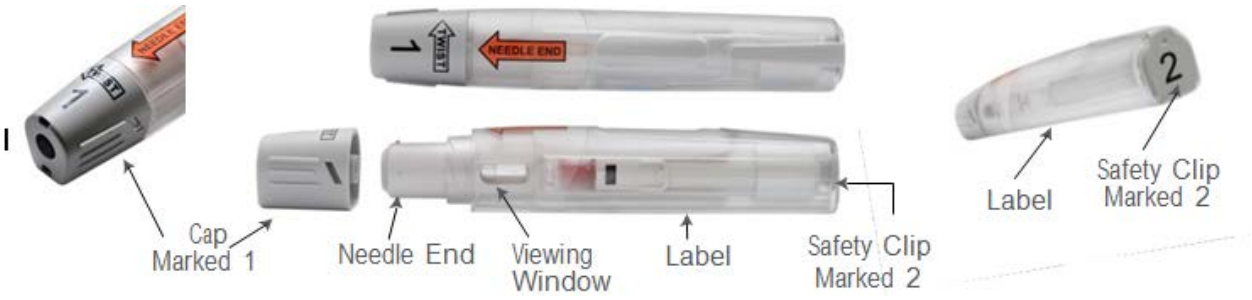
Appendix 1: Device Descriptions

The proposed Antares combination product will be supplied as a single-use prefilled autoinjector containing sterile, preservative-free Methotrexate Injection for subcutaneous administration of a fixed volume of 0.4 mL yielding final delivered doses of Methotrexate sodium equivalent to 10, 15, 20 or 25 mg Methotrexate. All doses of Methotrexate Injection, are contained within the same single-dose syringe with a 27- gauge, ½-inch needle with a soft needle shield within an autoinjector.



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Reference ID: 3343319

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SADAF NABAVIAN
07/18/2013

NDA 204824
Methotrexate SC Injection
Selected Requirements of Prescribing Information (SRPI)

The Selected Requirements of Prescribing Information (SRPI) version 2 is 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

NO 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *Due to the Box Warning the HL Section is more than half a page.*

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Reference ID: 3323738

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

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Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

YES 12. All text must be **bolded**.

Comment:

YES 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment: *Exceeds 10 lines*

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

Reference ID: 3323738

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

NO 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment: *Sponsor needs to inculde the phone number*

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS**".

Comment:

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Selected Requirements of Prescribing Information (SRPI)

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

YES 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment: *However revision to the BW is needed in regards to heading and title*

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use

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8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

NO 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: *Need to delete the subsections listed.*

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

YES 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment: *The MO recommended to delete the subjects afeter Warning*

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

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YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment: *Included on Page 9 of 28*

YES 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SADAF NABAVIAN
06/12/2013

LADAN JAFARI
06/12/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 204824 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Otrexup Established/Proper Name: Methotrexate Injection Dosage Form: Injection, SC Strengths: 10mg, 15mg, 20mg, 25 mg per 0.4 ml's		
Applicant: Antares Pharma, Inc. Agent for Applicant (if applicable):		
Date of Application: December 14, 2012 Date of Receipt: December 14, 2012 Date clock started after UN:		
PDUFA Goal Date: October 14, 2013	Action Goal Date (if different): October 11, 2013	
Filing Date: February 12, 2013	Date of Filing Meeting: January 25, 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3 (New Dosage Form)		
Proposed indication(s)/Proposed change(s): Rheumatoid Arthritis, JRA and moderate the severe arthritis		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☒ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

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☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 103738	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			PDUFA date falls on a holiday (10/14/13), therefore action date will be on Friday, 10/11/13.
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	S			To still be determined if the NDA needs to be split between DDDP and DPARP.
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

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User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:		X		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***		X		

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Designations and Approvals list at: ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***				

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If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 Years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?				
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

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☒ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			**X**	
• If yes, were all of them submitted on time?				
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?				
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			

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Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)]. ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***				

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:				

Pediatrics	**YES**	**NO**	**NA**	**Comment**

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PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			PeRC Scheduled for June 6, 2013
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			Request for full waiver
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		X		Only a position paper has been submitted justifying why a REMS is not required. Safety Team is aware and no further consult is needed at this time.
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI)			

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

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	☒ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented				

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

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SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			CDRH consult for the device (by CMC) and usability study.
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** September 13, 2011 ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** November 02, 2012 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***				

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ATTACHMENT

MEMO OF FILING MEETING

DATE: January 25, 2013

BLA/NDA/Supp #: 204824

PROPRIETARY NAME: Otrexup™

ESTABLISHED/PROPER NAME: Methotrexate Injection (b) (4)

DOSAGE FORM/STRENGTH: 10mg, 15mg, 20mg, 25mg (all doses per 0.4 ml in a prefilled syringe)

