CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204824Orig1s000

MEDICAL REVIEW(S)

M E M O R A N D U M

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

FROM:	Martha Donoghue, Medical Review Officer, DOP2
THROUGH:	Suzanne Demko, Team Leader, DOP2
THROUGH:	Patricia Keegan, Division Director, DOP2
TO:	File
SUBJECT:	Clinical Review of Study Proposal
SUBMIT DATE:	June 27, 2013
PRODUCT:	Methotrexate injection, for subcutaneous use (Otrexup™)
NDA:	204824
APPLICATION HOLDER:	Antares Pharma, Inc.
DATE:	October 25, 2013

Background:
On December 14, 2012 Antares Pharma submitted NDA 204824 for Otrexup (methotrexate injection for subcutaneous administration) under the provisions of 505b(2). The application referenced three listed products: NDA 8085 (methotrexate tablets, USP; Dava Pharmaceuticals, Inc.), NDA 11719 (methotrexate injection, USP; Hospira), and ANDA 40632 (methotrexate preservative-free injection; Bedford Laboratories). Approved labeling for these listed products is not in compliance with Physician Labeling Rule (PLR) requirements.

Otrexup is a single-use, pre-filled autoinjector containing 10, 15, 20, or 25 mg of methotrexate. In the original NDA submission, Antares Pharma submitted data showing that subcutaneous administration of Otrexup resulted in equal or greater bioavailability compared to orally administered methotrexate tablets and systemic exposure that was bioequivalent to the approved injectable product administered by the subcutaneous or intramuscular routes.

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested input from the Division of Oncology Products 2 (DOP2) to assist in the creation of the package insert for Otrexup in PLR format. In particular, DPARP sought advice regarding potential inclusion of oncology indications in the Otrexup label for consistency with approved labeling of other methotrexate products, and how best to bring approved labeling up to date with current scientific knowledge and PLR requirements.

Summary of Advice from DOP2
During the consultation process, DOP2 provided labeling advice through email and participation in several labeling meetings with representatives from DPARP and SEALD from July through September. Additionally, on August 8, 2013 DOP2 participated in a meeting with senior CDER management to discuss the approach to product labeling for Otrexup.

DOP2 recommended that Otrexup labeling exclude the oncology indications, citing several reasons. First, there are potential safety concerns related to the risk of accidental use of the autoinjector for intrathecal use for oncology indications. Second, the proposed doses and route of administration for Otrexup are not appropriate for use in many of the oncology indications for which methotrexate is typically used (which require intravenous dosing in grams rather than milligrams). Third, there does not appear to be a medical need for use of an autoinjector formulation of methotrexate to treat patients with cancer; cancer patients who require systemic methotrexate have central venous catheters due to the need for multiagent systemic chemotherapy and would therefore not benefit from having the option of subcutaneous administration. Finally, DOP2 expressed uncertainty regarding whether FDA has the regulatory authority to require that a drug approved through the 505(b)(2) pathway receive all the indications granted to the referenced listed products. DOP2 also recommended that safety information in the Otrexup label align with the safety information contained in the referenced labeled products as closely as possible because most of the toxicities observed in the oncology population can occur in patients who are treated with methotrexate for non-oncology indications (b) (4) . During the August 8, 2013 meeting, senior CDER management provided concurrence with this approach.

DOP2 also worked with DPARP and SEALD to reach agreement on specific issues throughout the label, including:

- Inclusion of the following Limitation of Use in Section 1: "Otrexup is not indicated for the treatment of neoplastic diseases."
- Deletion of dosing information for oncology indications, including removal of references to the intrathecal route of administration in Section 2.
- Inclusion of information in Section 5 for alignment with the Boxed Warning.

Throughout the labeling process, DOP2 provided advice as needed to assist with wording and organization of Section 6, and provided concurrence with the draft labeling that was sent to the Applicant, as requested by DPARP.

(b) (4)

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

/s/

MARTHA B DONOGHUE
10/25/2013

SUZANNE G DEMKO
10/28/2013

PATRICIA KEEGAN
10/28/2013

MEDICAL OFFICER - MEMO TO FILE

Date:	September 26, 2013
Subject:	Labeling issues for NDA 204824, Otrexup (methotrexate) for Injection
From:	Peter Starke, MD, Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Introduction

This memo summarizes the decisions made with respect to major labeling and indication issues for the proposed Otrexup (methotrexate) auto-injector submitted by Antares Pharma, Inc. These issues arose during the review cycle while making edits to the proposed labeling for the product, and were addressed through consultation with the Divisions of Oncology Products 2 (DOP2) and Dermatology and Dental Products (DDDP), the SEALD labeling team, and with the CDER senior management.

Background

This 505(b)(2) new drug application references three applications for methotrexate: NDA 11-719 for Methotrexate Injection EQ 50 mg base/2mL from Hospira, ANDA 40-632 for Methotrexate Preservative-Free Injection from Bedford, and NDA 08-085 for Methotrexate Tablets from Dava Pharmaceuticals. NDA 11-719 and NDA 08-085 currently reside in the FDA oncology division (DOP2). The proposed Trade Name for the product is Otrexup, and the PDUFA date is October 14, 2013 (action date October 11, 2013). Background regarding the product is below, followed by a summary of the labeling and indication issues.

Methotrexate is a folate analog metabolic inhibitor currently indicated for the treatment of neoplastic diseases, severe psoriasis, rheumatoid arthritis (RA), and polyarticular-course juvenile rheumatoid arthritis (JRA) now called polyarticular juvenile idiopathic arthritis (pJIA).

The proposed product is a drug/device combination consisting of a single-use, prefilled auto-injector intended for subcutaneous (SC) administration. It will be supplied in doses of 10 to 25 mg in 5 mg increments (10, 15, 20 and 25 mg). Because it is intended as a convenience formulation for self or caregiver use in the home setting, the applicant's proposed indications for this product are limited to RA, pJIA, and psoriasis, and do not include treatment of neoplastic diseases. The applicant also requested a new indication of moderate psoriasis, and this was considered by the Division of Dermatology and Dental Products (DDDP) and rejected (b) (4) .

No clinical trials were performed to support the application. Support for approval is based on:

1. The Agency's previous findings of the safety and effectiveness of methotrexate in patients with RA, polyarticular JRA (pJIA), and psoriasis.
2. Literature reviews that support the safety and efficacy of SC administration of methotrexate as an alternative to oral or IM administration of MTX for these conditions and for the age groups for which they are currently approved. The literature supports SC administration, with higher systemic exposure and improvements in efficacy when administered SC or IM

compared with similar oral doses, particularly at doses above 15 mg. The safety review of the literature and of the studies provided to this application did not reveal any new safety signals that would require additional labeling beyond those already labeled in the reference products.

3. A BA study (and MTX-11-003) in adults that supports efficacy with SC administration in patients with RA and psoriasis because it showed equal or greater bioavailability of the proposed MTX auto-injector product administered SC when compared to systemic exposure with orally administered MTX tablets.
4. A BE study (MTX-10-001) in adults that showed bioequivalence of systemic exposure between this auto-injector product administered SC in either the abdomen or the thigh and the approved injectable product administered with a needle and syringe either by the SC or IM route.
5. The applicant also performed an actual use labeling study (MTX-11-002) and a labeling and human factors study (MTX-11-004) to support the labeling and use of the proposed product, demonstrating that patients and caregivers could be taught to successfully use the product. These studies were requested by our CDRH colleagues.

Labeling Issues

Background

The labeling for methotrexate is very old, the listed originator oral and parenteral products having been approved in the 1950's. There are multiple generic products. None of the labels are in PLR format, although they have been updated at some point with the DESI indications, and the PI for the parenteral formulation is unified in that it contains includes oral dosing information. This will be the first methotrexate product to use PLR formatting. The labeling contains a Boxed Warning for multiple toxic effects as well as multiple Warnings and Precautions. There are no clinical trials listed in the Clinical Trials section, although a scattering of clinical information may be found in multiple sections, including the Clinical Pharmacology, Adverse Events, and Pediatrics sections, as well as in the D&A section.

The applicant wishes to update the labeling with some new clinical and other information and add clinical trials from the literature. However, this is not appropriate for a 505(b)(2) application for which the applicant is not the listed drug.

The doses used in RA, pJIA, and psoriasis range from about 5 mg to 30 mg. For RA, the recommended starting dose is 7.5 mg administered orally as a single weekly dose. For pJIA the recommended starting dose is 10 mg/m^2, and the route is not specified. For Psoriasis, the recommended starting dose is between 10 and 25 mg, administered orally, IM, or IV. For oncologic indications, doses range much higher (high-dose treatments, often with leucovorin rescue) and are administered IV and by other routes (intra-arterial, intrathecal).

Adverse events noted with methotrexate use span the full range of doses and indications, making separation of adverse events, warnings, and warnings contained in the Boxed Warning difficult or impossible based on the indication. Nevertheless, it is clear that some of these warnings and other wording are directed at the oncology indications, creating difficulty in separating out the labeling that is specific for one indication from that for the others.

Major Issues

Because this is the first instance of PLR labeling and the current labeling is not up to date with regard to today's science, two major issues arose during efforts to convert the existing labeling to PLR format and to edit the applicant's proposed additions. The first was whether to include the oncology indications in the labeling, and the second was how to address the scientific inconsistencies and lack of up to date information in the originator labels during the PLR conversion process.

Oncology Indications

The first major issue that the Agency addressed was whether to include the oncology indications in the labeling of this product since the product is bioequivalent to the parenteral product delivered either by the IM or SC routes. Of note, these indications were not requested by the sponsor. The rationale for not including the oncology indications relate to the packaging [as an auto-injector with limited doses available] and route of administration [SC, which is not used for oncology indications] of the proposed product. However, inclusion of the oncology indications would avoid creation of a product and label with indications that differ from those for the currently available products. Furthermore, given that it is not possible to separate the safety information in the current label by indication, doing so would simplify the path to creation of a label for this product. Additionally, a label including all the indications would not differ substantively from that of the originators and of their generics, (b) (4) for Otrexup.

Lack of a neoplastic disease indication was extensively discussed with DOP2 as well as with senior management, and the decision was made to exclude the oncology indications from the Otrexup labeling. This is acceptable for a number of reasons, including that the proposed doses and route of administration do not adequately address the needs for treatment of neoplastic diseases (for neoplastic indications, in addition to oral administration, higher doses are often used intravenously and the parenteral product may also be administered intrathecally and intra-arterially). This raises potential safety concerns with granting oncology indications for a product to be delivered subcutaneously and available only in limited doses.

Updating the Science

The second major issue was that much of the labeling language is not scientifically up to date, including some statements that are no longer scientifically accurate. Because of the problems with the wording in the labels for the listed drugs, updating the labeling for this product was quite difficult, and a decision had to be made whether to correct and update the information to bring it up to date with today's medical practices. However, to do so would mean that this product would have a substantially different label, (b) (4) Further, the sponsor did not perform studies or provide data to support substantial changes to the listed drugs' labels.

Examples of difficulties with updating the labeling with today's science include

1. Liver biopsies: For psoriasis, the current Warnings/Precautions section contains wording stating that a liver biopsy should be obtained pre-therapy or within 2 to 4 months after initiation of therapy, as well as after a total cumulative dose of 1.5 grams and after each

additional 1.0 to 1.5 grams dosed. The recommendations are somewhat modified for RA patients: "Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis)." If the Warnings were updated based on current scientific information, pre-treatment and concurrent treatment biopsies for patients with psoriasis would be modified to more closely match the language for RA patients. (b) (4) Furthermore, leaving the current language might language might constitute a risk to some patients.

2. Reproductive risks: The labeling for MTX contains a Boxed Warning for fetal death and congenital abnormalities, and Warnings for embryotoxicity, abortion, impairment of fertility, oligospermia, and menstrual dysfunction. For RA and psoriasis patients, MTX is Pregnancy Category X. Therefore, MTX is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks, and the labeling contains a Contraindication in pregnant women with psoriasis and RA, with use in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Because of prolonged effects post-treatment, the Contraindication specifically states that: "Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients." However, current recommendations call for avoiding pregnancy for 6 months after stopping MTX, both for females and for males. If the language were updated based on current scientific information, the recommendations would be changed to six months after therapy for male patients, and for at least six ovulatory cycles after therapy for female patients. However, doing so would give this product a competitive disadvantage in the marketplace compared with the labeling for other MTX products. Furthermore, leaving the current language might constitute a risk to some patients.

Although the sponsor of this product submitted the proposed labeling in PLR format, they did not submit sufficient information to fully update the labeling language to current scientific standards.

Other Labeling Issues

Other labeling issues included how to handle the Dosage and Administration section. The applicant wished to express the recommended starting doses based on Otrexup rather than on other formulations of methotrexate. However, as mentioned earlier in this review, the recommended starting doses for RA and pJIA for the listed drugs do not match those proposed for this product, and the recommended route of administration does not include SC dosing for any indication except pJIA. The D&A section also needs to accommodate for the fact that patients may switch back and forth between other formulations (including oral, the most commonly used formulation and route) and switched Otrexup, and that patients may require doses higher, lower, or in between the available Otrexup doses.

Labeling Decisions

In early August, DPARP requested guidance from senior management with regard to the labeling concerns discussed above. DPARP had already met with DOP2, DDDP, and the SEALD team to discuss a path forward for the labeling, and together, we began work on a 'mock' PLR label for this product maintaining all of the language of the listed products, including warnings, precautions, and adverse events for all of the indications. This 'mock' or 'generic' PLR label served as basis for creation of a label for this product that does not differ substantively from those for the listed originator and generic products. We considered but rejected possible inclusion of the oncology indications while severely limiting the Dosage and Administration section, similar to what was done for Fluoxetine 60 mg tablets in 2011 (see accompanying labels). We also considered how we could transpose the labeling to PLR and how to update the out-of-date statements. Because of the complexity of the labeling issues, DPARP, DOP2, DDDP, and SEALD requested input from CDER senior management regarding these issues prior to proceeding further. A meeting was held with representative of all of the divisions, SEALD, and CDER senior management on August 8, 2013, and the following decisions were made:

1. Keep the PDUFA timelines.
2. Do not request the applicant to add the oncology indications (i.e., to leave the proposed indications alone). (b) (4)
3. There was hesitancy about requiring a 505(b)(2) product to take on the task of updating the science for the reference product. Therefore, the decision was made to not update the language to today's scientific standards and transpose the out-of-date label from the originators to PLR keeping the language the same wherever possible rather than converting and updating the labeling. This required deviating from following all of the PLR conversion rules and guidances that are currently part of PLR conversions. (b) (4)
4. (b) (4)

Following this guidance, DPARP worked closely with DOP2, DDDP, and the SEALD team to create a new PI for this product. Using a backbone PI submitted by the applicant in PLR format, the labeling from the listed originator parenteral product was transposed to the document to ensure word-for-word capture of the language from the originator, after which the team set out to move the material into the correct locations and add language as required for PLR labeling. Once this was done, we considered the applicant's requests for labeling language, and added back only that language that was considered specific to and appropriate for this application. We then set about to define the limitations of use for the product, and finally, the Highlights.

Summary

Otrexup is a new subcutaneous auto-injector formulation of methotrexate. Although the reference product labeling (that is in old format) includes indications for neoplastic diseases as

well as RA and Psoriasis, the 505(b)(2) applicant has only proposed labeling Otrexup for the RA and Psoriasis indications. DOP2 agrees with the applicant's proposal for omitting the neoplastic diseases because the subcutaneous auto-injector would not provide appropriate dosing for these indications.

In addition, the applicant did a very poor job of PLR converting the applicable information from the old formatted methotrexate labeling into the new format. The currently approved methotrexate labeling has a significant amount of old information that needs updating and an adequate conversion could take months. (b) (4) The decision was made to adequately PLR convert the reference methotrexate labeling (b) (4)

Labeling 505(b) (2) products can be quite challenging. (b) (4)

DPARP worked directly with SEALD in the development of the Otrexup labeling. The approach was to keep the listed methotrexate product labeling information intact (with some exceptions) and move the information to the appropriate PLR labeling section. We removed efficacy information pertinent to the neoplastic diseases and added specific information pertinent to Otrexup (e.g., Dosage and Administration). We also added limitations of use for the oncology indication and D&A restrictions based on the available doses and route of administration for this product. It was a major challenge to place old information in the new format.

Attached is the draft IR explaining the Agency's reasoning and the version in of the PI that is being sent to the applicant. A teleconference is set with the applicant on

Drs. Jenkins and Woodcock have been notified of the issues related to this labeling because it is anticipated that the applicant may object because the draft labeling differs so much from their proposed labeling.

NDA 204824 - Otrexup (methotrexate) injection

Information Request

Draft 9/12/2013

We are providing the following initial labeling comments for your product. Additional comments, including comments about the Instructions for Use (IFU), trainer Instructions for Use (TIFU), and Patient Package Insert (PPI) will be forthcoming as our reviews progress.

1. We have made significant changes to the proposed Prescribing Information (PI) for your product. We recognize that Otrexup will be the first instance of Physicians Labeling Rule (PLR) labeling for a methotrexate product, and that you have proposed new language to deal with these changes. However, your product relies on listed drug labeling and you have not conducted studies that would justify having a PI with significant differences compared to the listed drug labeling. Thus, we did not accept most of your newly proposed language, choosing to carry over the labeling of the listed drugs to PLR format and keep as much of the language the same as the reference, after which we considered your proposed language and added information specific to and appropriate for your product.

   Note that the PI contains comments that may help you understand our reasoning for the changes that were made. Additionally, the document contains an embedded, highlighted comment in Section 2.4 that you will need to address, after which the comment should be deleted. Other highlighted areas relate to areas that need updating by you, such as dates and phone numbers. Please address these sections as well.

   Several examples of these changes include:

   a) PLR labeling necessitates moving information from one section to another within which the information is appropriately presented. We have moved many sections, paragraphs, and sentences, keeping the language the same as that of the listed drugs as much as possible.

   b) In certain instances, we deleted information that pertains to an indication (i.e., treatment of malignancies), dose (high-dose regimens and leucovorin rescue regimens), or route of administration (i.e., intrathecal administration) for which your product is not appropriate.

   c) The Dosage and Administration section was adjusted to deal with the fact that other formulations may need to be used for alternative doses and routes of administration, that the starting doses of methotrexate for RA and pJIA in the listed products differ from those available with Otrexup, and that patients are likely to be transferred to Otrexup after starting with other formulations.

   d) When a Boxed Warning appears in a labeling, the Warnings and Precautions section must contain the same information. We therefore made substantial changes to this section to include this information.

   e) The Clinical Studies section now contains studies from other parts of the labeling of the listed drugs, and does not include any of the information you proposed from the literature.

2. While we understand that you do not plan to co-package the active and "trainer" devices, we note that the proposed devices look very similar. This is a potential safety issue, in that the active and the trainer devices may be easily be confused with one another. To minimize confusion between the two devices, we recommend that the color gray only be used for demonstration "trainer" devices that contain no active drug, and that the active drug product not contain any visible components with a gray color. Revise the active and trainer products as follows.

   a) Revise the labeling on the trainer device to distinguish the trainer device from the active product:

      i. Replace the word (b) (4) with the word "TRAINER", and add the words "Contains NO needle and NO medicine." This information should be prominently displayed, such that the font for the word "TRAINER" is larger than that of "Otrexup".

      ii. Change the (b) (4) background color to gray.

      iii. Provide an additional instruction showing how to reset the trainer device.

   b) Revise the color scheme for the active product, taking into account the following:

      i. Choose a different color for the plastic twist-off cap (currently gray in color and marked as 1). This may be done as a post-marketing commitment (PMC) if you are unable to make these changes quickly.

      ii. Choose a different color for the safety clip (currently gray in color and marked as 2). This may be done as a PMC if you are unable to make these changes quickly.

      iii. Consider changing the cover on the needle guard (currently white in color and unmarked) that would allow it to be more easily recognized as the end containing the needle. For example, you may wish to consider changing it to orange to match the body color of the arrow pointing to the needle end.

