CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204824Orig2s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 19, 2013
From	Sarah Yim, M.D. Associate Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	204824/ original
Applicant	Antares Pharma, Inc.
Date of Submission	December 14, 2012
PDUFA Goal Date	October 14, 2013
Proprietary Name / Established (USAN) names	Otrexup™ / methotrexate injection
Dosage forms / Strength	10 mg/0.4 mL autoinjector, 15 mg/0.4 mL autoinjector, 20 mg/0.4 mL autoinjector, and 25 mg/0.4 mL autoinjector
Proposed Indication(s)	1. Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis 2. Moderate to Severe Psoriasis
Recommended:	*Approval, with revisions to proposed labeling*

1. Introduction

This is a 505(b)(2) new drug application (NDA) for a drug/device combination product (tradename: Otrexup) consisting of an injectable methotrexate (MTX) formulation in a single-use prefilled autoinjector intended for subcutaneous administration only. Four strengths are proposed: 10 mg, 15 mg, 20 mg, and 25 mg, each in a fixed volume of 0.4 mL. No MTX autoinjectors have yet been approved in the US.

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. MTX is currently available in 2.5 mg tablets (multiple companies), and 5, 7.5, 10, and 15 mg tablets (Barr). Injectable MTX is available from multiple companies in varying quantities of 25 mg/mL solution. Currently approved indications and routes of administration include neoplastic diseases (oral, intramuscular, intravenous, intra-articular, and intra-thecal routes), rheumatoid arthritis (oral route), polyarticular course juvenile rheumatoid arthritis (oral, intramuscular, subcutaneous routes), and severe psoriasis (oral, intramuscular, intravenous routes).

In this NDA, the applicant is seeking approval of their product and the subcutaneous (SC) route of administration for the rheumatoid arthritis (RA) and psoriasis indications, as well as the polyarticular juvenile arthritis indication which is already approved for subcutaneous administration in other parenteral MTX labels. The applicant is also seeking expansion of the psoriasis indication to include "moderate" psoriasis. To support the new route and indication, the applicant is relying on:

- Information in the published literature supporting the safety and efficacy of subcutaneously administered MTX for RA and psoriasis, as well as FDA's previous finding of safety and efficacy of MTX in these indications
- A bioequivalence (BE) study (MTX-10-001) showing SC MTX administered in the abdomen or thigh via the applicant's autoinjector is bioequivalent to approved parenteral MTX administered by needle and syringe via the SC or IM routes, and
- A relative bioavailability (BA) study (MTX-11-003) that showed equal or greater bioavailability of MTX SC administered via the applicant's autoinjector compared to the exposure obtained with orally administered MTX tablets.

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

Because the applicant is proposing labeling that differs from the approved listed drugs pertaining to psoriasis, this application was administratively split, and the review of the psoriasis-related proposals is being performed separately by reviewers from the Division of Dermatology and Dental Products (DDDP). This review will focus on the remainder of the application, and the RA indication in particular.

2. Background

In the 1940's, folic acid antagonists were first postulated as potential treatment for leukemias, with the first successful drug being the folate analog aminopterin, demonstrated by Sidney Farber in 1947 to induce remission in children with acute lymphocytic leukemia. Other folate analogs, such as MTX, soon followed in the 1950's. Due to methotrexate's improved tolerability and easier production, it became the preferred treatment for a number of malignancies and neoplasms.