APPLICANT: Antares Pharma, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Rheumatoid Arthritis (RA), Juvenile Rheumatoid Arthritis, and moderate to severe arthritis (Ps)

BACKGROUND: This is a new drug application in which the sponsor is proposing a new route of administration as subcutaneous administration of methotrexate injection indicated for RA, JRA, Ps.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sadaf Nabavian	Yes
	CPMS/TL:	Ladan Jafari	Via Phone
Cross-Discipline Team Leader (CDTL)	Theresa Michele		Yes
Clinical	Reviewer:	Peter Starke	Yes
	TL:	Theresa Michele	Yes
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		

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	TL:		

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Clinical Pharmacology	Reviewer:	Sheetal Agarwal	No
	TL:	Suresh Doddapaneni	No
Biostatistics	Reviewer:	Joan Buenconsejo	Yes
	TL:	Joan Buenconsejo (same)	Yes
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Andrew Goodwin	Yes
	TL:	Timothy Robison	Yes
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Arthur Shaw	Yes
	TL:	Alan Schroeder/Prasad Peri	Yes
Quality Microbiology *(for sterile products)*	Reviewer:	Erika Pfeiler	No
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

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Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Jaqueline Ryan (CDRH)		No
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

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or efficacy issues o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

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IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: to follow-up with CMC	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☒ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**: f/u with clinical	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

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CMC Labeling Review **Comments**: CMC labeling comments	☒ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Sarah Yim **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

	ACTIONS ITEMS
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day

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	filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

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for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

SADAF NABAVIAN
02/22/2013

LADAN JAFARI
02/25/2013

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Pulmonary, Allergy, and Rheumatology Products

Application Number: NDA 204824

Name of Drug: Otrexup™ (methotrexate) Injection

Applicant: Antares Pharma, Inc.

Submission Date: December 14, 2012

Receipt Date(s): December 14, 2012

Type of Labeling Reviewed: WORD/SPL

Background and Summary

The sponsor submitted a new drug application dated December 14, 2012, for a drug/device combination of methotrexate injection as a 505(b)(2) application. Currently methotrexate is approved for the indications of malignancy, rheumatoid arthritis, juvenile rheumatoid arthritis and severe psoriasis in several different dosage forms (oral, IV, IM and intrathecal). This new drug application provides for methotrexate as a new route of administration as a subcutaneous route for the indications of Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, and moderate to severe psoriasis.

Review

The following issues/deficiencies have been identified in the proposed labeling:

Highlight (HL) Section

- White space must be present before each major heading in the HL section
- For the Initial U.S. approval date, the original date of approval of the active ingredient must follow
- In the Highlights Limitation Statement, the name of the drug product must be in upper case
- In the Boxed Warning
    - All text must be bolded
    - The word “Warnings” must be replaced with “Warning” and be bolded in the center heading with the subject(s) of the Warning
- In the Dosage and Administration
    - Indicate administration (subcutaneous)
- Dosage Forms and Strengths
    - A concise summary of dosage forms and strengths including any appropriate subheadings (e.g., injection)

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Table of Contents (TOC)

- The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
- The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in upper-case letters and bolded.
- Do not include FDA-approved patient labeling as a subsection heading in the TOC.
- There should be no periods after the numbers for the section and subsection headings.

Full Prescribing Information (FPI) Section

- Boxed Warning
  - All text should be bolded
  - The word "Warnings" must be changed to "Warning" and be bolded in the center heading with the subject(s) of the Warning
- When post-marketing adverse reaction data is included, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

  "*The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.*"
- There should be no periods after the numbers for the section or subsection headings
- Dosage and Administration
  - Provide basic dosing information first, followed by other information relevant to dosage and administration. The sequence of information should reflect the relative importance of the information to safely and effectively administer the drug. In unusual circumstances, certain dosage or administration information may be so important that it should precede the basic dosage information (e.g., for subcutaneous use only). This critical information should be placed in the first subsection heading under DOSAGE AND ADMINISTRATION (e.g., 2.1 Important Administration Instructions) that identifies the critical nature of the information.
- Patient Counseling Information
  - Reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

    "See FDA-approved patient labeling (Patient Information and Instructions for Use)"
- Post-marketing Experience subsection
  - Include following statement (or appropriate modification) preceding the presentation of AR: "The following adverse reactions have been identified during post approval use of methotrexate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Recommendations

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I recommend that the recommendations noted above from my review be conveyed to the sponsor in the Filing Communication Letter.

Sadaf Nabavian, Pharm.D.
Regulatory Project Manager

Supervisory Comment/Concurrence:

Ladan Jafari
Chief, Project Management Staff

Drafted: SNabavian/February 19, 2013
Cleared: LJafari/February 21, 2013
Finalized: SNabavian/February 21, 2013
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW

Reference ID: 3265610

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/s/

SADAF NABAVIAN
02/22/2013

LADAN JAFARI
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