3. Follow labeling requirements outlined in 21 CFR 201.10(g)(2), 21 CFR 201.15(a)(5), and 21 CFR 201.15(a)(6) for all instances of appearance of the proprietary name and established name on the container, carton, Package Insert (PI), and Instructions for Use (IFU) of your drug product. In particular, we refer to the following:

   a) All instances of the established name should be at least half the font size of the proprietary name. The font should be easily readable and not in *italics*.

   b) Remove the (b) (4) from above the proprietary name in the carton and container labeling, as it distracts from the proprietary name.

   c) Increase the font size of "injection xx mg.0.4 mL" on all carton and container labels.

   d) Increase the font size of "for subcutaneous use only" on all carton and container labels.

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

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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/

PETER R STARKE
09/26/2013

JANET W MAYNARD
09/27/2013

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204-824
Priority or Standard	Standard
Submit Date(s)	December 14, 2012
Received Date(s)	December 14, 2012
PDUFA Goal Date	October 14, 2013
Division / Office	DPARP / OND
Reviewer Name(s)	Peter Starke, MD
Review Completion Date	August 19, 2013
Established Name	Methotrexate Auto-Injector
(Proposed) Trade Name	Otrexup™
Therapeutic Class	Folate analog metabolic inhibitor
Applicant	Antares Pharma
Formulation(s)	Solution for injection
Dosing Regimen	Subcutaneous injection
Proposed Indication(s)	Rheumatoid Arthritis (RA); Polyarticular Juvenile Idiopathic Arthritis (pJIA); [Moderate and Severe Psoriasis – see separate review]
Intended Population(s)	RA: adults pJIA: 2 years of age and older

MEDICAL OFFICER REVIEW

Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
December 14, 2012	December 14, 2012	SD-1	Original application
January 25, 2013	January 25, 2013	SD-3	Labeling
March 12, 2013	March 12, 2013	SD-4	Response to the deficiency/comments noted in the 74-day filing letter; revised labeling
April 8, 2013	April 8, 2013	SD-6*	Clinical information ("white paper") to support claim of moderate psoriasis*
April 10, 2013	April 10, 2013	SD-7	(b) (4)
May 7, 2013	May 7, 2013	SD-8	Response to IR of April 30, 2013
May 23, 2013	May 23, 2013	SD-10	Response to DMEPA IR of May 17, 2013
June 4, 2013	June 4, 2013	SD-11	Revised Form 356h
June 7, 2013	June 7, 2013	SD-13	Revised labeling (b) (4)

**Note*: Submission SD-6 was not reviewed in this document, and is listed for information purposes only. Please refer to the reviews performed by the Division of Dermatology and Dental Products for further details.

RECOMMENDED REGULATORY ACTION

NDA/Supplements: _X_ Approval

____ Complete Response

Other Action: ____

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of this application.

1.2 Risk Benefit Assessment

This is a 505(b)(2) new drug application submitted by Antares Pharma, Inc. for Methotrexate (MTX) Injection, a drug/device combination consisting of a single-use, prefilled auto-injector intended for subcutaneous (SC) administration. The application references three applications for methotrexate: NDA 11-719 for Methotrexate Injection EQ 50 mg base/2mL from Hospira, ANDA 40-632 for Methotrexate Preservative-Free Injection from Bedford, and NDA 08-085 for Methotrexate Tablets from Dava Pharmaceuticals. The proposed Trade Name for the product is Otrexup, and the PDUFA date is October 14, 2013.

MTX is a folate analog metabolic inhibitor currently indicated for the treatment of neoplastic diseases, severe psoriasis, rheumatoid arthritis (RA), and polyarticular-course juvenile rheumatoid arthritis (JRA), which is now called polyarticular juvenile idiopathic arthritis or pJIA. For the treatment of neoplastic diseases, methotrexate is currently labeled for administration by the oral, intramuscular (IM), intravenous (IV), intrathecal (IT), and intra-arterial (IA) routes, for psoriasis by the oral, IM, and IV routes, for RA by the oral and IM routes, and for pJIA by the oral, IM and SC routes.[1] The originator products were approved in the 1950s, and generics are also available for both oral tablets and parenteral formulations. This will be the first instance of an auto-injector formulation.

The proposed product will be supplied in doses of 10 to 25 mg in 5 mg increments. Because it is intended as a convenience formulation for self or caregiver use in the home setting, the applicant's proposed indications for this product are limited to RA, pJIA, and psoriasis, and do not include treatment of neoplastic diseases. However, the product is bioequivalent to parenteral methotrexate administered either IM or SC. Given the higher dosing used for most of the oncology indications and the fact that this product can only be administered by the subcutaneous route, it seems appropriate to limit the indications to RA, pJIA, and psoriasis as proposed by the sponsor rather than broadening the label to neoplastic diseases.

The proposed doses (from 10 mg to 25 mg in 5 mg increments) will cover most of the currently recommended doses for treatment of psoriasis and RA, but will not adequately

1 *Note*: The current labeling for the parenteral product does include SC administration for JRA. Therefore, this product does not represent a new route of administration for this condition, although it does represent a new route of administration for adults with RA and patients with psoriasis.

cover dosing for the entire pJIA population in children, which is typically dosed by mg/m^2 in doses starting at about 5 mg. Although the oncology indications are not being sought by the applicant, the proposed doses also do not adequately cover dosing for these conditions, which extend far higher by the IV route and may require leukovorin rescue. Issues with dosing raised by the limitations imposed by the product will necessitate limitations for use in the Dosing and Administration section of this product. This product will also be the first instance of Physicians Labeling Rule (PLR) labeling for a methotrexate product, necessitating differences between the labeling for this product from those of currently marketed originator and generic methotrexate products despite the fact that there is no particular advantage for use of this product over other products other than convenience. These differences will be minimized whenever possible.

The applicant has also proposed to extend the current indication for psoriasis from symptomatic control of “severe, recalcitrant, disabling psoriasis” to “moderate psoriasis”, which requires a risk/benefit assessment for the newly proposed dermatological indication beyond an assessment of risk/benefit for the use of methotrexate by the subcutaneous route in the home setting. Therefore, the application was administratively split to provide for review in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) and the Division of Dermatology and Dental Products (DDDP). This review focuses on the RA and pJIA indications in DPARP. For discussions of the psoriasis indication, please see separate reviews by the Division of Dermatology and Dental Products.

No clinical trials were performed to support this application. Support for approval of this application is based on:

1. The Agency’s previous findings of the safety and effectiveness of methotrexate in patients with RA, JRA (pJIA), and psoriasis, including Agency’s previous findings of the safety and effectiveness of SC administration in patients with JRA.
2. A BA study (and MTX-11-003) in adults that supports efficacy with SC administration in patients with RA and psoriasis because it showed equal or greater bioavailability of the proposed MTX auto-injector product administered SC when compared to systemic exposure with orally administered MTX tablets.
3. Literature reviews that support the safety and efficacy of SC administration of methotrexate for these conditions and for the age groups for which they are currently approved. The literature supports SC administration as an alternative to oral or IM administration of MTX, with higher systemic exposure and improvements in efficacy when administered SC or IM vs orally at similar doses, particularly when the doses are above 15 mg. The safety review of the literature and of the studies provided to this application did not reveal any new safety signals that would require additional labeling beyond those already labeled in the reference products.
4. A BE study (MTX-10-001) in adults that showed bioequivalence between this auto-injector product administered SC in either the abdomen or the thigh and the approved injectable product administered with a needle and syringe either by the SC or IM route.

The applicant also performed an actual use labeling study (MTX-11-002) and a labeling and human factors study (MTX-11-004) to support the labeling and use of the proposed product, demonstrating that patients and caregivers could be taught to successfully administer the product.

The studies submitted by the applicant to support this application are briefly summarized below.

- Study MTX-10-001 was a single dose bioequivalence study that compared systemic methotrexate exposure following SC administration with the proposed auto-injector device, with administration using a needle and syringe by either the IM route in the outer thigh or the SC route in the abdominal wall. Systemic exposure following administration by all three routes of administration was bioequivalent based on 90% confidence intervals (CI).
- Study MTX-11-003 was a single dose bioavailability study that compared systemic methotrexate exposure following SC administration of MTX using the proposed auto-injector device in the thigh and the abdominal wall, and with a similar dose following oral administration. The results demonstrated bioequivalence between the two SC injection sites using the auto-injector device. Bioavailability following SC administration with the auto-injector was higher than following oral administration, particularly at higher dose levels at and above 15 mg.
- Study MTX-11-002 was a multicenter, open-label, single-dose actual human use study that evaluated the ability of RA patients to self-administer the proposed MTX auto-injector after training. After training, all patients were able to perform a successful SC self-injection of study drug and completed all essential tasks successfully.
- Study MTX-11-004 was stated to have been a simulated-use, summative, usability testing, Human Factors study. As a simulated use study, it not involve administration of active drug or use of the device with a needle, and as such did not use a placebo device. The study is stated to have been designed to evaluate whether the device could be used by representative users (patients, caregivers, and healthcare providers [i.e., nurses]) under simulated use conditions “without generating patterns of failures that could result in negative clinical impact to patients or injury to device users”. Specifically, the study purported to test whether the instructions for use are adequate such that patients can use the device in an un-coached setting at home. However, this was not the case. All patients and caregivers received specific training in the use of the device, and the only participants who did not receive this training were the nurse participants. As a result, the study actually evaluated the entire training set and not specifically labeling comprehension of the instructions for use. That stated, with some reservations, the study appeared to show that the entire training set provides adequate instructions to allow appropriate use of the device.

The Pediatric Research Equity Act (PREA, 21 U.S.C. 355c) is triggered by this application for the RA [and psoriasis] indication[s], for which this product would represent a new route of administration. With respect to the RA indication, pJIA is

considered the pediatric form of RA, and the injectable product is already approved and labeled for use in children with pJIA. Therefore, the PREA requirements for RA are satisfied by the Agency's previous findings of safety and effectiveness for JRA (pJIA). Please refer to Section 2.6.2, Pediatric Issues, for further details.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

This is a 505(b)(2) new drug application submitted by Antares Pharma, Inc. for Methotrexate (MTX) Injection, a drug/device combination consisting of a single-use, prefilled auto-injector containing sterile, preservative-free MTX and intended only for subcutaneous (SC) administration. These characteristics make the product sufficiently different from the reference parenteral vial product(s) that the 505(b)(2) route is appropriate.

Methotrexate Tablets have been marketed since December of 1953 (NDA 08-085, Dava Pharmaceuticals Inc.) when the product was approved for the treatment of acute leukemia in adults. In addition to tablets, MTX is approved as an injection (NDA 11-719; approved 1959; Hospira) for intramuscular (IM), intravenous (IV), subcutaneous (SC), intra-arterial (IA), and intrathecal (IT) administration. Form 356h that accompanied the application referenced the generic Methotrexate Injection EQ 50 mg base/2mL (NDA 11-719; Hospira), which is listed in the Orange Book as a reference listed drug (RLD) and was the originator for the generic methotrexate injectable products (Table 3). However, due to the shortage of the Hospira Methotrexate Preservative Free drug product, the clinical studies for this application used Methotrexate Sodium Preservative Free from Bedford (ANDA 40-632, approved on August 12, 2005), which is also listed in the Orange Book as an RLD. Therefore, the application also needed to reference this product. Further, one of the clinical studies also used Methotrexate Tablets manufactured by Dava Pharmaceuticals as a comparator. Therefore, the Division informed Antares that the application should also reference NDA 08-085 for Methotrexate Tablets (Table 4). Antares sent in a revised Form 356h referencing all three products on June 6, 2013.

MTX is a folate analog metabolic inhibitor. It is currently approved for the following indications when administered by the routes as shown below:

Indication	Route
Neoplastic diseases	oral, IM, IV, IA, IT
Adults with severe recalcitrant disabling psoriasis that is not adequately responsive to other forms of therapy	oral, IM, IV
Adults with rheumatoid arthritis (RA) who have insufficient therapeutic response to, or are intolerant of, an adequate trial of first line therapy*	oral
Polyarticular-course juvenile rheumatoid arthritis (JRA) who have insufficient therapeutic response to, or are intolerant of, an adequate trial of first line therapy*	oral, IM, SC

* First line therapy for RA and JRA, as defined in the Indications and Usage section of the labels, includes full dose Non-steroidal anti-inflammatory agents (NSAIDS).

Polyarticular-course juvenile rheumatoid arthritis (JRA) is now called polyarticular juvenile idiopathic arthritis or pJIA, JIA being the more up-to-date classification terminology used to describe what used to be called JRA. Therefore, the newer terminology of pJIA is used in this application instead of the older terminology of JRA, except when specifically referring to the existing labeling or indications for marketed and approved products.

The prescribing information (PI) for MTX includes a Boxed Warning regarding the serious risks and limitations of use. The Pediatric Use sections for both the oral tablets and the injectable products state that "the safety and effectiveness [of methotrexate] in pediatric patients have been established only in cancer chemotherapy and in polyarticular course juvenile rheumatoid arthritis", i.e., RA and psoriasis do not currently carry pediatric indications.

The proposed product will be supplied in doses of 10 to 25 mg in 5 mg increments. Because it is intended as a convenience formulation for self or caregiver use in the home setting, the applicant's proposed indications for this product are limited to RA, pJIA, and psoriasis, and do not include treatment of neoplastic diseases. However, the product is bioequivalent to parenteral MTX administered either IM or SC. Given the higher dosing used for most of the oncology indications and the fact that this product can only be administered by the subcutaneous route, it seems appropriate to limit the indications to RA, pJIA, and psoriasis as proposed by the sponsor rather than broadening the label to neoplastic diseases.

The proposed doses (from 10 mg to 25 mg in 5 mg increments) will cover most of the currently recommended doses for treatment of psoriasis and RA, but will not adequately cover dosing for the entire pJIA population in children, which is typically dosed by mg/m^2 in doses starting at about 5 mg. Although the oncology indications are not being sought by the applicant, the proposed doses also do not adequately cover dosing for these conditions, which extend far higher by the IV route and may require leukovorin rescue. Issues with dosing raised by the limitations imposed by the product will necessitate limitations for use in the Dosing and Administration section of the PI for this product.

This product will also be the first instance of labeling in Physicians Labeling Rule (PLR) format for a MTX product, thereby resulting in some differences between the labeling for this product from those of currently marketed originator and generic methotrexate products despite the fact that there is no particular advantage for use of this product over other products other than convenience. Despite the formatting differences inherent in PLR, the Division will try to minimize these differences as much as possible. When and if the originators are updated to PLR labeling, most of those differences should disappear, although several may remain because of the fact that this is a drug/device combination.

The applicant has proposed to extend the current indication for psoriasis from symptomatic control of severe, recalcitrant, disabling psoriasis to moderate psoriasis, which requires a risk/benefit assessment for the newly proposed dermatological indication beyond an assessment of risk/benefit for the use of MTX by the

subcutaneous route in the home setting. Therefore, the application was administratively split to provide for review in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) and the Division of Dermatology and Dental Products (DDDP). This review focuses on the RA and JIA indications in DPARP. For discussions of the psoriasis indication, please see separate reviews by the Division of Dermatology and Dental Products.

2.1 Product Information

The proposed product is drug-device combination consisting of a single-use, single-dose, pre-filled, auto-injector fitted with a 27-gauge, ½ inch needle [full length] that delivers a fixed volume of 0.4 mL per injection as a sterile, preservative-free solution (Figure 1). Antares proposes that the device will contain the following MTX doses: 10, 15, 20, or 25 mg of MTX (concentrations of (b) (4), respectively). The needle is protected before use by a needle safety guard and a 'soft needle shield' that are built into the removable safety cap (shown in the figure below with a "1"). The product also includes a removable safety at the end opposite to the needle that prevents triggering of the device (marked as "2" in the figure), and a clear viewing window to allow direct visualization of the methotrexate in the syringe. Sharps protection is provided by the collar (shown in Figure 1 as 'needle end') that, when pressed against the skin to trigger the injection depresses to provide an exposed needle length of [at least] 2.5 mm, and when pressure is withdrawn re-extends beyond the needle and locks in place to prevent future needle sticks.

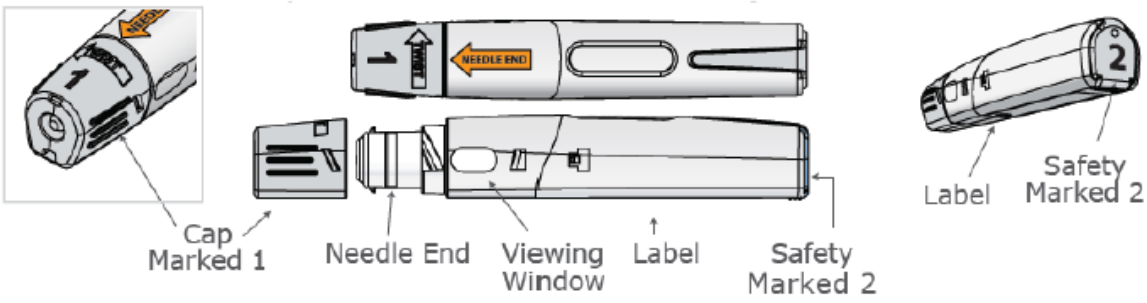

Figure 1. Representative schematic of the proposed device

Source: F1, p5; Module 3.2.P.1; description-and-composition.pdf

2.2 Tables of Currently Available Treatments for Proposed Indications

Methotrexate is a folic acid analogue that inhibits production of DNA, RNA, and proteins. Because it is structurally similarity to folate, MTX binds and inhibits the enzyme dihydrofolate reductase (DHFR), thereby preventing the formation of tetrahydrofolate, which is essential for purine and pyrimidine synthesis. Other approved folate analog metabolic inhibitors include trimethoprim, pyrimethamine, and pemetrexed.

The labeling for MTX for the treatment of adult rheumatoid arthritis (RA) and polyarticular juvenile rheumatoid arthritis (i.e., pJIA) reflects the treatment paradigms that were in place when the products were approved in the 1950s and over the following 20-30 years, whereas the treatments available these conditions have changed dramatically in the last ~20 years and additional information regarding the use of MTX for these conditions has also become available. As a result, the current labeling for the approved products is somewhat dated. Further, the current labeling is confusing with respect to the approved routes of administration for each indication. Although the originator labeling will not change with this application, the labeling for this product will reflect how MTX falls within the current treatment paradigms and modalities for these conditions.

The classes of therapies for RA and pJIA include non-steroidal anti-inflammatory drugs (NSAIDs), systemic and intra-articular glucocorticoids, conventional disease-modifying anti-rheumatic drugs (DMARDs); and biologic DMARDs. DMARDS slow or prevent structural progression of the disease. In the last several decades, MTX has emerged as the most widely accepted traditional DMARD because of its potency and well understood long-term effects. NSAIDs, which formerly were considered a core therapy, are now considered adjunctive therapy. Additionally, a number of highly effective biologicals have been approved that can be used alone or in combination with MTX, allowing individual tailoring of treatment to fluctuations in disease activity and drug-related toxicities.

Biologic DMARDs have revolutionized the treatment of RA over the past two decades. There are currently 10 small molecules (Table 1) and 9 biologic products (Table 2) approved for the treatment of RA.

Polyarticular juvenile idiopathic arthritis (pJIA) is a category of juvenile idiopathic arthritis (JIA), formerly called Juvenile Rheumatoid Arthritis (JRA). pJIA is similar to adult RA with articular manifestations being predominant. The prevalence of JIA has been estimated to be between 57 and 220 per 100,000 children younger than 16 years of age, with pJIA affecting approximately 2 to 17% of children with JIA. There are multiple biologic products currently FDA approved for the treatment of pJIA, two TNFα-inhibitors: adalimumab (Humira) and etanercept (Enbrel); one targeting the IL-6 signaling pathway: tocilizumab (Actemra); and one targeting T-cell co-stimulatory signaling pathway: abatacept (Orencia). The other TNF-inhibitor, infliximab (Remicade), was not shown to be effective in the treatment of pJIA, possibly because of the higher rate of immunogenicity and clearance than observed in adults.