Although aminopterin was investigated as a treatment for RA as early as 1951, and MTX as early as 1962, use of MTX for RA languished until the 1970's and 1980's. The reason for this disinterest is not known, but is postulated by some to be due to a greater enthusiasm for corticosteroids during that time frame. Throughout the 1980's interest in MTX blossomed, prompting an increasing number of clinical studies and controlled trials of MTX, and culminating in the FDA approval of MTX for RA in 1988.[1] Although the pivotal trials for the

[1] Coury FF and ME Weinblatt, Clin Exp Rheumatol 2010; 28 (Suppl 61):S9-S12.

approval of MTX evaluated oral MTX, the gastrointestinal tolerability issues, relatively poor oral absorption of MTX at higher doses, and ready availability of parenteral MTX quickly led practitioners to use parenteral MTX as an alternative for patients who were not tolerating oral MTX.[2] However, the labels of currently approved MTX products only specifically mention the subcutaneous route of administration for the polyarticular-course juvenile rheumatoid arthritis (now termed polyarticular juvenile idiopathic arthritis, or PJIA) indication, and only oral dosing is mentioned for RA.

Regulatory history

The Agency had multiple pre-submission interactions with Antares between 2009 and 2012, including several meetings within the Center for Drug Evaluation and Research (CDER) 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 Chemistry, Manufacturing, and Control (CMC) issues (5/14/2012), and one meeting with Center for Devices and Radiological Health (CDRH) to discuss a possible Investigational Device Exemption (IDE) submission for the proposed auto-injector product (4/25/2012).

Antares was asked to bridge between the SC, IM, and oral routes of administration as well as to 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]

At the EOP2 meeting in September 2011, the Division provided clarification regarding expectations for the bridging strategy, which Antares was advised should include a relative bioavailability bridge between the subcutaneous and oral routes in addition to the IM route, as approved dosing for RA is via the oral route of administration. The Division, in conjunction with CDRH consultants, also provided advice regarding device development. In addition to Human Factors studies, which are simulated use studies required by CDRH, the Division expressed the expectation to have real-use data in RA patients to assess for potential design flaws/mechanical failures related to the autoinjector.

In post-EOP2 written responses in February 2012, the Division provided requested feedback on the nonclinical local tolerance study (additional SC local toxicity study not necessary), the bridging oral/SC bioavailability study, and the real-use (or "actual-human-use") study.

At the pre-NDA meeting in November 2012, Antares specifically asked whether the proposed clinical development plan would support (b) (4) severe psoriasis, and the Division responded that to obtain an indication (b) (4) arthritis, 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. Expectations regarding the NDA content and format were also discussed.

[2] Visser et al, Ann Rheum Dis 2009 Jul; 68(7):1086-93.

3. CMC/Device

Primary CMC reviewer: Arthur B. Shaw, Ph.D.; CMC Supervisor: Prasad, Peri, Ph.D.
CDRH General Hospital Devices Branch: Jacqueline Ryan
Product Quality Microbiology Reviewer: Erika Pfeiler, Ph.D.

- **General product quality considerations**

Drug substance

Methotrexate is a yellow to orange, (b) (4), insoluble in water. The CMC information for methotrexate is covered in DMF (b) (4), which has been reviewed many times and has been found acceptable. A recent amendment contains a number of changes in the manufacturing which have been reviewed and found acceptable. The specifications and testing for the drug substance are provided in the NDA, both in terms of Certificates of Analysis (COAs) from the supplier and in terms of complete testing by the manufacturer of the drug product. The testing conforms to both the United States Pharmacopeia (USP) and the European Pharmacopeia (Ph.Eur.). All process-related impurities are well-controlled and degradation is minimal. The major degradant, (b) (4), is a metabolite of methotrexate and has no additional toxicity. The applicant has proposed a reduced testing program for release of the drug substance by the drug product manufacturer after the first commercial batches. The CMC review team has determined this to be acceptable.

Drug product

The drug product is formulated by titrating with sodium hydroxide to a neutral pH, (b) (4) (b) (4) methotrexate. There are no novel excipients. No preservatives are added, since the drug product is intended for single use in a custom injector. The drug product solution is sterile (b) (4) glass syringes and closed with a plunger with a rubber stopper. No leachables have been observed from the packaging components in direct contact with the drug product. The preparation, including sterilization, of the syringes and the plunger are covered in DMFs which have been reviewed by the product quality microbiology reviewer, Dr. Pfeiler, and found to be acceptable. The sterility aspects of the drug product manufacturing have been reviewed by Dr. Pfeiler and found to be acceptable.