Table 1. Approved small molecule products for the treatment of RA in the United States1

	Product	NDA	Sponsor	Year of Approval[2]
1	Sulfasalazine (AZULFIDINE)	7-073	Pfizer	1950
2	Methotrexate sodium (METHOTREXATE SODIUM)	8-085 (PO) 11-719 (IV)	Multiple	1953 1959

3	Hydroxychloroquine (PLAQUENIL)	9-768	Sanofi-Aventis	1955
4	Prednisone	Many ANDAs	Multiple	1955
5	Azathioprine (IMURAN)	16-324	Prometheus Labs	1968
6	Penicillamine (CUPRIMINE)	19-853	Aton	1970
7	Auranofin (RIDAURA)	18-689	Prometheus Labs	1985
8	Cyclosporine (NEORAL) Cyclosporine (SANDIMMUNE)	50-715 50-625	Novartis	1995 1990
9	Leflunomide (ARAVA)	20-905	Sanofi-Aventis	1998
10	Tofacitinib (XELJANZ)	203-214	Pfizer	2012

1 Other formulations (e.g., solutions) are not included in this table. Steroids and NSAIDs are approved for reduction of the signs and symptoms of RA; however, they are not included in this table.

2 The initial approval of these small molecules may have not been for RA.

Table 2. Approved biologic products for the treatment of RA in the United States

	Product	BLA (sponsor)	Year Approved for RA[1]	Characteristics	ROA
1	Infliximab (REMICADE®)	103772 (COBI)	1999	Monoclonal antibody (TNF inhibitor)	IV
2	Etanercept (ENBREL®)	103795 (Immunex)	1998	Fusion protein (TNF inhibitor)	SC
3	Anakinra (KINERET®)	103950 (Amgen)	2001	Human IL-1 receptor antagonist (IL-1 inhibitor)	SC
4	Adalimumab (HUMIRA®)	125057 (Abbott)	2002	Monoclonal antibody (TNF inhibitor)	SC
5	Abatacept (ORENCIA®)	125118 (BMS)	2005	Fusion protein (costimulation modulator – inhibits T-cell activation)	IV
6	Rituximab (RITUXAN®)	103705 (Genentech & Biogen Idec)	2006	Monoclonal antibody [anti-CD20 (B-cell depleter)]	IV
7	Golimumab (SIMPONI®)	BLA 125289 (COBI)	2009	Monoclonal antibody (TNF inhibitor)	SC
8	Certolizumab Pegol (CIMZIA®)	BLA 125160 (UCB)	2009	Fab fragment conjugated to PEG (TNF inhibitor)	SC
9	Tocilizumab (ACTEMRA®)	125276 (Roche)	2010	Monoclonal antibody (Il-6 receptor inhibitor)	IV

1 Infliximab was originally approved in 1998 for Crohn's Disease and rituximab was originally approved for non-Hodgkin's Lymphoma in 1997. Certolizumab Pegol was originally approved for Crohn's disease in 2008.

2.3 Availability of Proposed Active Ingredient in the United States

Methotrexate is available as oral tablets in multiple strengths and as an injectable solution (both preservative-free and with a preservative) in several strengths. Proprietary and generic forms are available. Many of the products are labeled as the sodium salt, which is an incorrect statement. There are no products in an auto-injector presentation, as is the proposed drug product. The Orange Book listings for injectable (Table 3) and oral (Table 4) MTX products are shown below. Two NDA products, NDA 08-085 for MTX tablets from Dava Pharmaceuticals, and NDA 11-719 for injectable MTX from Hospira, and one ANDA, ANDA 40-621 for preservative-free injectable MTX from Bedford, are listed as RLDs and are referenced in this application. Referenced products are shown in **Bold** font.

Table 3. Orange Book listing of Methotrexate injectable products as of 1/10/2013

Appl No	TE Code	RLD	Dosage Form	Route Strength	Proprietary Name	Applicant
A089341	AP	Yes	INJECTABLE; INJECTION	EQ 100MG BASE/4ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM	BEDFORD
A040632		**Yes**	**INJECTABLE; INJECTION**	**EQ 1GM BASE/VIAL**	**METHOTREXATE SODIUM PRESERVATIVE FREE**	**BEDFORD**
A089342		Yes	INJECTABLE; INJECTION	EQ 200MG BASE/8ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM	BEDFORD
A089343	AP	Yes	INJECTABLE; INJECTION	EQ 250MG BASE/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	BEDFORD
A089340	AP	Yes	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	BEDFORD
A090029	AP	No	INJECTABLE; INJECTION	EQ 1GM BASE/40ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	EBEWE PHARMA
A090039	AP	No	INJECTABLE; INJECTION	EQ 250MG BASE/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	EBEWE PHARMA
A090039	AP	No	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	EBEWE PHARMA
A040266	AP	No	INJECTABLE; INJECTION	EQ 1GM BASE/VIAL	METHOTREXATE PRESERVATIVE FREE	FRESENIUS KABI USA
A040263	AP	Yes	INJECTABLE; INJECTION	EQ 250MG BASE/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM	FRESENIUS KABI USA
A040263	AP	Yes	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM	FRESENIUS KABI USA
N011719	**AP**	**Yes**	**INJECTABLE; INJECTION**	**EQ 1GM BASE/40ML (EQ 25MG BASE/ML)**	**METHOTREXATE SODIUM PRESERVATIVE FREE**	**HOSPIRA**
N011719	AP	Yes	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ	METHOTREXATE SODIUM	HOSPIRA

Appl No	TE Code	RLD	Dosage Form	Route Strength	Proprietary Name	Applicant
				25MG BASE/ML)		
A040716	AP	Yes	INJECTABLE; INJECTION	EQ 1GM BASE/40ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	MYLAN INSTITUTIONAL
A040768	AP	Yes	INJECTABLE; INJECTION	EQ 250MG BASE/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	MYLAN INSTITUTIONAL
A040767	AP	Yes	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	MYLAN INSTITUTIONAL
A201529	AP	No	INJECTABLE; INJECTION	EQ 100MG BASE/4ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A201530	AP	No	INJECTABLE; INJECTION	EQ 1GM BASE/40ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A201529	AP	No	INJECTABLE; INJECTION	EQ 200MG BASE/8ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A201529	AP	No	INJECTABLE; INJECTION	EQ 250MG BASE/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A201529	AP	No	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A200171	AP	No	INJECTABLE; INJECTION	EQ 100MG BASE/4ML (EQ 25MG BASE/ML)	METHOTREXATE PRESERVATIVE FREE	PHARMACHEMIE BV
A040843	AP	No	INJECTABLE; INJECTION	EQ 1GM BASE/40ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	PHARMACHEMIE BV
A040853	AP	No	INJECTABLE; INJECTION	EQ 250MG/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	PHARMACHEMIE BV
A040850	AP	No	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	PHARMACHEMIE BV

Table 4. Orange Book listing of Methotrexate oral products as of 1/10/2013

Appl No	TE Code	RLD	Dosage Form	Route Strength	Proprietary Name	Applicant
A040385		No	TABLET; ORAL	EQ 10MG BASE	TREXALL	BARR
A040385		Yes	TABLET; ORAL	EQ 15MG BASE	TREXALL	BARR
A081099	AB	No	TABLET; ORAL	EQ 2.5MG BASE	METHOTREXATE SODIUM	BARR
A040385		No	TABLET; ORAL	EQ 5MG BASE	TREXALL	BARR
A040385		No	TABLET; ORAL	EQ 7.5MG BASE	TREXALL	BARR
N008085	**AB**	**Yes**	**TABLET; ORAL**	**EQ 2.5MG BASE**	**METHOTREXATE SODIUM**	**DAVA PHARMS INC**

Appl No	TE Code	RLD	Dosage Form	Route Strength	Proprietary Name	Applicant
A081235	AB	No	TABLET; ORAL	EQ 2.5MG BASE	METHOTREXATE SODIUM	MYLAN
A040054	AB	No	TABLET; ORAL	EQ 2.5MG BASE	METHOTREXATE SODIUM	ROXANE

2.4 Important Safety Issues With Consideration to Related Drugs

NA

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Agency had multiple pre-submission interactions with Antares between 2009 and 2012, including several meetings with CDER and CDRH to discuss the requirements for an NDA submission (pre-IND: 2/5/2009, End-of-Phase 2: 9/13/2011, pre-NDA: 11/2/2012), one set of post-meeting Written Responses (2/10/2012), one response to an email request regarding CMC issues (5/14/2012), and one meeting with CDRH to discuss a possible IDE submission for the proposed auto-injector product (4/25/2012).

The intended route of administration for this product is via subcutaneous (SC) injection. While the Dosage and Administration section of the reference MTX product allows for IM or SC dosing as an alternative to oral dosing for polyarticular course JRA, the labeling for adult RA includes only oral administration and is otherwise ambiguous as to the appropriate route of administration. For psoriasis, the oral, IM and IV routes are represented in the labeling, but the SC route is not. Therefore, the Division stated that Antares' proposal for dosing via the SC route would be considered a new route of administration that would need to be supported by clinical information including relative bioavailability data and clinical data supporting safety and efficacy of subcutaneous administration. Antares was asked to bridge between the SC, IM, and oral routes of administration as well as provide clinical data, which could be satisfied by submission of published literature rather than conducting new efficacy and safety trials. The applicant was told that the new route of administration would likely trigger PREA, and that the entire age range of 0-16 years would need to be addressed. [pIND meeting 2/5/2009]

With submission of the NDA, Antares has requested extending the indication for psoriasis from symptomatic control of severe, recalcitrant, disabling psoriasis to moderate psoriasis, which will require a risk/benefit assessment for the proposed dermatological indication. (b) (4)

At the pre-NDA meeting in November 2012, Antares specifically asked whether the proposed clinical development plan would support an indication (b) (4) in addition to severe psoriasis, and the Division responded that to obtain an indication of (b) (4), Antares would need to provide substantial evidence of effectiveness of MTX in patients with this condition because it is unlikely that the literature would provide sufficient clinical support for this indication. Because Antares proposed a new

indication that might require clinical support, a 74-day comment was generated to indicate that the applicant will need to remove this indication from the proposed labeling, and to submit revised labeling that matches the approved indication for the reference MTX injection products. In response, Antares submitted a white paper and additional literature, which they claim support the extended indication. Following this submission, the NDA was administratively split to accommodate substantive reviews in two review divisions. This review focuses on the RA and pJIA indications conducted in DPARP. For the psoriasis indications, please refer to separate reviews conducted by the Division of Dermatology and Dental Products (DDDP).

2.6 Other Relevant Background Information

2.6.1 Trade Name

Antares has requested a proposed Trade Name of Otrexup™ for the product, which was reviewed by the Office of Surveillance and Epidemiology (OSE) and found to be acceptable.

It is important to note that Antares has previously called the proposed auto-injector device by the names 'Vibex™' and 'Medi-Jet™'. However, the company has not requested consideration of either of these names as part of the Trade Name for the product. Because Antares referred to these names in the studies and throughout the application, the names appear in this review when referring to the MTX auto-injector product used in the submitted studies. Whether these two product names imply any differences in the auto-injectors used in the studies is not stated, but this does not appear to be the case.

2.6.2 Pediatric Issues

Methotrexate is currently approved for the indication of treatment of rheumatoid arthritis when administered by **oral** route; for the indication of JRA (pJIA), when administered by **oral**, **IM** or **SC** routes, and for the indication of severe recalcitrant disabling psoriasis when administered by **oral**, **IM** or **IV** routes. The application therefore triggers the Pediatric Research Equity Act (PREA, 21 U.S.C. 355c) for the indications of RA and severe psoriasis, for which this is a new route of administration. Additionally, the applicant has proposed a new indication of moderate psoriasis, which also triggers PREA as a new indication. The addition of an auto-injector to an injectable MTX, making this a drug/device combination, does not trigger PREA as this change is not considered to be a new dosage form.

The RA indication triggers PREA because the RA indication is not labeled for SC dosing. However, RA is an adult disease, and pJIA is its pediatric counterpart. Pediatric assessments for RA are therefore performed in children with pJIA down to 2 years of age, the lowest age that pJIA can be diagnosed. For these indications, the applicant has asked for a waiver for children ≤6 years because dosing [for pJIA] is

based on body surface area (BSA) and the proposed product cannot be varied in small dosing increments that would be required for dosing in pediatric patients according to BSA or weight. This is based on the fact that the lowest proposed dose for this product of 10 mg is only appropriate for children starting at about 7-8 years of age and around 28 kg (62 pounds). However, DPARP disagrees with this waiver request. As a 505(b)(2) application, the applicant has relied on the Agency's previous findings of safety and effectiveness by the SC route in children with pJIA for the injectable formulation in pJIA. Once the links have been provided for this drug to the reference products, and since the reference parenteral products are already labeled for SC administration in patients with JRA (pJIA), PREA is satisfied and the pediatric assessment is considered complete for children 2 years of age and older. The Dosage and Administration Section of the label will reflect the limitations for dosing below 10 mg and for increments that cannot be accommodated with the product's available dosing. A waiver is appropriate for patients under 2 years of age because the disease does not exist.

With regard to the psoriasis indications, the applicant has asked for a waiver in children 0 to 17 years because the product does not present a meaningful therapeutic benefit over the available already marketed generic products. DDDP agrees with granting of a waiver but disagrees with the applicant's reasoning or justification. The current labeling states that the safety and efficacy of MTX for psoriasis have not been established in children. Further, MTX has the potential for serious toxic reactions (which can be fatal), and the labeling carries a BOXED WARNING for multiple safety concerns. Additionally, periodic liver biopsy is recommended during the treatment of patients with psoriasis. As a result, DDDP believes that the safety concerns posed by the drug outweigh the potential benefits of treatment in pediatric psoriasis. Therefore, DDDP plans to grant a full waver of studies in the pediatric population with psoriasis for safety reasons, and will label the product accordingly.

Both Divisions discussed their recommendations with the Pediatric Review Committee (PeRC) on June 4, and PeRC concurred with the recommendations stated above.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No ethical or data integrity issues were noted during the review of this application.

3.2 Compliance with Good Clinical Practices

The applicant has stated that the studies submitted to this NDA were conducted in accordance with the Declaration of Helsinki and with all applicable laws and regulation, and were in compliance with Good Clinical Practice Guidelines. The protocols and informed consent documents were reviewed by Institutional Review Boards for each center prior to initiation of the study.

3.3 Financial Disclosures

Financial disclosure forms were submitted and reviewed for the two biopharmaceutical studies. No issues were noted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

There were no significant review issues noted in this application noted by either the ONDQA (CMC) reviewer, Dr Shaw, or by the CDRH reviewer. The company has provided stability data and requested 24 months expiry dating. The CMC reviewer agrees.

Functionality testing specifications for the device are as follows:

A) Viewing Window as received: Not obstructed

B). Needle Shield: Strips with safety cap removal

C) Device triggers: Ram released

D) Exposed needle length: ≥2.5 mm

E) Lock Out Function: Collar lock out

F) Viewing window, post-triggering: Obstructed

The specifications also call for a delivery time of (b) (4), which is adequate.

In terms of needle exposure, 2.5 mm is short enough to avoid IM injection, and this is acceptable. Since the product is bioequivalent between IM and SC dosing, no clinical issues are raised if an IM injection were to occur.

4.2 Clinical Microbiology

No microbiological issues were noted in the application. The drug substance is sterile (b) (4) filling of the syringe. Both processes are performed at (b) (4) and sterility assurance monitoring processes are in place to assure and maintain sterility.

4.3 Preclinical Pharmacology/Toxicology

The only pharmacology/toxicology information submitted with this application was a toxicology report for qualification of leachables and extractables in the product, including data for seven organic compounds and three metals. The data were reviewed by

pharmacology/toxicology team, who came to the conclusion that there are no nonclinical concerns related to the safety qualification of the impurities, leachables, and extractables in the proposed product.

4.4 Clinical Pharmacology

The clinical pharmacology of this product was assessed in 2 open-label, randomized, 3-way crossover phase 2 studies (Study MTX-10-001 and Study MTX-11-003). The studies are discussed within Section 5.3.1 of this review, and brief summaries are presented below.

Study MTX-10-001 was a single dose bioequivalence study that compared systemic methotrexate exposure following SC administration with the proposed auto-injector device, with administration using a needle and syringe by either the IM route in the outer thigh or the SC route in the abdominal wall. Systemic exposure following administration by all three routes of administration was bioequivalent based on 90% confidence intervals (CI).

Study MTX-11-003 was a single dose bioavailability study that compared systemic methotrexate exposure following SC administration of MTX using the proposed auto-injector device in the thigh and the abdominal wall, and with a similar dose following oral administration. The results demonstrated bioequivalence between the two SC injection sites using the auto-injector device. Bioavailability following SC administration with the auto-injector was higher than following oral administration, particularly at higher dose levels at and above 15 mg.

4.4.1 Mechanism of Action

NA. No new information was submitted with this application.

4.4.2 Pharmacodynamics

NA. No new information was submitted with this application.

4.4.3 Pharmacokinetics

See Section 5.3.1 of this review for details of the BA/BE studies performed for this application.

5 Sources of Clinical Data

No clinical trials were performed for this application. The application includes a literature review summarizing the safety and effectiveness of SC administration, and a development program that included two clinical pharmacology studies and two use and

handling studies. The Division does not consider any of these studies to be clinical trials for the purposes of exclusivity determination. The program was discussed over multiple interactions with the Agency. Clinical pharmacology was assessed in two open-label, randomized, 3-way crossover studies (MTX-10-001 and MTX-11-003) designed to compare systemic exposure when dosed subcutaneously (SC) via the proposed MTX auto-injector with SC and IM dosing via a needle and syringe (MTX-10-001) and to compare SC administration with the proposed MTX auto-injector dosed in the abdomen and thigh with oral administration (MTX-11-003). Safety and usability was assessed in one open-label, single-dose study (MTX-11-002) in RA patients, and usability and handling of the device was assessed in one simulated use study using a dummy device (MTX-11-004).

5.1 Tables of Studies/Clinical Trials

Table 5. Studies Submitted to the Application

Study	Type	Design	Product	Doses (mg)	N
Clinical Pharmacology studies					
MTX-10-001	BE	R, OL, MC, 3-way crossover in subjects ≥18y with RA on treatment with MTX	Vibex MTX SC MTX SC abd wall MTX IM outer thigh	10, 15, 20, or 25 10, 15, 20, or 25 10, 15, 20, or 25	R 38 C 36
MTX-11-003	BA	R, OL, 3-way crossover in subjects ≥18y with RA on treatment with MTX	Oral MTX Vibex MTX SC abd Vibex MTX SC thigh	3 weekly doses	R 49 C 47
Use and handling studies					
MTX-11-002	AHU	OL, MC, SD single-arm in subjects ≥18y with RA	Vibex MTX SC abd wall	10, 15, 20, or 25	R 101 C 101
MTX-11-004	User study	Two one-on-one sessions (1 wk apart) to evaluate training on use of the device based on the IFU, device label, and HCP training script	Vibex MTX placebo	1st Session: training 2nd Session: Evaluation of simulated device use	50 RA 15 Lay caregivers 17 HCP

AHU = (Actual human use) device handling and use study; R = randomized; C = completed; IFU = information for use; HCP = health care professional

Note: 'Medi-Jet™' and 'Vibex™' are names that Antares has previously used to refer to their proposed auto-injector device and/or drug/device combination product. However, Antares has not proposed to use either as part of the Trade Name. Because Antares referred to these names in the studies and throughout the application, they also appear in this review when used by the company to refer specifically to their proposed methotrexate auto-injector.

Source: synopses-indiv-studies.pdf

5.2 Review Strategy

The studies submitted to the application were reviewed along with the literature supports submitted to the application.

5.3 Discussion of Individual Studies/Clinical Trials

The applicant submitted published literature to support efficacy and safety of SC dosing for JRA and psoriasis, but did not perform any clinical trials for this application. Two clinical pharmacology studies were performed, along with two use and handling studies.

5.3.1 Clinical Pharmacology Studies

Clinical pharmacology was assessed in 2 open-label, randomized, 3-way crossover phase 2 studies (Study MTX-10-001 and Study MTX-11-003).

5.3.1.1 Study MTX-10-001

Initiation Date:	January 17, 2011
Completion Date:	May 31, 2011
Investigation Sites:	(b) (4)
Bioanalytical Laboratory:	(b) (4)

Study MTX-10-001 was an open-label, single-dose, 3-way crossover PK study that compared systemic MTX exposure following SC administration with the proposed MTX auto-injector ["Vibex"] device, with administration of preservative-free MTX using a needle and syringe by either the IM or the SC route in 36 subjects ≥18 years with RA who were on methotrexate treatment for at least 3 months prior to the study. The study was performed at two clinical sites in the United States. The comparator product used in this study was Methotrexate Sodium Preservative Free from Bedford (ANDA 89-340, approved on September 16, 1986), which is listed in the Orange Book as an RLD.