The drug is formulated at four different strengths to be delivered at a fixed volume of 0.4 mL by the device. The drug product specifications are adequate to support different expiration dates for different strengths. 24 months for 10 mg/0.4 mL and 15 mg/0.4 mL and 33 months for 20 mg/0.4 mL and 25 mg/0.4 mL. The controlling parameter is the appearance of the degradant (b) (4) which is controlled at NMT (b) (4) %. This level of the impurity has been found to be acceptable by the pharm/tox reviewer, Dr. Andrew Goodwin.

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

Device

The pre-filled syringes (PFS) are loaded manually into a custom device, covered by a device master file (MAF (b) (4)). The device along with the syringe inside is the to-be-marketed product, a drug-device combination. The device is designed to deliver a fixed volume with no measuring by the patient. The needle is completely covered when not in use so that the chances of accidental injection or exposure to the needle are minimized. When the device is activated by pressure against the skin, the force of delivery is controlled by a spring in the device, not by the patient. The specifications call for a delivery time of (b) (4) which is adequate. The needle is the correct length (exposed needle length approximately 2.5 mm) to ensure that the drug is administered subcutaneously. After the device is actuated there is no drug remaining in the syringe and there are no exposed needles. A demonstration device, containing no drug, will be supplied by the company to health-care professionals to train patients in the use of the product. No major deficiencies were found by the CDRH reviewer Dr. Ryan for MAF (b) (4).

Two use and handling studies were performed to evaluate the ability of patients to follow the instructions for use and use the device (MTX-11-002) and to evaluate the usability of the device (without medicine or needle) in a simulated use setting (MTX-11-004). These studies will be described in further detail in Section 8 below.

- **Facilities review/inspection**

The drug substance is manufactured at (b) (4) which has a satisfactory CGMP status as of (b) (4). The retest date of (b) (4) months is supported by data in the DMF.

The prefilled syringe manufacturer is (b) (4), which was found satisfactory from a cGMP point of view as of (b) (4).

The site for assembly, packaging and labeling of the combination product is (b) (4) which was found satisfactory from a cGMP point of view as of (b) (4).

- **Other notable issues (resolved or outstanding)**

The CMC review team has concluded that the application may be approved from a CMC perspective.

4. Nonclinical Pharmacology/Toxicology

Primary pharmacology/toxicology reviewer: Andrew Goodwin, Ph.D.;
Pharmacology/Toxicology team leader: Timothy Robison, Ph.D., DABT

- **General nonclinical pharmacology/toxicology considerations**

The pharmacologic and toxicologic properties of methotrexate are well known from the 60 years of clinical use in humans. No nonclinical studies were required for NDA submission with the exception of the toxicology evaluation of leachables and extractables from the drug product, which included seven organic compounds and three metals. The data were reviewed by Dr. Goodwin and determined to be acceptable.

- **Other notable issues (resolved or outstanding)**

The applicant submitted a small, non-GLP study in Gottingen minipigs. Commercially available methotrexate injection (25 mg/mL) or sodium chloride for injection was administered by needle and syringe or autoinjectors, in a cross-over fashion at Days 1 and 8. Minor transient injection site reactions were associated with the autoinjector whether it administered MTX or saline. At the PIND meeting of February 2009, the Division advised the sponsor that a four-week local toxicity study with full histopathology in one species would be expected to support the safety of the subcutaneous route of administration. However, in subsequent communications, the Division noted that if there were adequate human data to support the safety of SC MTX, the four-week nonclinical local toxicity study would not be necessary.

The pharmacology/toxicology team has concluded that as the safety profile of methotrexate is well-established based on clinical experience by multiple routes of administration, including the subcutaneous route, no nonclinical safety studies are required and the data submitted are adequate to support approval of the NDA from the nonclinical perspective.