Inclusion criteria included: stable on concomitant medications for 3 months; no medical conditions or medications that would interfere with study outcomes; chest x-ray within 6 months; use of a highly effective form of contraception for females of child-bearing potential; and capable of understanding and following the protocol instructions and

requirements. Exclusion criteria included: pregnant or lactating females; chronic or acute renal disease; history of malignancy except basal/squamous cell carcinoma; any clinically significant disease that might interfere with the study; considering surgical procedures during the study; acute illness within 7 days; donated blood or plasma within 56 days; history of excessive alcohol consumption or drug abuse; administration of an investigational compound within 3 months; taking medications known to affect the PK of MTX; or unable to follow instruction in English or comply with the study procedures. Subjects were to be withdrawn for any medical reason determined by the investigator, although after returning to good health or after the adverse event resolved and was found to be not related to study drug, a subject could return to complete the study.

On three successive weeks, the subjects were randomized to receive weekly doses of methotrexate 10, 15, 20 or 25 mg, depending upon which dose matched the patient's current dosing regimen. Treatments included SC administration with the Vibex device in the abdominal wall, or administration using a needle and syringe by either the SC route in the abdominal wall or the IM route in the outer thigh (*vastus lateralis*).

The study population was primarily female (69.4%) and white (97.2%), with a mean age and weight of 62.1 years and 83.5 kg, respectively [p43, mtx-10-001-report-body.pdf].

There were no deaths and no serious adverse events (SAEs). A total of 4 subjects had 6 treatment-emergent adverse events (TEAEs) during the study, including two subjects with a maculopapular rash (one subject twice and one subject once), one subject with nasopharyngitis, one subject with injection site erythema and hematoma after the 25 mg SC dose with a needle and syringe, and one subject one subject with worsening hypertension. All AEs resolved except the worsening hypertension, which was a continued problem at the time of database lock.

PK parameters are shown in Table 6 and shown graphically in Figure 2 and Figure 3. Systemic exposure following administration by all three routes of administration was bioequivalent based on 90% confidence intervals (CI) for the geometric LS means.

Table 6. MTX-10-001, Dose-normalized PK parameters, PK pop

Parameter Mean (SD)	Vibex MTX	Needle and syringe	
	SC	SC	IM
N	36	36	36
C_{max} (ng/mL/mg)	21.43 (8.31)	22.38 (10.26)	23.37 (7.19)
T_{max} (hr)	1.24 (0.48)	1.32 (0.64)	1.24 (0.85)
½ life (hr)	3.57 (0.69)	3.59 (0.66)	3.51 (0.68)
$AUC_{0\text{-}inf}$ (ng•hr/mL/mg)	118.14 (42.30)	122.63 (40.65)	116.71 (41.39)

Source: T8, p52; mtx-10-001-report-body.pdf

Table 7. MTX-10-001, Geometric LS Means and Comparisons, PK pop

Parameter	Vibex MTX	Needle and syringe		Ratio (90% CI)
	SC	SC	IM	[Vibex to Needle and Syringe]
AUC_{0-24} (ng•hr/mL/mg)	111.3	115.7		96.22 (92.3, 100.3)
			110.1	101.14 (97.1, 105.4)
AUC_{0-inf} (ng•hr/mL/mg)	112.6	117.0		96.24 (92.3, 100.3)
			111.2	101.28 (87.2, 105.6)
C_{max} (ng/mL/mg)	20.2	20.9		96.76 (87.9, 106.5)
			22.5	89.79 (81.6, 98.8)

Source: T8, p52; T9, p53; T10, p54; mtx-10-001-report-body.pdf

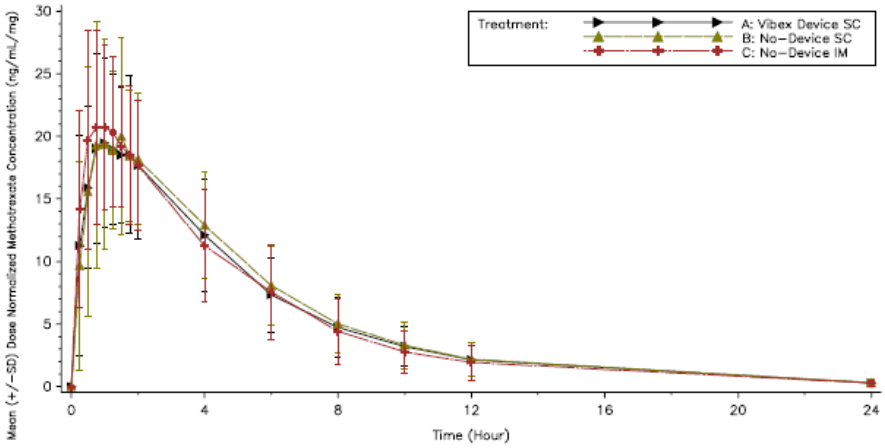

Figure 2. MTX-10-001, Mean dose-normalized MTX concentration vs time, by treatment, original scale, PK pop

Source: F1, p49; mtx-10-001-report-body.pdf

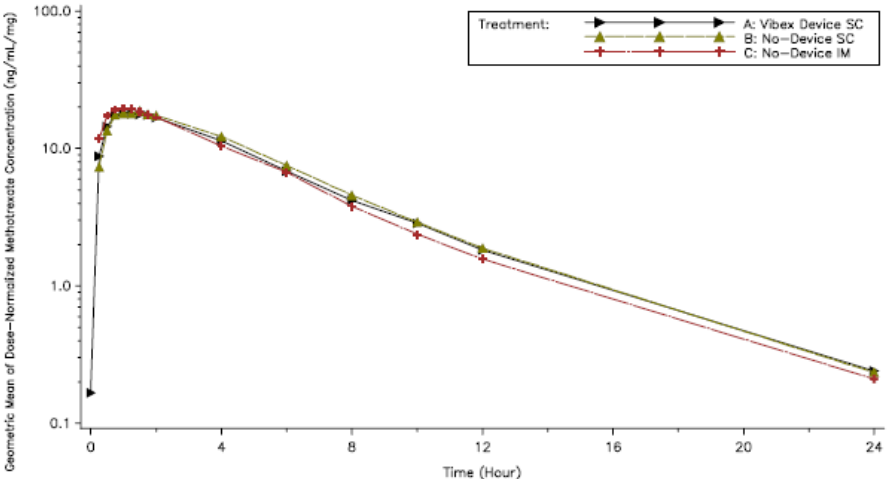

Figure 3. MTX-10-001, Geometric mean dose-normalized MTX concentration vs time, by treatment, log scale, PK pop

Source: F2, p50; mtx-10-001-report-body.pdf

Conclusion

This open-label PK study demonstrated bioequivalence between MTX delivered SC using the proposed auto-injector, SC using a needle and syringe, and IM using a needle and syringe. It therefore supports interchangeability of dosing administered using the proposed device SC in the abdomen with dosing administered either IM and SC using other parenteral forms of MTX.

5.3.1.2 Study MTX-11-003

Initiation Date: May 2, 2012

Completion Date: July 26, 2012

Investigation Sites: (b) (4)

Bioanalytical Laboratory: (b) (4)

Study MTX-11-003 was open-label, single dose, 3-way crossover bioavailability study that compared systemic MTX exposure following SC administration using the proposed auto-injector ["Vibex"] device in either the thigh or the abdominal wall with a similar dose following oral administration in 50 patients ≥18 years with RA who were on methotrexate treatment for at least 3 months prior to the study. The study was performed at four clinical sites in the United States. The comparator product used in this study was Methotrexate Tablets manufactured by Dava Pharmaceuticals Inc. (NDA 08-085, approved on December 7, 1953), which is listed in the Orange Book as an RLD.

Inclusion criteria included: stable on concomitant medications for 3 months; no medical conditions or medications that would interfere with study outcomes; chest x-ray within 6 months; use of a highly effective form of contraception for females of child-bearing potential; and capable of understanding and following the protocol instructions and requirements. Exclusion criteria included: pregnant or lactating females; aspartate aminotransferase, or bilirubin >3x the ULN; chronic or acute renal disease; history of malignancy except basal/squamous cell carcinoma; any clinically significant disease that might interfere with the study; considering surgical or dental procedures during the study; acute illness within 7 days; positive for HIV, HbSAg, or Hepatitis C antibodies; donated blood or plasma within 56 days; history of excessive alcohol consumption or drug abuse; administration of an investigational compound within 3 months; taking medications known to affect the PK of MTX, or unable to follow instruction in English or comply with the study procedures. Subjects were to be withdrawn for any medical reason determined by the investigator, although after returning to good health or after the adverse event resolved and was found to be not related to study drug, a subject could return to complete the study.

On three successive weeks, the subjects were randomized to receive weekly doses of methotrexate 10, 15, 20 or 25 mg, depending upon which dose matched the patient's current dosing regimen. Treatments included SC administration using the Vibex MTX device in either the thigh or the abdominal wall with a similar dose following oral administration.

The study population was primarily female (63.3%) and white (89.9%), with a mean age and weight of 61.4 years and 86.5 kg, respectively [p44, mtx-11-003-report-body.pdf].

One subject experienced an SAE of myocardial infarction that resulted in death. Subject 001-030, on MTX 25 mg, was a 79 year old male with a history of RA ((b) (6)), hypertension, CHF, MI ((b) (6)), and coronary artery disease. (b) (6) days after he received his first dose of study drug he developed jaw and chest pain, and subsequently died in his sleep the next day. The coroner ruled the cause of death to be MI, although an autopsy was not performed.

One subject experienced an SAE of sick sinus syndrome (Subject 001-008, 72 year old male, MTX 15 mg), which was severe but considered unrelated to study drug and resolved by the end of the study. One subject (MTX 10 mg) discontinued due to a

TEAE of worsening rheumatoid arthritis on the same day as the first dose of study drug. Two other subjects experienced a TEAE, including one subject with nausea and one subject with fatigue.

PK parameters are shown in Table 8 and Table 9, and shown graphically in Figure 4 through Figure 8. The results demonstrate bioequivalence between the two SC injection sites using the proposed MTX auto-injector device. However, bioavailability was higher following SC administration with the proposed device than following oral administration, particularly at the higher (20 and 25 mg) dose levels at which a plateau of systemic exposure is reached (Figure 4).

Table 8. MTX-11-003, Dose-normalized PK parameters for SC injection routes

Parameter Geometric LS Mean	Vibex MTX		Ratio (90% CI)
	SC abdomen	SC thigh	
N	49	47	
C_{max} (ng/mL/mg)	20.5	17.8	115.63 (108.83, 122.86)
$AUC_{0\text{-}inf}$ (ng•hr/mL/mg)	133.9	129.1	101.82 (99.39, 104.31)

Source: T12, p61; mtx-11-003-report-body.pdf

Table 9. MTX-11-003, Geometric LS Means and Comparisons by Dose Level, PK pop

Parameter	Oral	Vibex MTX		Ratio (90% CI) [Vibex to Oral]
		SC abdomen	SC thigh	
MTX 10 mg				
$AUC_{0\text{-}24}$ (ng•hr/mL/mg)	1223.7	1507.6		123.20 (115.7, 131.2)
			1441.5	117.80 (110.5, 125.6)
$AUC_{0\text{-}inf}$ (ng•hr/mL/mg)	1246.9	1537.3		123.29 (115.8, 131.3)
			1470.3	117.91 (110.7, 125,9)
C_{max} (ng/mL/mg)	247.2	242.5		98.11 (85.3, 112.8)
			178.4	72.17 (62.6, 83.2)
MTX 15 mg				
$AUC_{0\text{-}24}$ (ng•hr/mL/mg)	1752.0	1994.0		113.82 (106.1, 122.1)
			1992.7	113.74 (106.1, 122.0)
$AUC_{0\text{-}inf}$ (ng•hr/mL/mg)	1786.6	2039.7		114.17 (106.3, 122.6)
			2040.6	114.22 (106.3, 122.7)
C_{max} (ng/mL/mg)	349.4	266.8		76.35 (70.0, 83.3)
			259.9	74.38 (68.2, 81.1)
MTX 20 mg				
$AUC_{0\text{-}24}$ (ng•hr/mL/mg)	1927.2	2501.8		129.81(118.4, 142.3)
			2542.1	131.90 (120.3, 144.6)
$AUC_{0\text{-}inf}$ (ng•hr/mL/mg)	1949.7	2539.8		130.27 (118.8, 142.9)
			2581.8	132.42 (120.7, 145.3)
C_{max} (ng/mL/mg)	440.4	410.4		93.18 (78.7, 110.3)
			385.7	87.57 (74.0, 103.6)

Parameter	Oral	Vibex MTX		Ratio (90% CI) [Vibex to Oral]
		SC abdomen	SC thigh	
MTX 25 mg				
AUC_{0-24} (ng•hr/mL/mg)	1987.8	2887.5		145.26 (130.5, 161.5)
			2708.6	136.26 (122.2, 152.0)
AUC_{0-inf} (ng•hr/mL/mg)	2012.4	2933.9		145.80 (131.1, 162.2)
			2745.3	136.42 (122.4, 152.0)
C_{max} (ng/mL/mg)	423.5	491.4		116.02 (98.6, 136.5)
			395.9	93.47 (79.1, 110.5)

Source: T9, p55; T10, p57; mtx-11-003-report-body.pdf

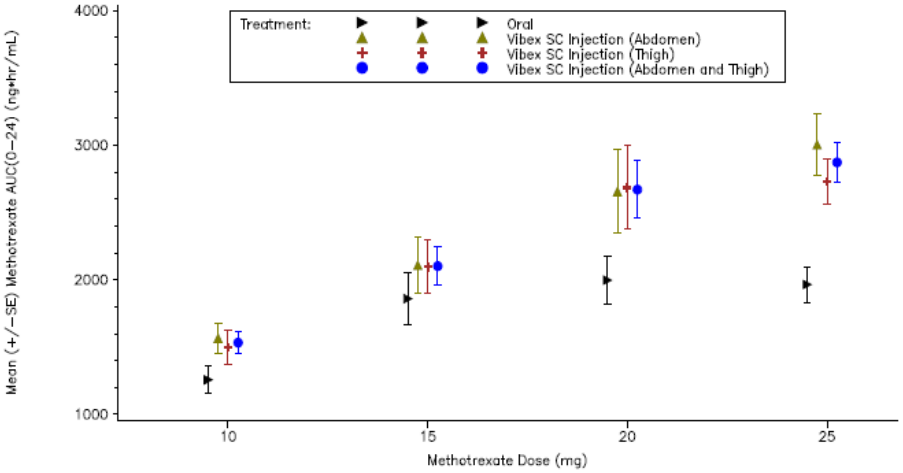

Figure 4. MTX-11-003, Plot of mean AUC0-14 (ng•hr.mL) by dose group and treatment, PK pop

Source: F3, p18; clinical-overview.pdf

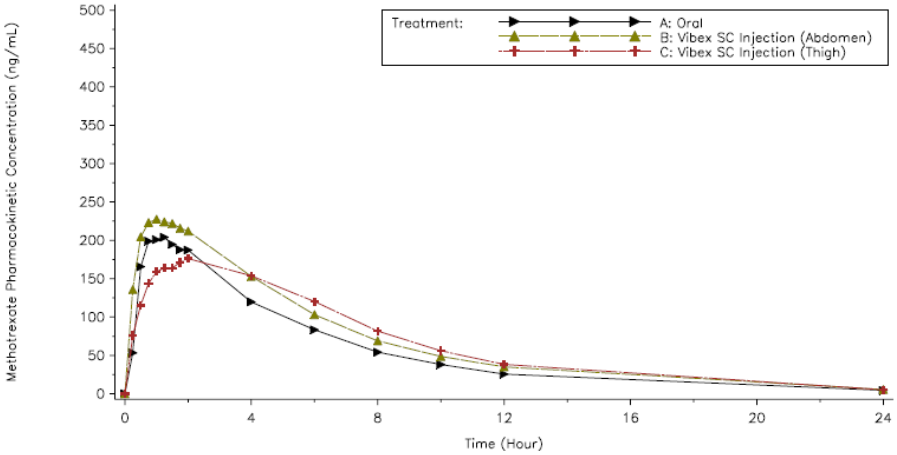

Figure 5. MTX-11-003, Mean MTX concentration vs time, by treatment, original scale, PK pop, MTX 10 mg dose group

Source: F1, p46; mtx-11-003-report-body.pdf

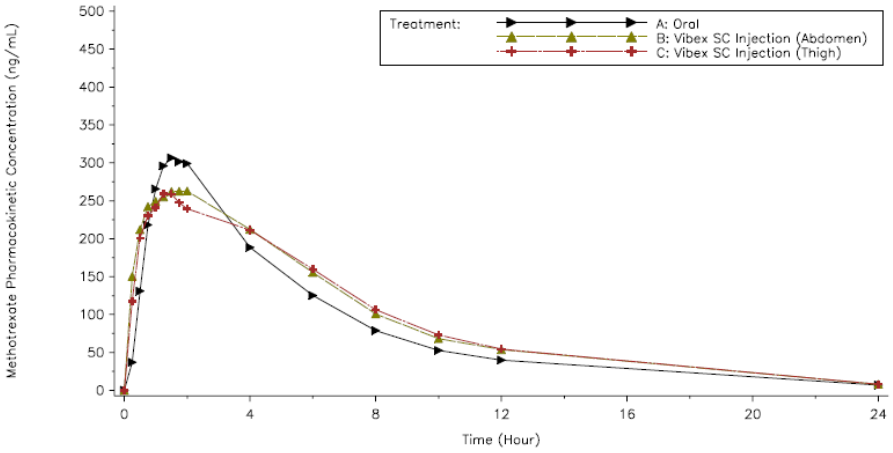

Figure 6. MTX-11-003, Geometric mean MTX concentration vs time, by treatment, PK pop, MTX 15 mg dose group

Source: F2, p47; mtx-11-003-report-body.pdf

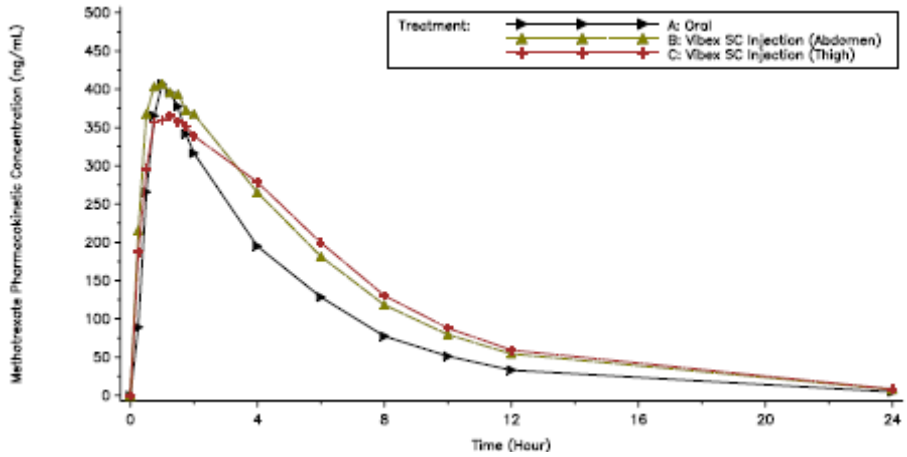

Figure 7. MTX-11-003, Geometric mean MTX concentration vs time, by treatment, PK pop, MTX 20 mg dose group

Source: F3, p47; mtx-11-003-report-body.pdf

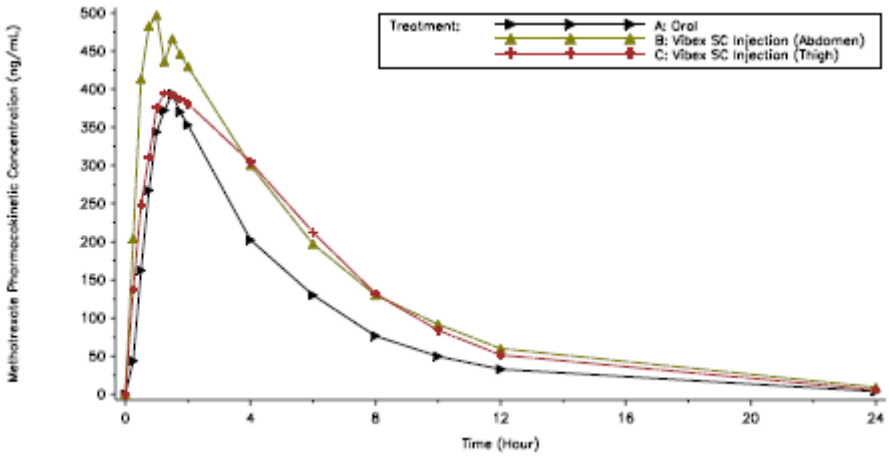

Figure 8. MTX-11-003, Geometric mean MTX concentration vs time, by treatment, PK pop, MTX 25 mg dose group

Source: F4, p48; mtx-11-003-report-body.pdf

Conclusion

This open-label PK study demonstrated bioequivalence between methotrexate delivered SC using the proposed MTX auto-injector either in the abdomen or the thigh. The study therefore supports interchangeability of abdominal wall and thigh sites for SC injection in the labeling.