5. Clinical Pharmacology/Biopharmaceutics

Primary clinical pharmacology reviewer: Sheetal Agarwal, Ph.D.
Clinical pharmacology team leader: Satjit Brar, Pharm.D, Ph.D

- **General clinical pharmacology/biopharmaceutics considerations**

This NDA references three previously approved methotrexate products: NDA 11719 (Hospira's methotrexate injection, the reference listed drug for parenteral MTX products), NDA 8085 (Dava's oral methotrexate tablets, the reference listed drug for oral MTX products), and ANDA 40-632 for Bedford's methotrexate injection, which was used for the applicant's bioequivalence study due to difficulty in sourcing the Hospira MTX injection product.

Study MTX-10-001 evaluated the PK of Antares' MTX autoinjector (tradename Otrexup) compared to approved methotrexate injection administered by needle and syringe. Results of this study showed that the Cmax and AUC of methotrexate, after administration via the Antares MTX autoinjector, are similar to the same dose of subcutaneous (SC) or intramuscular (IM) injections of the approved parenteral MTX product. The 90% confidence intervals of the ratios of the geometric least-squares (LS) means of dose-normalized Cmax and AUC parameters for the test product (Antares MTX autoinjector) were within the bioequivalence range of 80% to 125% when compared to the SC and IM administration of approved parenteral MTX.

Study MTX-10-003 evaluated the PK of the Antares MTX autoinjector as compared to methotrexate oral tablets. The intent of this study was to allow for bridging to approved RA doses and inform SC dosing. Results indicated that methotrexate exposure (AUC) was higher with the Antares MTX autoinjector compared to oral methotrexate at all dose levels tested (10, 15, 20, and 25 mg). However, the quantitative difference in systemic exposure was not the same across the doses, and ranged between ~13% higher (at the 15 mg dose) to 36% higher (at the 25 mg dose). This is consistent with the known properties of orally administered MTX; oral bioavailability drops at high doses, likely due to a saturable intestinal active transport absorption mechanism with low capacity characteristics.[3] This study also provided data to show that methotrexate exposure with the Antares MTX autoinjector is similar when administered in the abdomen or thigh and that both these sites can be used as potential injection sites.

Other relative bioavailability studies of SC MTX in the literature

Jundt et al. 1993.[4] This study evaluated the relative bioavailability of low dose MTX administered as tablet, oral solution, and SC injection to that of IM injection in patients with rheumatoid arthritis (RA). Twelve patients meeting the American College of Rheumatology criteria for RA had serial blood MTX concentration samples drawn over a 24-h period after receiving their normal weekly MTX dose. Relative bioavailability of the tablet and oral solution formulations was determined by comparison of the AUC for the 2 different oral formulations as a percentage of the AUC for IM injection. Also, relative bioavailability of the SC formulation was compared to IM in 6 of the patients. Results showed that bioavailability of the oral solution and oral tablet were similar, but approximately 15 percent less than the IM. The relative bioavailability of MTX via SC and IM routes was similar.

Hoekstra et al. 2004.[5] This study evaluated the bioavailability of higher oral doses of MTX compared to SC MTX. A pharmacokinetic analysis was performed in 15 patients with RA taking a stable dose of MTX (> or = 25 mg weekly). Separated by 2 weeks, a pharmacokinetic analysis was performed in each patient after oral and subcutaneous administration of the same dose of MTX. The median MTX dose was 30 mg weekly (range 25-40 mg). The mean

[3] Abolmaali et al., Cancer Chemother Pharmacol, 2013, 71:1115-1130.
[4] Jundt JW et al., J Rheumatol 1993 Nov; 20(11):1845-9.
[5] Hoekstra M et al., J Rheumatol 2004 Apr; 31(4):645-8.

bioavailability after oral MTX was 0.64 (range 0.21-0.96) compared to subcutaneous administration (i.e. SC administration resulted in 26% higher exposure). There was a statistically significant difference in the bioavailability of the two administration regimens.

Thus study MTX-10-003 results were consistent with the oral/SC relative bioavailability of MTX reported in the published literature.

- **Other notable issues (resolved or outstanding)**

Clinical study site inspections were not requested for the two relative bioavailability (BA) studies mentioned above, as the studies were not designed to show bioequivalence as a basis for approval, but rather were intended to provide a PK bridge to the approved products to be able to utilize the Agency's previous findings of safety and efficacy with the approved MTX products. Therefore the relative BA studies were not considered pivotal and inspections were not requested.

The clinical pharmacology team finds the NDA acceptable for approval from a clinical pharmacology perspective.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Primary clinical reviewer: Peter Starke, M.D.
Statistical reviewer: Joan Buenconsejo, Ph.D.

- **Efficacy review**

As discussed in Section 5 above, compared to oral MTX tablets, the exposure (AUC) of methotrexate given subcutaneously via the Antares MTX autoinjector was approximately 13 to 36% higher, depending on the dose. Therefore the efficacy of SC MTX could be presumed based on exposures that are equal or greater than exposures via the approved oral route of administration. This is also based on the assumption that clinically significant immunogenicity is unlikely with the change in route of administration, since this is a small molecule chemical.

In addition to this pharmacokinetic (PK) bridge, the applicant summarized the clinical efficacy and safety data on SC MTX from the literature, as requested by the Agency. This literature includes one randomized, controlled trial (Braun, 2008) in addition to multiple other studies.

Braun et al, 2008.[6] This was a 6-month randomized, double-dummy, controlled trial in 384 MTX-naïve RA patients who were randomized 1:1 to either 15 mg of SC MTX + placebo oral tabs or 15 mg of oral MTX + placebo SC injection. Injections were administered via prefilled syringe. At Week 16, patients who did not meet 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. These patients were counted as nonresponders for the Week 24 endpoint. Results at Week 24 were as follows:

Table 1: SC vs. Oral MTX, ACR Responses at Week 24

	ACR20	ACR50	ACR70
SC MTX	78%*	62%	41%*
Oral MTX	70%	59%	33%

*diff vs. oral p <0.05

Similar results were observed for the components of the ACR response criteria, such as number of swollen joints and number of tender joints, and Health Assessment Questionnaire Disability Index (HAQ-DI), as well as for another composite efficacy measure, the Disease Activity Score (DAS)-28. At Week 16, 30 patients were switched from 15 mg orally to 15 mg SC with an additional 30% of them achieving an ACR20 response at Week 24. Twenty-two patients were switched from 15 mg to 20 mg SC with an additional 23% of them achieving an ACR20 at Week 24.

Supportive studies

Parker et al. 2004.[7] 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 8 RA patients (5 females) 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. 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.

Thornton et al. 2008.[8] This was a prospective study to investigate the effectiveness of SC MTX in a cohort of patients for whom oral MTX was ineffective or not tolerated. Thirty patients were enrolled and assessed at 3 and 6 months after switching to SC MTX. Based on

[6] Braun J et al., Arthritis Rheum 2008; 58(1):73-81.
[7] Parker CT et al., J Am Osteopath Assoc. 2004; 104(1):7-8.
[8] Thornton C et al. Rheumatology (Oxford). 2008; 47(9):1438.

European League Against Rheumatism (EULAR) response criteria, 20/27 (74%) of patients had a good response at 3 months and 13/25 (52%) had a good response at 6 months.

Bakker et al. 2010.[9] As part of a 2-year prospective, randomized, open-label multi-center trial in Netherlands comparing two MTX regimens intended to evaluate the benefit of "tight control" of RA patients, 57/151 patients were switched from oral to SC MTX (21 due to adverse effects on a mean oral dose of 25 mg/week, and 36 due to lack of efficacy at a maximum dose of 30 mg/week). After switching to SC MTX, 36 patients experienced additional improvement by 1 and 4 months post switch and 21 did not.