The study did not demonstrate bioequivalence between administration using the proposed MTX auto-injector SC and oral administration. Subcutaneous dosing was associated with a linear increase in systemic exposure with progressively higher doses, whereas oral dosing with progressively higher doses was associated with non-linear systemic exposure resulting in a plateau of systemic exposure at doses above 15 mg orally. This finding was not unexpected, given the known limitations of oral methotrexate dosing with progressively higher doses imposed by saturation of gut absorption. Given this phenomenon, IM or SC dosing provides a viable alternative approach to increasing oral doses of MTX above 15 mg with resultant increases in GI side effects.

5.3.2 Device Usability Studies

Two use and handling studies were performed to evaluate the ability of patients to follow the instruction set and use the device (MTX-11-002), and usability of the device (without medicine or a needle) in a simulated use setting (MTX-11-004).

Comment: It should be noted that, while they may have been requested by the Agency and may provide some informative results, these studies are not appropriate for and will not be described in the labeling for this product. They do not meet the requirements of a clinical trial, and will not be listed as studies essential to the application.

5.3.2.1 Study MTX-11-002

Study MTX-11-002 was a multicenter, open-label, single-dose, phase 2 study that evaluated the ability of adult patients with RA to use of the Vibex MTX auto-injector device and its associated instructions after having received training in the use of the product.

The study was conducted at 8 clinical sites in the United States between May and July of 2012. The report states that the protocol was reviewed by the (b) (4) (b) (4) was conducted in accord with the Declaration of Helsinki and applicable Good Clinical Practice guidelines, and appropriate informed consent was obtained prior to initiation of any study procedures.

Patients had to have been on MTX therapy for at least 3 months prior to enrollment, and were assigned to a dose of study MTX based on their baseline MTX dose. The study included a screening visit, a single training and treatment visit, and a follow up visit. The study report states that primary objective was to assess the usability of the device after standardized training by site personnel and review of the written instructions. The study also served a role in evaluating device reliability and robustness. At the End-of-Phase 2 (EOP2) meeting (September 13, 2011), the Agency had recommended that device reliability and robustness data be collected after actual use in at least 100 patients. This study fulfilled that recommendation. However, from the Agency's perspective the main reason for a study such as this one is to assess whether the training program and Instructions for Use (IFU) are adequate to assure that patients with RA can learn to self-administer a dose. Regardless of the study objective, it is entirely possible that all could have been met via a study that did not include administration of active drug to patients.

Training consisted of standardized verbal instructions (version 1.9, included as Appendix B of the study report), a demonstration of the proper use of the device, and review of the written patient instructions (version 1.9, included as Appendix C of the study report). Comparison shows that the written IFU that were provided to patients were very similar [although not identical] to the proposed IFU submitted with the application, and the standardized verbal instructions also are similar. Differences include that the IFU included drawings whereas the final IFU includes pictures, and the instruction set only included injection into the abdomen rather than either the abdomen or thigh.

After the training and an assessment of the injection site, patients were asked to independently self-administer a dose of MTX SC via the Vibex device using the written instructions (IFU) for guidance. Site personnel observed the self-injection attempt and recorded the outcomes on an Essential Tasks questionnaire. Elements of the questionnaire included: SC administration by the patient; SC injection was intentional; injection was administered in the appropriate location on the abdomen; patient removed cap marked "1"; patient removed cap marked "2"; patient held device at injection site, patient confirmed that the window as obstructed). After the injection, patients rated injection site pain using a visual analog scale (0-100 mm VAS) and completed an ease of use questionnaire. Used devices were collected and inspected to confirm delivery.

Negative outcomes were reviewed with the patients, and patient comments and observations were collected. After a post-dose injection site assessment and vital signs, patients were discharged with follow-up the following day. The primary endpoint was successful SC self-injection, which was defined as intentional SC self-injection administered by the patient in an appropriate location on the abdomen; and the device functioned appropriately as determined by inspection of used devices, including confirmation that the window was obstructed, the ram was released, and the needle guard no longer retracted.

A total of 101 RA patients were enrolled at 8 sites in the United States, and 101 completed the study. A total of 12 (11.9%), 54 (53.5%), 31 (30.7%), and 4 (4%) patients were classified as American College of Rheumatology RA classification Stage I, II, III, and IV, respectively, and 10 (9.9%), 59 (58.4%), 31 (30.7%), and 14 (1%) patients were classified as being in functional status Class I, II, III, and IV, respectively. Most (n=81, 80.2%) had previous experience with SC injections, and most (n=83, 82.2%) had experience with self-injection devices, of whom 31 (30.7%) had previous experience with an auto-injector device.

All patients were able to perform a successful SC self-injection of study drug and completed all essential tasks successfully, regardless of radiographic disease stage or functional status. All devices functioned appropriately, as confirmed by site personnel. The study report states that 98% of patients found the device easy to use and 100% of patients found the instructions and training clear and easy to follow. Most (94%) patients answered all 5 training confirmation questions correctly, indicating a high level of understanding of the standardized training and written instruction set.

One patient in the 20 mg MTX group experienced a TEAE of headache immediately after self-injection, one patient in the 25 mg group experienced an SAE of sick sinus syndrome, and one patient in the 20 mg MTX group experienced a TEAE of exostosis. There were no injection site AEs, and the most commonly reported pain value was 1 mm on the VAS (Day 1 mean 3.6, range 0-72; Day 2 mean 1.4, range 0-21).

Conclusion

This single dose study in RA patients demonstrated that patients can learn to use the proposed auto-injector device and perform a successful auto-injection after a scripted training demonstration following a script that is similar to and based on the proposed IFU. There were no local reactions to subcutaneous injection of methotrexate with the proposed device, and there were no issues with device functioning or device failures. The study therefore supports use of the device in RA patients, although it does not specifically demonstrate that the proposed IFU and device are adequately labeled. Please refer to results of study MTX-11-004 for further details.

5.3.2.2 Study MTX-11-004

Study MTX-11-004 was a training device-only study that did not involve the administration of MTX or the use of a device with placebo or a needle. The study is

stated to have been a summative, simulated-use, usability testing and design validation (Human Factors) study to evaluate the proposed Vibex MTX auto-injector device and its associated documentation, including the IFU, on-device label, and health care provider (HCP) training script. The study report states that the objective was to assess whether the device could be used by representative users under simulated use conditions without generating patterns of failures that could result in negative clinical impact to patients or injury to device users. In other words, one of the main reasons for this study was to assess whether the training program and IFU were adequate.

Comments about the design of the proposed study were provided by CDRH at the EOP2 meeting on September 13, 2011. The study was conducted by (b) (4), in January 2012.

Study Design

The study included two sessions spaced one week apart. The week between sessions was intended to be reflective of the intended once-weekly dosing interval and to assess the impact of training decay in those participants who received training in Session 1. Seventy-five individuals were recruited, including 17 RA patients, 16 lay caregivers, and 17 healthcare professionals (nurses). Healthcare professional participants participated in Session 2 only, but all others participated in both Sessions 1 and 2. Session 1 (Day 1) was a **training session** in which participants watched an in-person demonstration according to the HCP script, had the opportunity to practice with a resettable demonstration device, and were then observed performing one successful simulated injection. Session 2 (Day 8) included no training; participants simulated a single injection using a commercial-quality dummy device (identical to the commercial device but with no needle). The IFU was available for reference in both sessions.

Since a training session was part of the study design for all but experienced healthcare professionals (nurses), this study was not designed to be a label comprehension study in that it was not designed to directly evaluate whether patients and caregivers could appropriately follow and use the IFU without further training. Rather, the study evaluated the entire instruction set, including a training session and the IFU itself. Since the training script was not included in the study report, it was requested in an IR dated April 30, 2013, and provided in a submission dated May 7, 2013. The script covered the following areas: review of the injector parts, how to check the injector to make sure that it is viable and not expired, selecting and preparing the skin site for injection, preparing the injector for use, how to perform an injection, and the labeling on the injector (which is stated to be the same as that in the IFU). As such, the training script was based on the proposed IFU, but also included more information than is provided in the IFU.

The primary evaluation criteria for the study were 1) the participant's ability to deliver a successful injection to the patient, and 2) the medication was delivered without potential for harm to the patient or caregiver. The study evaluated the participant's ability to complete each task in the injection process, as documented in the IFU, with ten critical tasks identified and evaluated:

- inspection of the contents of the syringe

- location of the appropriate injection site
- removal of the cap (1)
- removal of the safety (2)
- griping the device in hand
- placement of the needle end perpendicular to and directly against the injection site
- firm pushing of the needle end into the injection site to trigger the device
- holding for 3 seconds after hearing the audible "click"
- removal of the device from the injection site
- visual confirmation that the viewing window is occluded.

Study Population

The RA patients included: 13 females and 4 males; ages: n=5 45-54y, n=5 55-64y, n=7 ≥65y; 13 required help to grip or open things; 7 had tender joints of whom 5 had tender hand joints; with 0-11 (average = 2) swollen joints [0-10, average = 1, hand joints]. Of the 17 RA patients recruited, 9 had no experience with self-injections, 5 had experience with a syringe injection, and 3 had experience with an auto-injector.

The lay caregivers included: 14 females and 2 males; ages: n=1 25-34y, n=7 45-54y, n=4 55-64y, n=4 ≥65y. Of the 16 lay caregivers, 7 had experience injecting others and 9 did not.

The professional caregivers included: 17 females, no males; ages: n=1 18-24y, n=1 25-34y, n=2 35-44y, n=8 45-54y, n=4 55-64y. Of the 17 professional caregivers, 11 had experience auto-injectors and 6 did not. For most (n=7), the experience was based on insulin injections, with one each for migraine medications, enoxaparin, and epinephrine. Other than auto-injector experience, the medical training and experience of these caregivers was not stated in the report. This was requested in an IR dated April 30, 2013, and submitted on May 7, 2013. All of the professional caregivers were registered nurses (RNs) and two were nurse practitioners, and their experience with SC injections varied from 1x to 30x per week.

Results

Overall, the study report states that 81 of the 83 trials were successful; however, two were unsuccessful (1 patient, 1 health care professional), of which one event raises concern about the training device and one event was raises concern about a safety issue.

- One healthcare professional (RN) failed to deliver a successful injection after she pointed the needle end of the device toward her own hand. The study report notes that she initially appeared to be overwhelmed by the IFU, stating that she would need further instruction to use the device. However, the report also states that when

given a second device, she read the IFU and was able to follow the step-by-step directions and deliver a successful injection.

This report raises the concern that the two ends of the device are not clearly enough distinguished such that accidental injection into the hand will be prevented.

- One RA patient (participant #4) delivered an incomplete injection because she held the device at the injection site for less than 1 second. The report states that the patient was startled by the click, but immediately realized that she had done it wrong and was able to complete a simulated injection using a second device.

The report also states that the reason that the patient was startled by the click is that "the training device did not make any sound", whereas the commercial-quality dummy device did. Starting with participant #5, training Session 1 was modified such that the moderator demonstrated the use of the device using a commercial-quality dummy device rather than with a trainer device, to allow participants to become familiar with the sound. However, this also raised the concern that the trainer and the actual device differ in a substantive way regarding the lack of presence of a "click" with use of the trainer device. Further, health care professional will not have a commercial-quality dummy device available for training. Therefore, the modification of the training Session 1 created an artificial environment that no longer mimicked the training that might occur in the health care professional's office setting.

To resolve issues with the trainer device brought up by the study results, in an IR dated April 30, 2013, Antares was asked to state whether the trainer device was modified, and to explain any differences in the clicking sound between the trainer and the live device. Antares responded on May 7, stating that:

> "The Otrexup demonstrator (demo) is designed so an audible "click" is made when the Otrexup demo is triggered. The Otrexup demo "click" sound is very similar to the real Otrexup device "click", but the Otrexup demo "click" is slightly softer (i.e. not quite as loud).
>
> The mechanism by which the click sound is generated in both the Otrexup demo and the real Otrexup device is the same. Both the Otrexup demo and the real Otrexup device make a "click" when the device is triggered, and in both cases this is accomplished by the "release of a spring". However, the type of spring, latch and trigger used are different between the two devices in order to allow resetting of the Otrexup demo. In the real Otrexup device a standard compression spring is being released when the Otrexup device is triggered – which results in the "click" sound. In the Otrexup demo a flat leaf spring is being released when the device is triggered – which results in the Otrexup demo "click" sound. A flat leaf spring is used in the Otrexup demo because the Otrexup demo has to be re-settable so it can be reused for multiple training as applicable, whereas the real Otrexup device is only used one time i.e. disposable.
>
> In addition, the bushing, lock ring and ram have been removed from the Otrexup demo as the dose deliver mechanism is not required in the Otrexup demo unlike the Otrexup device."

To evaluate the trainer, the actual device, and the instruction set in the IFU, TIFU and on the devices labeling, and to further understand the similarities and differences between the trainer and the actual device, examples of the trainer and live devices were requested and evaluated by the clinical review team as well as reviewers in ONDQA and CDRH. Please see the Section 9.2 of this review for further details.

Table 10 shows the task-by-task results including most of the critical steps and several safety steps that had not been identified as critical but were nonetheless important. The two missing so-called critical steps not included in this table were removal of the device from the injection site and visual confirmation that the viewing window was occluded. However, those steps are far less important than the three additional steps that are included, i.e., hand in front of the needle, potential needle stick post injection, and device failures.

Success rates for IFU comprehension questions are shown in Table 11. Most individuals were able to answer the comprehension questions correctly.

In a submission dated May 22, 2013, the applicant responded to an IR from the Division of Medication Error Prevention and Analysis (DMEPA) and stated that no placebo was used in the device in this study and there were no cases of accidental firing during the study. DMEPA raised this as a concern because multiple participants were noted to not leave the auto-injector in place for the full 3 seconds as stated in the proposed labeling instructions. Since no placebo was used, the study did not evaluate whether the full simulated injection was received [pooling of liquid would have been noted during the simulation if the full injection was not received]. However, the actual use study (MTX-11-002) demonstrates that patients could learn to use the device and successfully administer injections, so this is not a significant issue.

Table 10. MTX-11-004, Task-by-task results of successful steps

Step	Successful step	
	n (n=89)[1]	%
Inspected the window prior to injection	86	96.6
Removed the safety	89	100.0
Removed the cap	89	100.0
Selected the proper injection location	88	98.9
Held device properly for injection[2]	87	97.8
Injected the entire dose (>3 sec. and proper force)	86	96.6
Gripped device properly for injection	89	100.0
Locked the white needle guard	87	97.8
Recognized a full injection[3]	85	95.5
Because of red indicator	*81*	
Because heard click	*3*	
Because held for 3 sec.	*1*	
Hand in front of needle during injection[4]	1	1.1
Potential needle stick post injection	0	0.0
Device failure	0	0.0

1 Includes the two separate trials for patients and lay caregivers, one trial for professional caregivers, and 6 additional trials (some participants were given a new device during their first trial if they had confusion operating the device or performed a step incorrectly).
2 Holding the device properly means that the participant held the device with the needle end pointed downward at a 90° angle to the injection site.
3 All injection steps except "recognized a full injection" were measured objectively by the Study Monitor. This was a subjective measure based upon participant responses.
4 Note: This error was committed by the same participant (Nurse # 13) described under incomplete injection performances. It was the only safety-related use error observed.

Source: T2, p10; mtx-11-004.pdf

Table 11. MTX-11-004, Success Rates for Yes/No IFU Comprehension Questions

According to the IFU, is it OK to…	**Correct Response**	**Number Correct (*n* = 82*)**	**Percentage rate (%)**
Use the device if the contents look slightly yellow?	Yes	74	90
Use the same location for each injection?	No	71	87
Inject next to your naval (within 2 inches)?	No	77	94
Twist the cap to remove it?	Yes	80	98
Remove device from the injection site after 2 seconds?	No	81	99
Call your doctor if you inject and do not see red in the window?	Yes	74	90
*Includes the responses from patients and lay caregivers during Sessions one and two (minus one lay caregiver who did not have time to respond during session one) plus the professional caregivers.			

Source: T3, p12; mtx-11-004.pdf

Conclusion

This was a summative, simulated-use, so-called usability testing and design validation (Human Factors) study. Since a training session was part of the study design for all but experienced healthcare professionals (nurses), this study was not designed to be a label comprehension study in that it was not designed to directly evaluate whether patients and caregivers could appropriately follow and use the IFU when presented to them without further training. Rather, the study evaluated the entire instruction set, including a training session based on the IFU as well as the IFU itself. The study provides insight into two issues with the proposed trainer device and the proposed instructions for use. One patient was startled by the "click" of the commercial-quality dummy device because, according to her, the trainer device was not associated with a click. However, this is not the case. One healthcare giver did not follow the directions and inappropriately handled the device such that she could have received a needle stick in the hand. This is a safety issue pointing to the need to explore whether additional safeguards need to be put into place to prevent similar instances in the clinical setting.

6 Review of Efficacy

6.1 Efficacy Summary

Support for approval of this application is based on the Agency's previous findings of safety and effectiveness of MTX in patients with RA and JRA [and psoriasis], published literature to support efficacy and safety of SC dosing for RA, pJIA, [and psoriasis], and a bioavailability study (MTX-11-003) that supports the effectiveness of SC MTX by demonstrating higher systemic exposure dose for dose when MTX is administered SC than orally, particularly as doses extend above 15 mg. Support also comes from a bioequivalence study (MTX-10-001) that showed bioequivalence between the proposed product injected into either the abdomen or the thigh with both SC and IM injection using a needle and syringe. Please see Section 5.3 for details of these studies.

The published literature to support efficacy and safety of SC dosing for RA and pJIA that was submitted to the application was reviewed and is outlined in the next section of this review, Section 6.2. Please refer to the reviews from the Division of Dermatology and Dental Products for discussion of the psoriasis indication. The literature supports SC administration as an alternative to oral or IM administration of MTX, with higher systemic exposure and improvements in efficacy when administered SC or IM vs orally in similar doses, particularly in doses above 15 mg. It therefore supports the use of the proposed product as a convenience alternative to using a needle and syringe for at-home self or caregiver injection of methotrexate.

The applicant also submitted two use and handling studies that are reviewed in Section 5.3.2 and have some implications for appropriate labeling of the instructions for use.

6.2 Indications

This section reviews the literature submitted with the application to support use of the proposed product for the RA and pJIA indications.

The sponsor conducted Medline and Embase literature searches. Only papers in English or English translations of systematic reviews, meta-analyses, randomized controlled trials, and treatment guidelines were included, where the MTX interventions were administered chronically by the SC, IM, parenteral, or oral routes, the disease was RA/JRA, and the endpoints were safety, efficacy, PK, or human pharmacology.

6.2.1 Rheumatoid Arthritis (RA)

6.2.1.1 Background

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune (i.e., immune self-tolerance) disorder of unknown etiology characterized by symmetric, erosive synovitis

that results in progressive joint destruction, deformity, and physical disability. Disability from RA can have a profound impact on patients and families, resulting in major economic loss and more than 9 million physician visits and over 250,000 hospitalizations annually. The wrists, metacarpophalangeal (MCP), and proximal interphalangeal (PIP) joints are the most frequently involved joints. Extra-articular manifestations include fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and hematologic abnormalities. Despite therapy, the course for most patients is chronic and fluctuating. RA occurs more frequently in females (2-3:1) and affects between 0.5 to 1% of the adult population worldwide, and 0.7-1.3% of the adult population in the United States. Genetic factors play a role in the disease and its severity, with alleles that confer the greatest risk located within the major histocompatability complex (MHC). In addition, environmental factors such as cigarette smoking increase the risk for developing the disease (RR = 1.5-3.5). Self-reactive T cells drive the chronic inflammatory response, with CD4+ T cells playing an important role along with activated B cells and macrophages. TNF-α is a pivotal cytokine in the pathobiology of synovial inflammation, upregulating adhesion molecules on endothelial cells, promoting the influx of leukocytes into the synovial microenvironment, activating synovial fibroblasts, and stimulating angiogenesis, pain receptor sensitizing pathways, and osteoclastogenesis. [ACR 2002; Shah 2012]

The clinical diagnosis of RA is largely based on signs and symptoms of chronic inflammatory arthritis, with laboratory and radiographic results providing important supplemental information.

Classification criteria developed jointly by American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) in 2010 help to distinguish patients at the onset of disease with a high likelihood of evolving into a chronic disease with persistent synovitis and joint damage, thereby helping to identify patients who would benefit from early introduction of disease-modifying therapy.

Medications used for the treatment of RA may be divided into broad categories: nonsteroidal anti-inflammatory drugs (NSAIDs); glucocorticoids, such as prednisone and methylprednisolone; conventional disease-modifying anti-rheumatic drugs (DMARDs); and biologic DMARDs. DMARDS slow or prevent structural progression of the disease. In the last several decades, NSAIDs, which formerly were considered a core therapy, are now considered adjunctive and MTX has emerged as the DMARD of choice for the treatment of RA. Additionally, a number of highly effective biologicals have been approved that can be used alone or in combination with MTX, allowing individual tailoring of treatment to fluctuations in disease activity and drug-related toxicities.

6.2.1.2 Literature Review

The applicant summarized the literature with respect to SC MTX treatment of RA and other rheumatic diseases, as well as the literature with respect to IM MTX treatment. The literature for SC MTX treatment included including two randomized controlled trials [Braun 2008, Parker 2004] and multiple other studies and clinical reports. Dosages of

SC MTX ranged from 5 mg to 30 mg once a week. Most studies were 6 to 12 months in duration. The MTX SC use literature is summarized below.

Arthur AB, et al, 1999

These authors reviewed their experience with the safety, efficacy, and practicality of self-administered parenteral gold or MTX in RA and psoriatic arthritis patients at a clinic in Canada between 1992 and 1995. Forty patients (27 women) who were improved and stable on parenteral medication were taught to self-administer their medication. Patients were assessed for disease activity and outcome measures at the time of referral and every 3 months. Variables included tender and swollen joint count, erythrocyte sedimentation rate (ESR), pain visual analog score (VAS), and Health Assessment Questionnaire (HAQ).

Sixty-five percent of patients performed self-injection and 35% received injections at home from a partner. The mean active joint count and ESR remained stable during self-injection, and 70% continued self-injection after a mean of 34 months. Side effects of self-injection included superficial irritation at the injection site in 2 patients and dosing error in 2 patients with no adverse effects. Clinic visits were reduced from weekly to once every 12 weeks in patients on MTX. Satisfaction surveys identified time saving and convenience as major benefits.

The authors concluded that with basic instruction and close supervision, self-injection of antirheumatic drugs is safe, practical, and effective in selected patients.

Arthur V, et al, 2001 and 2002

These authors conducted a 13-week study in the UK to compare the safety and efficacy of methotrexate administered by intramuscular and subcutaneous routes, and to teach patients to self-administer methotrexate subcutaneously. It appears that they reported on the study twice, once in a letter to the editor in 2001, and again as a stand-alone paper in 2002.

Eight patients (6 females, 2 males; 4 RA, 2 psoriatic arthritis, 1 Wegener's granulomatosis, and 1 polymyositis) with a mean age 43 and a mean disease duration of 11 years 4 months were enrolled. Variables of disease activity were measured at week 1 and week 13. Nurse specialists administered weekly IM MTX at weeks 1 to 3 and weekly SC MTX at weeks 4 to 6, and serum MTX levels were measured 1 hour after each administration. During weeks 4 to 6, patients were given instruction for self-administration by practical demonstration and with the addition of written information, during weeks 7 to 9 patients self-administered (pre-drawn) MTX by SC injection under supervision and during weeks 10 to 12 the participants self-administered the (pre-drawn) MTX at home. At week 13 patients returned to the clinic.

No significant differences were noted between SC and IM MTX administration with respect to pain, fatigue, early morning stiffness, tender joints, erythrocyte sedimentation rate (ESR), or C-reactive protein (CRP) levels. PK analysis revealed no significant difference in serum levels between IM and SC injections. The authors concluded that self-administration of SC MTX is effective for patients with reasonable dexterity.

Bakker et al, 2010

This study was part of a 2-year, prospective, randomized, open-label, multi-center trial conducted in the Netherlands that compared two methotrexate regimens to evaluate the utility of "tight control" in RA patients who had a disease duration of <1 year and were naïve to DMARDs and glucocorticoids. Patients in the tight control arm of the trial were evaluated in this study. MTX was initiated at 7.5 mg/week orally and increased by 5 mg/week until remission, a maximum tolerable dose was reached, or a maximum dose of 30 mg/week was reached. Remission was predefined using the criteria of swollen joint count = 0, and 2 of 3 of the following: tender joint count ≤ 5, ESR ≤ 20 mm/h, and VAS ≤ 20 mm). Patients not attaining remission or reaching the maximum tolerable oral dose were switched to the equivalent SC dose. The change in the patient's 'disease activity score in 28 joints' (DAS28)[2] was evaluated after 1 month on SC MTX and compared with the average monthly change in DAS28 in the preceding 3 months. If the predefined goal of remission at the subsequent visit was not met, cyclosporine therapy was added.

Of 151 patients enrolled, 57 were switched from oral to SC MTX (21 due to AEs on mean oral dose of 25 mg/week, and 36 due to lack of efficacy at a maximum dose of 30 mg/week). After 1 month on SC MTX, the mean decrease in DAS28 was 0.30 points ($p < 0.05$), with similar results regardless of the reason for switching. Over the 4-month evaluation period, the decrease in DAS28 was 0.5 points ($p < 0.01$), with similar results for patients switching because of AEs (0.4 points, $p > 0.05$) and lack of efficacy (0.6 points, $p < 0.001$) (Figure 9). Following the switch to SC MTX, 36 patients responded (i.e., has an equal or better course of DAS28 compared to the preceding months) and 21 did not (cyclosporine treatment was added).

The authors concluded that switching from oral to SC MTX can provide further improvement at equivalent or higher doses once the maximum tolerated oral dose is reached.

2 DAS28 is a quantitative measure of disease activity used to clinically monitor the treatment of RA. There are several versions of DAS, but all measure the disease burden using the number of swollen or tender joints (up to 28), self-assessed patient global health on a VAS 0-100 scale, and either ESR or CRP. A formula is used to calculate the final score.

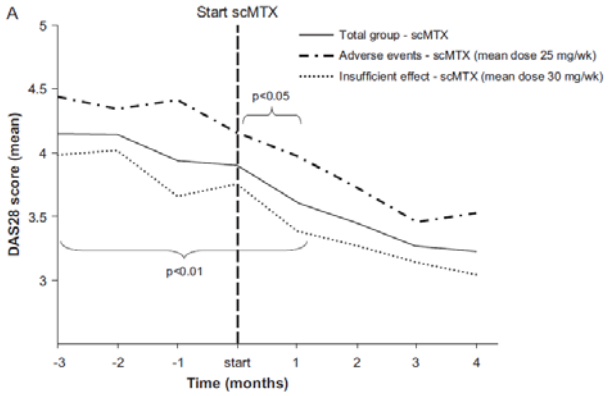

Figure 9. Bakker et al, 2010. DAS28 for patients switched to SC MTX.

Braun et al, 2008

This was a 6-month, multicenter, double-blind, randomized, placebo-controlled 2-arm trial comparing the clinical efficacy and safety of methotrexate administered either SC or orally in patients with RA. The trial was conducted in Germany between 2003 and 2005, and supported by medac GmbH.

MTX-naïve patients with active RA and a disease activity score in 28 joints (DAS28) of ≥4, were randomized 1:1 to: 15 mg subcutaneous MTX (one prefilled syringe containing 15 mg of MTX + 2 placebo tablets) or 15 mg of oral MTX (two 7.5-mg tablets of MTX + 1 prefilled syringe containing placebo). All patients took 5 mg of folic acid the day after their MTX dose. At week 16, patients who did not meet the ACR criteria for 20% improvement (ACR20) were switched from 15 mg orally to 15 mg SC, or from 15 mg SC to 20 mg SC, and continued for the remaining 8 weeks in a blinded fashion. The primary endpoint was the percentage of patients with an ACR20 response at week 24. Secondary endpoints included ACR50 and ACR70 responses as well as tolerability of SC versus oral treatment.

A total of 384 patients (median age 59 years, ~ 75% females, median time since diagnosis 2.1-2.5 months, median DAS28 6.1-6.3, and 125 [62%] RF positive) were enrolled: 194 in the SC group and 190 in the oral group.

At 24 weeks, the percentage of patients with ACR20 and ACR70 responses were 78% vs 70% ($p < 0.05$) and 41% vs 33% ($p < 0.05$) for SC vs. oral dosing, respectively, although the ACR50 at 24 weeks was not significantly different (SC 62% vs oral 59%). Patients with a disease duration ≥ 12 months had higher ACR20 response rates (SC 89% vs oral 63%). The number of swollen joints (SC 2 vs oral 3; $p = 0.04$), the number of tender joints (SC 3.5 vs oral 6; $p = 0.08$), median HAQ score (SC 0.4 vs oral 0.5), and median DAS28 (SC 3.3 vs oral 3.7) were lower in patients taking SC injections than in patients taking oral tablets.

After 16 weeks, 52 patients (14%) were classified as ACR20 non-responders and treatment was switched: 30 were switched from 15 mg orally to 15 mg SC, resulting in an ACR20 response in an additional 30% of patients at 24 weeks; and 22 were

switched from 15 mg to 20 mg SC, resulting in an ACR20 response in an additional 23% of patients at 24 weeks.

Tolerability was similar between treatments. Overall, 66% of SC MTX–treated patients reported an adverse event during the study, compared with 62% of oral MTX–treated patients. Similar percentages had SAEs. AEs of moderate severity with at least 3% incidence are shown in Table 12.

Table 12. Braun 2008. AEs of moderate severity with at least 3% incidence

AE	SC MTX (n=193)	Oral MTX (n=188)
Abdominal pain	17 (8.8)	20 (10.6)
Diarrhea	5 (2.6)	13 (6.9)
Dyspepsia	13 (6.7)	11 (5.9)
Loss of appetite	14 (7.3)	6 (3.2)
Nausea	32 (16.6)	23 (12.2)
Stomatitis	6 (3.1)	7 (3.7)
Vomiting	7 (3.6)	6 (3.2)
Increased ALT	3 (1.6)	8 (4.3)
Bronchitis	4 (2.1)	7 (3.7)
Headache	4 (2.1)	8 (4.3)
Nasopharyngitis	9 (4.7)	10 (5.3)

The authors concluded that SC injection of MTX is more effective than oral administration at the same dosage, suggesting that the increase in bioavailability with SC administration translates to superior efficacy over an equivalent oral dose.

Griffin & Erkeller-Yuksel, 2004

In a letter to the editor, these authors summarized prospective data from 22 patients with RA who were switched from a mean oral dose of 17.5 mg MTX to parenteral therapy (subcutaneous or intramuscular) at the same dose before consideration of addition of a biologic agent. Over a period of 6 months, significant reductions were found in swollen joint count ($p < 0.05$), tender joint count ($p < 0.01$), pain VAS ($p < 0.01$), patient's self-assessment VAS ($p < 0.02$), and physician's global assessment ($p < 0.02$). The HAQ did not change during this period. The authors recommended switching from oral to parenteral MTX before considering biological treatments.

Hameed et al, 2010

This is a retrospective report on 103 patients (30 males, 73 females; mean age 55 [range 20 to 83] years) who were switched from oral to SC MTX either for lack of efficacy (Group A, n=40; 32 RF positive) or intolerance (Group B, n=63; 48 RF positive) over a 12 month period of time at the Kingston Hospital HNS Trust, London, UK. Most patients (98%) in Group B had GI intolerance. Doses of MTX were not stated. Patients were followed for 3 months with no dropouts. In Group A, the mean DAS 28 improved from 4.8 on oral MTX to 4.2 in SC MTX ($p=0.006$, CI 0.9, 1.03), and 4 patients achieved

remission (DAS28 <2.6). In Group B, the mean DAS28 improved from 4.1 on oral MTX to 3.0 on SC MTX (p=0.0001, CI 0.9, 1.5), and 15 patients achieved remission. SC MTX was reported to be better tolerated than oral MTX, although no specifics were given.

Muller-Ladner et al, 2010

This was an open-label, prospective, within-patient controlled, multicenter study to determine the preference, satisfaction, usability and local tolerability of two SC administered MTX formulations of different concentrations. The study was performed at 16 centers in Germany between 2007 and 2008. The fist author received consulting and speaker fees (less than 10.000 USD) from medac GmbH, and 3 other authors are stated to have been employees of medac GmbH.

Patients received a dose of 20 mg of MTX SC for 6 weeks: 2 ml of a 10 mg/ml solution once weekly for 3 weeks, followed by 0.4 ml of a 50 mg/ml solution once weekly for another 3 weeks. Unfortunately, the study design did not incorporate a 2-way crossover, so all patients were switched in one direction only. The 1st and 4th injections were administered by study personnel, whereas the 2nd, 3rd, 5th, and 6th injections were self-administered. Questionnaires and visual analogue scales were used to document satisfaction, usability and local tolerability.

A total of 132 patients 18 to 75 years with active RA and a DAS28 >2.6 were enrolled. 93.0% of patients preferred the concentrated formulation vs. 2.3% who preferred the less concentrated formulation (95% CI: [87.1%; 96.7%] (p<0.0001). AEs were about equal between treatment groups. With regard to local tolerability, the more concentrated formulation is stated to have been slightly better tolerated, but no further details were provided.

Parker et al, 2004

This prospective, randomized crossover trial assessed the clinical utility of increasing the MTX dose from 20 mg/week to 25 mg/week either orally or SC in RA patients with active RA refractory to their current DMARD regimen. After ≥8 weeks of oral MTX at a dose of 20 mg/week, eligible patients were randomly assigned to receive 25 mg/week administered either SC or orally for 8 weeks and then crossed over to the alternate route for an additional 8 weeks. Patients were evaluated by blinded assessors using the modified HAQ, patient's global assessment, physician's global assessment, joint counts, and ESR.

Eight patients (5 females; 5 RF positive at study start) with median age of the patients was 47.5 years (range 34 to 78 years) and the median duration of disease activity was 15 years (range 8 to 20 years) were evaluated. Two patients had a significant response when MTX was administered SC. One of these patients showed no improvement after 8 weeks of oral MTX at 25 mg/week, but achieved an ACR20 improvement when crossed over to SC MTX. The other patient achieved an ACR50 while on SC MTX, but returned to her active baseline level when crossed over to oral MTX. Following

completion of the study, the patient switched back to SC MTX and achieved an ACR50 again.

The authors concluded that some patients with active RA who are taking 20 mg/wk or oral MTX may respond to 25 mg/wk if the route of administration is changed to SC injection.

Stamp et al, 2011

This was a 6-month study that evaluated the effects of switching from oral to SC MTX on red blood cell methotrexate polyglutamate (RBC MTXGlun) concentrations, disease activity, and adverse effects in patients with RA. It was conducted at the University of Otago, Christchurch, New Zealand, between 2005 and 2008, and was supported by the Health Research Council of New Zealand and Arthritis New Zealand.

Thirty patients (23 females, 7 males; mean age 51.8 years [range 32 to 70]; mean duration 7.7 years [range 0.75 to 21]; 87% RA positive) with inadequate disease control and/or intolerable adverse events while on a stable dose of weekly oral MTX were switched to SC MTX at their same dose and evaluated over 6 months. The median MTX dose was 20 mg/week (range 10 to 20 mg/week), and no patients had the dose changed during the study. All patients received 5 mg/week folic acid 3-4 days after MTX dosing. Disease activity was evaluated using swollen joint count, tender joint count, modified HAQ, physician global scores, and patient pain and global scores. A response was defined as a >0.6 reduction in DAS28 score.

Comparing week 0 with week 24, there was a trend toward improvement in DAS28 (3.27 vs 2.56, p = 0.064), with a mean change of 0.47 (range -1.5 to 5.19) in the 26 patients who had complete DAS28 scores. Improvements were noted in swollen joint count (p = 0.001), pain VAS (p = 0.014), patient's global score (p = 0.04), and modified HAQ (p = 0.03), but no improvements were noted in total joint count, patient fatigue, CRP, or ESR. Ten (10 of 26) patients had an improvement in their DAS28 score of >0.6 (responders), and 16 patients had an improvement of ≤0.6 (non-responders). Responders had a higher mean baseline DAS28 compared with non-responders (4.0 ± 0.4 vs 2.6 ± 0.3, p = 0.011), and all patients with a baseline DAS28 >3.0 were responders. Improvement in DAS28 was associated with an increase in RBC MTXGlu5 and MTXGlu3-5 concentrations. Furthermore, in the increase in MTXGlun occurred more rapidly in responders than in non-responders, suggesting that long-chain polyglutamates are important to the clinical effect of MTX.

Thornton et al, 2008

This was a prospective study to investigate the effectiveness of SC MTX in a cohort of patients with RA for whom oral MTX was ineffective or not tolerated. The study also assessed the need for treatment with a biologic agent in the event of failure of SC MTX. The study was conducted in the Rheumatology Clinic at Wexham Park Hospital, Slough, UK between 2004 and 2006.

Thirty consecutive clinic patients (26 females, 4 males; mean disease duration 15.3 years [range 2 to 46]) were recruited. The reasons for switching from oral MTX were

lack of efficacy (n=23) and intolerance (n=7). Patients were assessed at baseline, and at 3 and 6 months after switching to SC MTX. Efficacy endpoints included tender joint score, swollen joint score, patient's global assessment of disease activity, CRP, and DAS28 at each visit. Patients initiated SC MTX at a mean dose of 14.3 mg (range 7.5 to 17.5 mg). After 6 months of treatment, the mean dose was 19.9 mg (range 12.5 to 25 mg). The authors reported that 3 patients discontinued treatment at 3 months due to leucopenia (1) or poor compliance (2), and 2 stopped treatment at 6 months due to lack of efficacy (1) or nausea (1). Five reported minor side-effects: nausea (4), injection site reaction (1).

Compared with baseline, patients had with a mean reduction in DAS28 score of 2.34 at 3 months ($p < 0.001$) and 2.09 at 6 months ($p < 0.001$). Based on European League Against Rheumatism (EULAR) response criteria, 20 of 27 patients (74%) had a good response when evaluated at 3 months, and 13 of 25 patients (52%) maintained this at 6 months. Eleven patients met British Society of Rheumatology criteria for anti-TNF-α therapy at baseline, of whom 8 had a good response after 3 months of SC MTX, and none needed anti-TNF-α therapy at 6 months. Two of the 3 patients who failed to respond at 3 months required anti-TNF-α therapy at 6 months.

The authors concluded that the study provides evidence of the efficacy of SC MTX in controlling active RA in patients who fail to respond to, or are intolerant of, oral MTX, and that switching from oral to parenteral administration may suppress or delay the need for treatment with anti-TNF-α therapy.

6.2.1.3 Discussion

As requested by the Agency, the applicant has submitted bioequivalence data and published literature to support the SC route of administration in patients with RA. My review of the data presented supports the proposed dosing administered by the SC route for these patients. Further, my review of these data does not reveal any specific safety concerns with this route of administration beyond those already labeled. Study-10-001 showed bioequivalence between IM and SC administration of MTX, and Study MTX-11-003 showed higher bioavailability with IM and SC dosing than with oral doses above 15 mg. These data are consistent with clinical results of published studies, including two randomized controlled trials [Braun 2008, Parker 2004] and multiple other studies and clinical reports, suggesting equal or greater efficacy with SC dosing and no increase in safety concerns.

Parenterally administered MTX is also recommended for the treatment of RA in essentially all published treatment guidelines, including those from the American College of Rheumatology (ACR). [Singh, 2012] The updated ACR guideline recommends MTX as either first line monotherapy or in combination with other DMARDs prior to resorting to biologic DMARDS. DMARDs are now recommended for both early and established disease. Although the ACR guideline does not include recommendations with regard to the route of administration, SC administration is recommended by all of the other guidelines. [Pavy et al, 2006; Visser et al, 2009; Visser

& van der Heijde, 2009; Verstappen & Hyrich, 2010; Ataman et al, 2011; da Mota et al, 2012]

Therefore, based on the information presented by the applicant, the proposed SC route for administration of MTX in adults with RA is acceptable.

6.2.2 Polyarticular Juvenile Idiopathic Arthritis (pJIA)

6.2.2.1 Background and Terminology

Juvenile Idiopathic Arthritis (JIA), previously called Juvenile Rheumatoid Arthritis (JRA), is defined by the International League of Associations of Rheumatology (ILAR) as arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks and for which other known conditions are excluded. JIA is a heterogeneous condition that is relatively common in childhood, with an estimated prevalence of about 57 to 200 per 100,000 children younger than 16 years of age. While both result in arthritis, RA and JIA are considered different diseases even though they share the same pathophysiology and the armamentarium of drugs used to treat RA are generally used (with a few exceptions) for childhood forms as well.

JIA and JRA are terms used classify the forms of juvenile chronic arthritis, with JRA being an older classification system and JIA being more recently introduced. Whereas under the JRA classification system three subtypes were identified (systemic, pauciarticular, and polyarticular), under the newer JIA classification system seven subtypes are identified. As a result, the term JIA is now preferred, both to help distinguish the condition as different from adult RA and because the newer classification system provides for more accurate delineation of and less confusion between subtypes or forms. This newer terminology has been adopted by the clinical community and also by the Agency. Therefore, JIA is used in this review even though the currently approved MTX labels use the older JRA terminology.

Subtypes of JIA include [Petty 2001; Beukelman 2011]:

- systemic (sJIA). This form, formerly called systemic JRA (sJRA), is characterized by fever, arthritis, salmon pink rash, lymph node involvement, and internal organ involvement.
- oligoarticular JIA (oJIA). Formerly called pauciarticular-course JRA, this form was renamed to distinguish it from the polyarticular form. It affects 4 or fewer joints in the first 6 months.
- polyarticular JIA (pJIA). This form, formerly called polyarticular-course JRA, affects 5 or more joints in the first 6 months. It is subdivided into rheumatoid factor (RF) positive and RF negative subtypes.
- enthesitis-related arthritis. Enthesitis is the point at which a ligament, tendon, or joint capsule attaches to the bone. This form includes juvenile ankylosing spondylitis and arthritis associated with inflammatory bowel disease.

- psoriatic arthritis, i.e., arthritis associated with psoriasis.
- undifferentiated arthritis.

JIA is an autoimmune disease, in which the body's immune system mistakenly attacks some of its own healthy cells and tissues resulting in inflammation of joints that can lead to joint damage. The most common symptom is persistent joint swelling, pain, and stiffness that is typically worse in the morning or after a nap. The knees, hands and feet are commonly affected. Patients with systemic disease often have fever and skin rash that may wax and wane, swollen lymph nodes, and internal organ involvement, including the lining of the hears. Eye involvement (uveitis) is common, particularly in children with oligoarthritis type.

As noted previously in this review, the prevalence of JIA has been estimated to be between 57 and 220 per 100,000 children younger than 16 years of age, with pJIA affecting approximately 2 to 17% of children with JIA. pJIA is similar to adult RA with articular manifestations being predominant. It is therefore considered the childhood equivalent of RA. However, RA and pJIA are considered different diseases even though the same armamentarium of drugs used to treat RA are generally used (with a few exceptions) for many of the childhood forms as well. While sJIA may occur in children younger than 2 years of age, most authorities consider that pJIA rarely occurs before 2 years of age; therefore, the Agency has generally used a cutoff of 2 years of age as the lower age bound for this condition.

First line treatment of JIA typically involves use of nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, naproxen, and naproxen sodium [aspirin is an NSAID, but typically is not used for this condition]. If NSAIDS do not relieve the symptoms, so-called disease-modifying anti-rheumatic drugs (DMARDs) are used. MTX is considered to be a DMARD, along with corticosteroids and biologic agents. However, MTX is currently approved only for the treatment of "polyarticular-course JRA who have an insufficient therapeutic response to NSAIDS" without regard to whether the patient is RF positive or negative. While clinical guidelines for treatment of JIA do include MTX as part of the treatment regimen for other forms of JIA when arthritis is active (e.g., systemic JIA with active arthritis) or when disease activity is high (e.g., oligoarticular JIA with high disease activity) [Beukelman 2011], and while it is clear from the literature that MTX is used in this fashion in the clinical setting, the applicant has not requested expansion beyond pJIA to other JIA subtypes. Specifically, the applicant submitted literature intended to support SC use of MTX rather than to support use of MTX for other forms of JIA. Therefore, the scope of this review is restricted to pJIA, and the literature review in the next section summarizes the key articles that support such use.

6.2.2.2 Literature Review

The applicant reviewed the current literature for use of IM and SC forms of MTX in JRA/JIA. They identified 5 studies that evaluated a total of 551 patients ranging in age from <2 to 28 years who were treated with dosages between 5 to 40 mg once weekly for

6-12 months, with one study evaluating patients out to 138 months. The results of these studies are briefly summarized below.

Alsufyani et al, 2004

This was a retrospective analysis of patients with JIA who were treated with SC MTX after failing oral MTX because of lack of efficacy or intolerable adverse events. The study cohort consisted of patients with JIA treated at the University of British Columbia, Vancouver, BC, Canada between 1988-2001. A total of 61 (43 females, 18 males; mean age of 11.9 years, range 3-20 years) who had disease duration ≥6 months and 3 or more active joints prior to initiation of treatment with methotrexate were included in the analysis. Disease subtypes included: 8 systemic, 25 polyarticular (12 RA positive), 14 oligoarticular, 5 enthesitis-related, and 4 unclassified. All patients had received oral methotrexate for ≥3 months at a weekly dosage of at least 10 mg/m^2 (if tolerated) and received oral folic acid (1-2 mg daily). The average disease duration was 10.9 months (range 2-99 months) and the average age at time of treatment with oral methotrexate was 11.9 years (range 3-20).

Forty patients (66%) fulfilled the criteria for improvement after oral MTX, and 31 patients were switched from oral to SC MTX: 13 with no improvement, and 18 who had improved but had insufficient clinical improvement (n = 7) or nausea (n = 11). After 3 months on SC MTX at a mean dose of 15.4 mg/m^2 (range 5-20), 23 of 30 patients (77%) showed statistically significant improvement ($p < 0.05$) in a variety of outcome measures compared to pre-SC values on oral MTX.

A total of 15 patients were reported to have “toxicity” related to oral MTX (11 with nausea and 4 with raised serum liver enzyme levels). Nine of the 11 patients with nausea experienced a complete resolution of symptoms after switching to SC MTX; the other 2 patients had less severe nausea that was tolerable on SC MTX. All 4 children with raised liver enzymes were able to remain on oral MTX as the abnormalities resolved after temporary discontinuation of oral MTX.

Four children experienced transient toxicity related to SC MTX (liver enzyme abnormalities, or mild lymphopenia); 2 required temporary discontinuation of treatment, after which treatment was reinstituted without recurrence.

The authors concluded that for patients who fail oral MTX either because of inefficacy or toxicity, the use of SC MTX has a high likelihood of success, with more than 70% of patients achieving clinically significant improvement without clinically significant toxicity.

Ravelli et al, 1998

This was a prospective, open label, multi-center study to compare the efficacy of MTX after oral and IM administration in children with juvenile chronic arthritis (JCA). The study was conduced at 11 centers in Italy, enrolling children with a diagnosis of JCA according to the criteria set by the European League Against Rheumatism (EULAR) including children with a disease duration of at least 6 months with at least 3 joints with active arthritis that was not adequately controlled in NSAIDS or DMARDS.

A total of 257 patients (89 with polyarticular, 72 with pauciarticular, 95 with systemic) with a mean age 9.35 years (range 1.7-28 years) were treated with oral (n=127) or IM (n=129) MTX at a dose of 10 mg/m^2/week over a 6 month period. Response was defined as a ≥50% reduction in number of joints with active arthritis and/or the articular severity score. After 6 months the response rate was 58% in the oral cohort and 61% in the IM cohort. Higher response rates were observed in the pauci-polyarticular (60% in oral, 71% in IM) when compared to the systemic subtype patients (53% in oral, 45% in IM). The frequency of adverse reactions (Table 13) was generally similar between treatment groups, and no patients were discontinued due to an adverse reaction.

The authors concluded that MTX at the conventional dose regimen is equally effective in children with JCA when administered orally or by intramuscular injections.

Table 13. Ravelli 1998. Frequency of adverse reactions by route of administration

Adverse Reaction	Oral (n=125)	IM (n=126)
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Source: Ravelli 1998, Table 2, page 182

Ruperto et al, 2004

This was a randomized, multi-center trial conducted in Europe, Brazil, Israel, Korea, Mexico, Turkey, and the United States. The trial evaluated the efficacy and safety of parenteral methotrexate at intermediate (15 mg/m^2/week) and higher (30 mg/m^2/week) dosages in patients with polyarticular-course JIA who failed to improve after 6 months of oral, SC, or IM MTX at standard doses (8-12.5 mg/m^2/week). In the screening phase, 595 patients with JIA (325 with polyarthritis, 183 with extended oligoarthritis, and 87 with systemic-onset arthritis) were treated for a mean (±SD) of 5.6 ±1.5 months. MTX was administered orally in 463 children (78%), SC in 101 children (17%), and IM in 31 children (5%) at a mean ±SD dose of 10.0 ±2.3 mg/m^2/week. Of these, 430 (72%) improved in ACR 30, 133 (23%) did not improve, and 32 (5%) were lost to follow-up. Eighty eligible non-responders (mean age 8.2 ±6 years) were then randomized to receive either intermediate (n=40) or higher (n=40) dose MTX SC or IM once weekly for an additional 6 months.

After 6 months, there were no significant differences in response rates between the intermediate dose and higher doses for ACR30 (62.5%, 95% CI 46%-77% vs. 57.5%, 95% CI 41%-73%, p = 0.65), ACR 50 (57.5%, 95% CI 41-73% vs. 55%, 95% CI 38-71%, p = 0.82), or ACR70 (45%, 95% CI 29-61% vs. 47.5, 95% CI 32-64%, p = 0.82), respectively. However, nine patients (5 in the intermediate dose group and 4 in the high dose group) met the definition of complete disease control.

In the screening phase, 25 patients interrupted their MTX treatment temporarily or completely: 10 due to laboratory abnormalities (8 elevated transaminase, 2 leukopenia), 9 due to gastrointestinal symptoms (3 nausea, 4 vomiting, 1 mouth sores, 1 loss of appetite), 5 due to infections (2 upper respiratory tract infection, 2 urinary tract infection, 1 pneumonitis), and 1 due to focal seizures.

In the treatment phase, the number of patients who dropped out of the study due to MTX-related toxicity was similar between the intermediate- and the higher-dose group and did not differ from the dropout rate observed in the screening phase. Of the 40 patients who were randomized to receive the intermediate dose of MTX, 34 (85%) completed the trial and 6 (15%) dropped out: 3 due to a disease flare that required treatment with steroids (1 also required treatment with intravenous immunoglobulin and cyclosporine), 2 due to adverse events (1 with severe alopecia and 1 with seizures that were not related to MTX), and 1 due to withdrawal of parental consent. Of the 40 patients randomized to receive the higher dose of MTX, 29 completed the trial (72.5%) and 11 (27.5%) dropped out: 5 due to an adverse event (2 with nausea, loss of appetite, and general malaise, 1 with documented acute familial pancreatitis, 1 with dizziness, syncope, and unconsciousness, and 1 with papilloedema from a large arterovenous malformation), 3 due to an insufficient therapeutic effect requiring treatments (1 received sulfasalazine, 1 received etanercept, and 1 received prednisone), 2 due to withdrawal of parental consent, and 1 lost to follow-up.

Comparing the intermediate- with the higher-dose MTX group, there were no differences in the frequency of moderate or severe adverse events that were attributed as possibly or definitely related to MTX (although a trend toward more frequent toxicity was observed in the higher-dose group) and there were no differences in the frequency of patients with laboratory abnormalities. The most common adverse events (combined treatment groups) were nausea (n=17, 21%), vomiting (n=9, 11%), mouth sores (n=8, 10%), loss of appetite (n=6, 7.5%), hair loss (n=4, 5%), and malaise (n=4, 5%). No patient experienced diarrhea, pneumonitis, rash, or hepatomegaly. All other adverse events were mild and were considered to be unrelated to the MTX treatment. The most common laboratory abnormalities (combined group) were levels of AST and/or ALT greater than twice the ULN on at least 1 determination (n=4, 5%) and leucopenia $\leq 4{,}000/mm^3$ on at least 1 determination (n=4, 5%).

The authors concluded that a trial of parenteral administration of an intermediate dose (15 mg/m^2/week) of MTX is warranted in JRA patients who do not respond to standard doses of 10 mg/m^2/week, whereas a higher dose (30 mg/m^2/week) provides no additional therapeutic benefit.

Tukova et al, 2010

This was a dose-escalation comparative PK study in responders and non-responders, to investigate whether methylenetetrahydrofolate reductase (MTHFR) C677T and A1298C polymorphisms and erythrocyte concentration of methotrexate (EMTX) could serve as predictors of methotrexate efficacy and toxicity in patients with JIA. The study was performed at the University of Prague between 2005 and 2008.

Patients with JIA and disease activity requiring MTX for at least 3 months were recruited for the study. Only patients within the extreme ends of the response spectrum were enrolled, i.e., patients who were full responders to MTX treatment and patients who non-responders. Criteria for inactive disease included: no active arthritis; no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; normal erythrocyte sedimentation rate (ESR) or CRP; and physician's global assessment of disease activity indicating clinical disease quiescence. [Wallace 2004] To be considered a non-responder the patient must have been treated with a minimum weekly dosage of 15 mg/m^2 SC for at least 3 months and at least 3 of any 6 JIA core set variables could not have improved by a minimum of 30% and no more than 1 of the remaining variables could have improved by >30%. Prior to study entry, patients were treated with a dose escalation protocol with initial weekly doses of 7.5-10 mg/m^2 orally, with titration up to 15 mg/m^2 (maximum 20-25 mg). Patients requiring more than 10 mg/m^2 were switched to SC dosing, although SC dosing was also used as the primary route of MTX administration in children under 4 years of age and patients with high disease activity. Most patients received folic acid supplementation (5-10 mg/week), and all were allowed one NSIAD, usually ibuprofen.

The ACR30 was used to define improvement. Efficacy was assessed monthly during dose escalation, and every 3 months once patients were on a stable dose. Outcome measures included number of joints with active arthritis, joints with limited range of motion, physician's global assessment of disease activity, parent's global assessment of the child's overall wellbeing, disability index of the Childhood Health Assessment Questionnaire (CHAQ), and erythrocyte sedimentation rate (ESR).

Genetic analyses and EMTX and folate assessment were performed in 69 patients (30 males, 39 females) with mean age 9 years (range 2.5 -19.6 years), of whom 51 (74%) were classified as complete responders and 18 (26%) as non-responders. In the non-responders, disease activity persisted despite 37% higher subcutaneous dosages of methotrexate than in responders who received the drug orally (n = 24) or subcutaneously (n = 27) ($p < 0.0001$). No significant relationship was found between EMTX and treatment efficacy. Analysis of MTHFR allele and genotype frequencies in relation to response failed to detect any significant association.

The study report does not state whether there were any differences in AEs based on route of MTX administration. Mild to moderate MTX toxicity was noted in a total of 21 patients (30.4%), with GI complaints (mucosal, nausea, vomiting, abdominal pain) in 16, hepatopathy in 3, and alopecia in 2 patients. Other adverse effects (bone marrow suppression, behavioral changes, nodulosis) were not seen. The frequency of overall adverse effects was 29.4% in responders (15/51) and 33.3% in non-responders (6/18) ($p = 0.77$).

Wallace et al, 2012

This was a randomized, partial double-blind, placebo-controlled trial conducted at 15 sites in the United States between May 2007 and October 2010. The trial was funded by NIH but received support from Amgen, the manufacturer of etanercept. The objective of the trial is stated to have been to evaluate whether aggressive therapy early

in the course of RA positive and RA negative pJIA can induce clinical inactive disease within 6 months. However, all patients received open-label SC MTX, with the differences between the treatment arms being the addition of blinded etanercept and prednisolone or their corresponding placebos. As a result, it primarily focused on whether the addition of these medications would change the outcomes in these children when added to SC MTX as a baseline treatment.

Patients were randomized to receive either: (Arm 1, n = 42) open-label MTX (0.5 mg/kg/week, maximum 40 mg) SC, blinded etanercept (0.8 mg/kg/week, maximum 50 mg), and blinded prednisolone (0.5 mg/kg/day, maximum 60 mg, tapered to 0 by 17 weeks, or (Arm 2, n = 43) open-label MTX (same dosage), etanercept placebo, and prednisolone placebo. All patients also received 1 mg/day of folic acid and were allowed to receive NSAIDs as concomitant therapy.

The study design was somewhat complex; a diagram of the study phases is shown in Figure 10. The primary outcome measure was clinical inactive disease at 6 months, defined as no joints with active arthritis; no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; ESR in the normal range; and a physician's global assessment of disease activity score of 0. An exploratory phase lasted up to 12 months after enrollment to determine the rate of clinical remission on medication (i.e., 6 months of continuous clinical inactive disease) at 12 months. Patients who did not achieve an improvement in their ACR Pediatric 70 after 4 months of blinded treatment were considered treatment failures, placed in the exploratory phase of the trial, and treated with open-label medications similar to Arm 1 and placed in the exploratory phase of the trial.

Figure 10. Wallace et al, 2012. Diagram of the study phases.

The trial included 85 children (22 males, 63 females) ages 2-16 years who had disease duration <12 months. The mean age at baseline was 10.5 ± 4.3 years and the mean disease duration was 5.1 ± 0.6 months; 73 (85.9%) patients were white, 5 (5.9%) were black, and 7 (8.2%) were classified as other.

The study did not meet its primary endpoint, i.e., SC MTX plus etanercept and prednisolone was not significantly better than SC MTX alone. After 4 months 30 of 42

patients in Arm 1 and 19 of 43 patients in Arm 2 had achieved at least an ACR Pediatric 70 and continued in the double-blind study. By 6 months, clinical inactive disease had been achieved in 17/42 (40%) in Arm 1 and 10/43 (23%) in Arm 2 (x^2 = 2.91, p = 0.088). After 12 months, clinical remission was achieved in 9 patients in Arm 1 and 3 patients in Arm 2 (p = 0.053).

Three patients experienced SAEs: pneumonia, a psychotic event that resolved with tapering of prednisolone, and septic hip joint. In addition, the following AEs were reported: 4 elevated transaminase levels resulting in study withdrawal; 1 low white blood cell count; 1 peritonsillar abscess; 1 worsening of a pre-existing, recurrent herpes simplex virus infection; and 1 pneumonia. Infection rates were as follows: 18 infections occurred during 247 months of MTX monotherapy (0.87/year); 16 occurred during 297 months of MTX and etanercept therapy (0.65/year), and 17 occurred during 360 months of MTX, etanercept, and prednisolone therapy (0.57/year).

The authors concluded that early treatment with SC MTX with or without additional therapy in children with recent-onset polyarticular JIA can result in clinical inactive disease by 6 months and clinical remission on medication within 12 months of treatment in a substantial proportion of patients.

6.2.2.3 Discussion

As requested by the Agency, the applicant has submitted bioequivalence data and published pediatric literature to support the SC route of administration in patients with pJIA. My review of the data presented supports the proposed dosing administered by the SC route for pJIA. Further, my review of these data does not reveal any specific safety concerns with this route of administration in children beyond those already labeled. Study-10-001 showed bioequivalence between IM and SC administration of MTX, and Study MTX-11-003 showed higher bioavailability with IM and SC dosing than with oral doses above 15 mg. These data are consistent with clinical results of published studies suggesting equal or greater efficacy with SC dosing and no increase in safety concerns. [Arthur 2001; Ravelli 1998; Ruperto 2004; Tukova 2010; Wallace 2012]

Parenterally administered MTX is also recommended for the treatment of pJIA in essentially all published treatment guidelines, including those from the American College of Rheumatology (ACR) [Beukelman 2011], the Working Groups for Children and Adolescents with Rheumatic Diseases in Germany [Niehues 2005], and Pediatric Rheumatology Austria [Niehues & Lankisch 2006]. Further, a survey on the use of MTX by pediatric rheumatologists in Canada showed that most (78.6%) used oral MTX initially, but for more severe cases or when dose escalation was necessary, SC administration was the preferred route. [Chedeville 2007] Therefore, based on the information presented by the applicant, the proposed SC route for administration of MTX in children is acceptable.

My review revealed that, just as for adults, children with pJIA do not require weekly visits for supervision of care and laboratory tests to monitor MTX therapy. Therefore, the condition is appropriate to home treatment using an auto-injector device.

The currently approved recommended dosing regimen for the treatment of pJIA is based on body surface area (BSA), with doses adjusted incrementally every 2 to 4 weeks to achieve an optimal response. The recommended starting dose is 10 mg/m^2 administered once weekly, with dose escalation to 15-30 mg/m^2/week, if needed. The dosing regimen allows for administration of MTX orally, IM, or SC. These doses are supported by doses recommended in clinical guidelines and by my review of the pediatric literature.

Antares has revised the proposed Dosage and Administration section to dose children with pJIA starting with 10 mg and allow dosing increases in 5 mg increments to match the applicant's lowest proposed dose of 10 mg, with availability of higher doses in 5 mg increments up to 25 mg. They state that "patients requiring doses less than 10 mg/week may not be suitable for treatment" with Otrexup, and therefore, doses lower than 10 mg are not proposed. Consistent with this approach, Antares has requested a waiver of pediatric studies below 6 years of age because they state that their proposed product cannot be varied in small dosing increments that would be required for dosing in pediatric patients according to BSA or weight and the product is not likely to be used in a substantial number of patients in this age group.

Since dosing of MTX for the treatment of pJIA is based on BSA, the recommended starting dose should be based on BSA and not based on body weight or a standardized dose, as proposed by the applicant.

It should be noted that MTX doses for patients with pJIA are often lower than the lowest proposed dose of 10 mg weekly, which corresponds (based on a dose of 10 mg/m^2) to a BSA of 1.0 and a weight of about 28 kg (62 lb) (Figure 12). Assuming average height for weight, the 10 mg dose corresponds to 50th percentile for boys around 8 years of age and 50th percentile for girls around 8.5 years of age (Figure 11). Since pJIA is considered to begin around 2 years of age, the lowest starting dose of 10 mg for this product will therefore not be sufficient to allow for use in all pediatric patients. Based on the CDC growth charts (Figure 11), the lowest weight would likely be about 10 kg, which corresponds to a BSA (Figure 12) of 0.47 m^2, and a dose of 5 mg. Intermediate doses of 7.5 mg and 12.5 mg would allow dosing for most age and weight groups. Corresponding weights for standardized doses of 5, 7.5, 10, and 12.5 mg in children are shown in Table 14, using a dose of 10 mg/m^2 and assuming an average height for weight. However, since PREA (triggered by the new route for RA) is satisfied by the fact that MTX is already labeled as safe and effective in children 2 years of age and older with pJIA when administered by the SC route, no additional doses are required under PREA. Nevertheless, the Division will ask the sponsor to consider development of 5 and 7.5 mg doses to fill this gap.

Antares has requested a waiver of PK studies in children of all ages, and a waiver of PK studies in children is appropriate from an ethical perspective because the information is available from data in adults. Antares has also requested a waiver of pediatric studies

for RA/pJIA below 6 years of age because they state that their proposed product cannot be varied in small dosing increments that would be required for dosing in pediatric patients according to BSA or weight and the product is not likely to be used in a substantial number of patients in this age group. However, this is not appropriate. Rather, the pediatric assessment will be considered to be complete for 2 years of age and older, and a waiver will be granted from birth to 2 years of age because the disease does not exist in this age range.

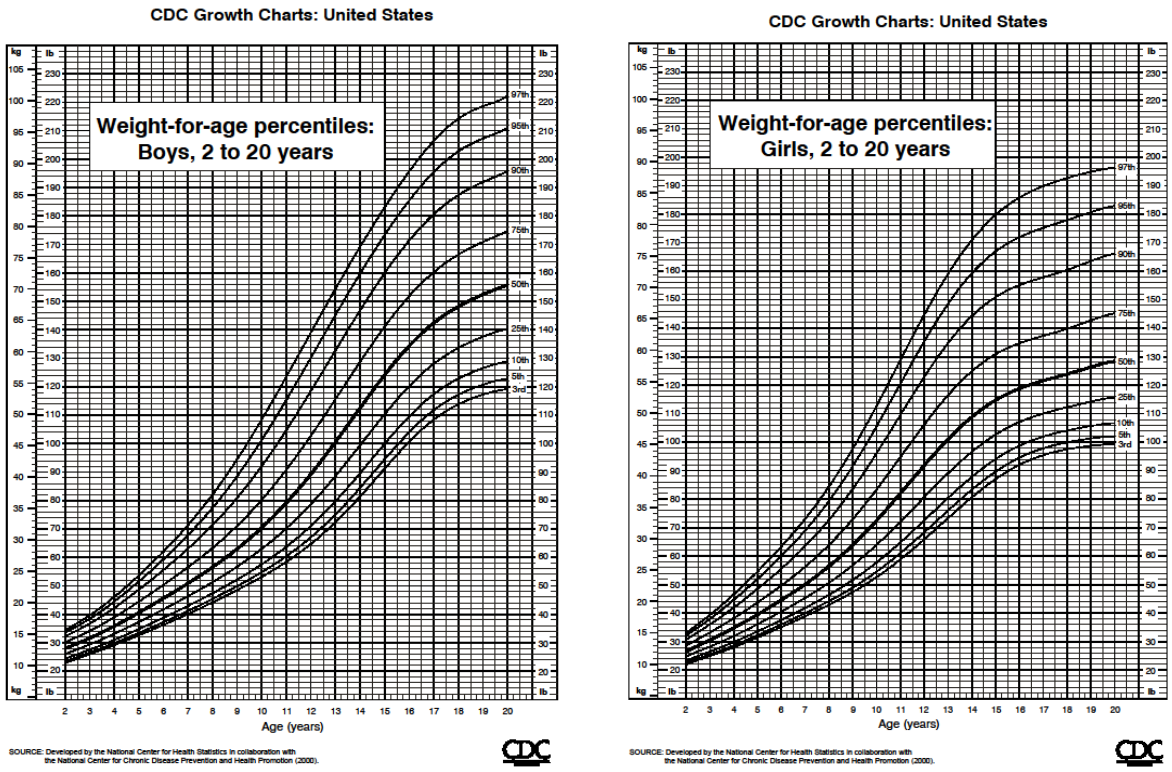

Figure 11. CDC growth charts for boys and girls 2-20 years of age

Source: http://www.cdc.gov/growthcharts/clinical_charts.htm, Accessed 5/1/2013.

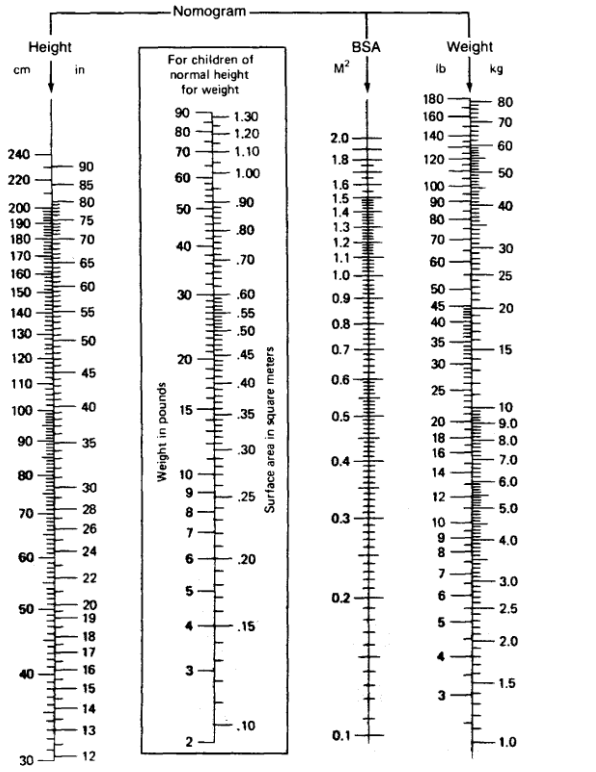

Figure 3–1. West Nomogram (for Estimation of BSA). The BSA is indicated where a straight line connecting the height and weight intersects the BSA column or, if the patient is roughly of normal proportion, from the weight alone (enclosed area). (Nomogram modified from data of E. Boyd by C. D. West; from Vaughan, V. C., and R. J. McKay, eds., *Nelson Textbook of Pediatrics*, 12th ed., Philadelphia: Saunders, 1983.)

Figure 12. Nomogram for estimation of body surface area (BSA)

Source: See notation within the figure.

Table 14. Corresponding weights for standardized 10 mg/m^2 doses in children

Dose mg	BSA	Weight*	
		kg	lb
5	0.5	11.5	25
7.5	0.75	18	40
10	1.0	28	62
12.5	1.25	38	84
*Assumes an average height for weight			

7 Review of Safety

Safety Summary

Two BA/BE studies are submitted, and one actual use study in patients and were reviewed for safety. All were single dose studies, and no unexpected findings were noted.

Review of the literature does not reveal any specific safety concerns beyond those already labeled for oral use in patients with RA, and oral, IM, and SC use in patients with pJIA. Since no clinical trials were submitted and the literature does not add any new safety data for use via the subcutaneous route of administration, the rest of the safety section in this review is blank.

Adult RA care guidelines recommend monitoring with periodic blood counts, creatinine, and liver functions, and these are generally followed in children as well. The recommendations also call for use of folate supplementation while on MTX, although the current labeling for the MTX products state the opposite.

The guidelines also propose that Varicella vaccination should be administered to children who are candidates for MTX because children taking MTX may be immunocompromised and, therefore, may have a more severe clinical course if infected with varicella. [Chedeville 2007] That said, varicella is also a significant risk in adults. With varicella vaccine now a part of the routine childhood vaccination program in the United States, this is less of an issue for children, but many are still not immunized and many adolescents and adults have either not been immunized or have not had the disease. Therefore, this recommendation is suggestive that a Precaution be added to evaluate whether the patient is immune to Varicella and to consider the use of Varicella vaccine before initiating therapy with MTX.

7.1 Methods

NA

7.2 Adequacy of Safety Assessments

NA

7.3 Major Safety Results

NA

7.4 Supportive Safety Results

NA

7.5 Other Safety Explorations

NA

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new information is submitted with this NDA. Methotrexate is already labeled as causing chromosomal damage, although the risk of neoplasia in humans is unknown.

7.6.2 Human Reproduction and Pregnancy Data

No new information is submitted with this NDA. Methotrexate is already labeled as Pregnancy Category X, with a contraindication for use in pregnancy and in breastfeeding mothers.

7.6.3 Assessment of Effects on Growth

No new information is submitted with this NDA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No new information is submitted with this NDA. Methotrexate is already labeled for much higher doses when used for treatment of neoplastic diseases, and for use of leucovorin to diminish the toxicity and counteract the effects in overdosage.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

The applicant has submitted published literature to support the use of the proposed product by the SC route. Since no specific safety concerns were noted, the reviewer teams did not request an evaluation of postmarketing safety reports to see if additional safety concerns have been reported.

9 Appendices

9.1 Literature Review References

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9.2 Labeling Recommendations

9.2.1 Device, Trainer Device, and Instruction Set

This section summarizes the evaluation of the trainer, the actual device, and the instruction set in the proposed IFU, TIFU and on the devices labeling that was performed by the clinical review team as well as reviewers in ONDQA and CDRH. Note that this section is specific to labeling of the instructions for use, and not to other aspects of the labeling.

Examples of the trainer and live devices were requested and evaluated by members of the review teams, including DPARP, DDDP, ONDQA, OSE, and CDRH. All proposed labeling and labeling instructions were reviewed.

9.2.1.1 Proposed Device and Trainer

A placebo live device (i.e. with a needle) was reviewed alongside a trainer device. It was noted that the proposed live device looks very similar to the trainer device. Both have clear plastic body and gray cap (marked as 1) and safety clip (marked as 2). As a result, the actual product is not sufficiently distinguished from the trainer that the two might not be confused. In fact, this reviewer almost made that mistake while looking at the two proposed devices. To address this, the applicant will need to change the color of the two caps to distinguish the live device from the trainer. However, this may not be sufficient. Since the plastic bodies on the trainer and live devices are clear and see-through, the main differences will be the color of the caps and the labeling. Therefore, it

is recommended that the plastic body of the trainer also be changed in such a way as to distinguish it as well.

Additionally, the proposed trainer labeling is not clearly marked that the device a trainer device. The TIFU and trainer labeling uses the terminology [redacted](b) (4), and not the terminology of 'trainer', and it does not it state 'for practice only'. It does say that it contains no needle and no medicine, but the print is too small to clearly identify it as a trainer. The applicant will need to address these issues.

9.2.1.2 Proposed IFU

Upon review, it was noted that the proposed IFU includes pictures (labeled as Figures C and D) showing the device being gripped in a manner opposite to that in which it would be used, and therefore in a manner that could lead to accidental needle sticks. The applicant will be asked to replace these pictures with pictures showing the product being gripped correctly.

It was also noted that the preparations for use do not include washing hands or instructions for preparing the skin for an injection.

9.2.2 PI and PPI

Labeling revisions are ongoing at the time of completion of this document. Therefore, this section only provides a brief summary of the main issues found during initial review of the PI and PPI, and is not intended as a complete review of the labeling.

As is appropriate, the proposed PI is in PLR format, whereas the reference products are not. Changes to PLR format involve significant reorganization of sections of the labeling and revision of certain aspects of the labeling language. That said, the expectation is that this product would not differ substantially from the current reference products based on such a reorganization. In fact, an effort will be made not to update the labeling for this product to today's science, which might make the labeling for this product differ substantively from those of the reference products. [redacted](b) (4) Wording will therefore be kept the same as much as possible, although it may appear in different sections because of the PLR format differences.

However, because the product is an auto-injector intended only for SC administration and is available only in limited dosage strengths, the Indications and Dosage and Administration sections will necessarily differ substantively from the current labeling, with Limitations of Use added for other routes of administration and for doses that cannot be achieved by the proposed product. For example, the current dosing recommendation for treatment of pJIA is based on body surface area (BSA). Since many of the doses that may be required in younger children will not be available or cannot be achieved with use of this product, the D&A recommendations will need to be significantly revised.

In a number of instances, the applicant has taken the opportunity to make revisions to the labeling that are not necessarily appropriate, and the PI will be revised to correct these oversteps.

The PI for the reference products use the older terminology of pJRA, and the applicant as continued to use that approach for the labeling of this product. The terminology will be changed to match that currently being used by the Agency [and the professional community]; therefore, pJIA will be used instead.

9.3 Advisory Committee Meeting

An Advisory Committee meeting was not held during the review of this product.

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/s/

PETER R STARKE
08/19/2013

THERESA M MICHELE
08/20/2013

CLINICAL FILING CHECKLIST

NDA:	**204-824**
Drug Name:	**Methotrexate Auto-injector**
Applicant:	**Antares Pharma, Inc.**
Type:	**NDA**
Stamp Date:	**December 14, 2012**
PDUFA Date:	**October 11, 2013**
Review Date:	**February 8, 2013**

This is a 505(b)(2) new drug application submitted by Antares Pharma, Inc. for a drug/device combination of Methotrexate (MTX) Injection in an auto-injector, referencing Methotrexate Sodium Injection EQ 50 mg base/2mL (NDA 11-719). MTX is a folate analog metabolic inhibitor currently indicated for the treatment of malignancies, severe psoriasis, and rheumatoid arthritis (RA) including polyarticular-course juvenile rheumatoid arthritis (JRA). The proposed product is a single-use, single-dose, pre-filled, auto-injector (called a Medi-Jet) containing 10, 15, 20, or 25 mg of MTX as a sterile preservative-free solution for subcutaneous injection. The product includes a single-dose syringe with a 27-gauge, ½ inch needle that delivers a fixed volume 0.4 mL per injection. The needle is protected before use by a needle safety guard and safety cap, and after use by a soft needle shield.

The proposed indications for this product include RA, JRA, moderate to severe psoriasis[1], but not treatment of malignancies. The applicant has requested a proposed Trade Name of Otrexup™. Because the applicant has requested an extension of the psoriasis indication, discussion is underway with regard to whether the application will be administratively split by indication, with Original 1 for RA and JRA to be reviewed in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), and Original 2 for moderate to severe psoriasis to be reviewed in the Division of Dermatology and Dental Products (DDDP). However, in the interim, DDDP has provided DPARP with the following comment to forward to the applicant:

> We note that you have proposed labeling for moderate psoriasis. As a 505(b)(2) application, the indication for your product should match that for the listed product, as appropriate, given the limitations of an auto-injector product intended for home administration. Provide revised labeling that matches the labeled indication for psoriasis for the reference product.

The clinical program included 4 clinical studies, and was discussed over multiple interactions with the Agency. Clinical pharmacology was assessed in 2 open-label, randomized, 3-way crossover bioavailability studies (MTX-10-001 and MTX-11-003) designed to compare systemic exposure when dosed subcutaneously (SC) via the Medi-Jet with SC and IM dosing via a needle and syringe (MTX-10-001) and to compare SC administration with the Medi-Jet dosed in the abdomen and thigh with oral administration (MTX-11-003), device handling and safety was assessed in 1 multicenter, open-label, single-dose study (MTX-11-002), and usability of the device was assessed in 1 summative device usability study using a dummy device (MTX-11-004). Additionally, the application includes a literature review summarizing the efficacy and

[1] The reference product does not include an indication for treatment of moderate psoriasis.

safety of the new route of SC administration because SC administration is not currently in the label for treatment of either RA/JRA or psoriasis[2].

The application will trigger PREA because as a new drug-device combination it will have a new dosing regimen, and because of the new route of administration. The applicant has requested a waiver of pediatric PK studies in all ages, and specifically for pediatric studies in children less than 6 years of age because the product cannot be varied in small dosing increments that would be required for dosing in pediatric patients according to BSA or weight and the product is not likely to be used in a substantial number of patients in this age group.

The application is all-electronic in eCTD format. There are no missing data elements, and the application is fileable from a clinical perspective. There is one 74-day comment for the application.

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic in eCTD format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Clinical overview and clinical summaries
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Clinical overview and clinical summaries
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Approved Product. Risk-benefit submitted in the clinical overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2) referencing Methotrexate Sodium Injection EQ 50 mg base/2mL (NDA 011719)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to			X	Approved drug product.

[2] The reference product includes oral, IM, IV, and intrathecal routes of administration, but not SC dosing.

	Content Parameter	Yes	No	NA	Comment
	determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:				Dose already established.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			X	
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?				
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[3]) been exposed at the dose (or dose range) believed to be efficacious?			X	Approved drug product.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been			X	

[3] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	Content Parameter	Yes	No	NA	Comment
	exposed as requested by the Division?				
23.	Has the applicant submitted the coding dictionary[4] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA 13.1
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The applicant has submitted a request for a waiver for patients less than 6 years of age because the dosage cannot be varied for this age group and the product is not likely to be used in a substantial number of patients in this age group.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			For PK studies
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			For PK studies
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	No efficacy studies
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	No efficacy studies
CASE REPORT FORMS					

[4] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. We note that you have proposed labeling for moderate psoriasis. As a 505(b)(2) application, the indication for your product should match that for the listed product, as appropriate, given the limitations of an auto-injector product intended for home administration. Provide revised labeling that matches the labeled indication for psoriasis for the reference product.

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/s/

PETER R STARKE
02/08/2013

THERESA M MICHELE
02/08/2013