Several other articles were submitted describing the SC MTX experience in different groups of RA patients, ranging from 8 to 132 patients, and appear generally similar to the SC experience described in the articles mentioned above. These additional articles are described in detail in Dr. Starke's clinical review.

The applicant also summarized the literature supporting subcutaneous MTX administration in children with juvenile idiopathic arthritis (JIA). These are also described in Dr. Starke's review. However, as the approved MTX labels already note subcutaneous administration as an available route of administration for JIA, evidence to support the efficacy of this route of administration in JIA is not necessary and will not be described here. See Section 10 below for further details pertaining to the PJIA indication.

- **Notable efficacy issues both resolved and outstanding**

Given that the SC route of administration results in 13 to 36% higher exposure compared to orally administered MTX, the efficacy of SC MTX may reasonably be extrapolated from the evidence supporting the efficacy of orally administered MTX for RA. This conclusion is additionally supported by the randomized controlled study by Braun et al (which showed that SC MTX at the same dose resulted in a similar or higher proportion of ACR responders compared to oral MTX), and other published literature. Dr. Starke and I are in agreement that there is adequate evidence to support the efficacy of the subcutaneous route of administration of MTX in RA.

8. Safety

- **Safety summary**

The range of doses currently approved for MTX are summarized in Table 2 below.

[9] Bakker MF et al. Ann Rheum Dis. 2010; 69(10):1849-52.

Table 2: Approved Doses of MTX

Indication	Dose Regimen
Trophoblastic diseases	15 to 30 mg daily oral or intramuscularly (IM) x 5 days; repeat as needed after rest period
Leukemia	Induction: 3.3 mg/m^2 (6 to 7 mg for avg. US adult[10]) daily until remission Maintenance: 30 mg/m^2 (54 to 61 mg for avg. adult) two times/week oral or IM or 2.5 mg/kg (187 to 217 mg for avg. adult) intravenously (IV) every 14 days
Lymphoma	Burkitt's Stage I-II: 10 to 25 mg/day orally for 4 to 8 days; repeat as needed after rest period; Stage III: with other therapy: 0.625 to 2.5 mg/kg daily (~47 to 217 mg)
Mycosis fungoides	5 to 50 mg once weekly or 15 to 37.5 mg twice weekly
Osteosarcoma	12 to 15 grams/m^2 (~21 to 31 grams for avg. US adult) IV, to achieve serum concentration of 1000 µM, with leucovorin rescue
Psoriasis	10 to 25 mg/week oral, IM or IV, adjust to response, >30 mg/week not recommended
Adult RA	Only starting dose is specified: 7.5 mg orally once weekly in single or divided dose, adjust to response.
Polyarticular-course Juvenile Rheumatoid Arthritis (PJIA)	Start 10 mg/m^2 once weekly and adjust to response. For doses 20 to 30 mg/m^2/week (0.65 to 1.0 mg/kg/week), IM or SC dosing may be better tolerated.

Source: Hospira MTX Prescribing Information

The experience with MTX over all the approved indications covers a much wider range of doses than those associated with RA, which by convention does not typically exceed 30 mg/week.[11] The toxicity of MTX is well known, based on the high doses of it used to treat neoplastic diseases—an order of magnitude higher (i.e. 20 to 30 grams) for the treatment of osteosarcoma, which approximates the maximum tolerated dose, and requires leucovorin rescue. Subcutaneous administration of MTX for RA involves doses at the low end of the MTX therapeutic range, and a 36% higher exposure with the Antares MTX autoinjector (study MTX-10-003) would not be expected to result in significant additional toxicities.

Although the most common toxicities observed with MTX are gastrointestinal toxicities such as nausea, stomatitis, and gastrointestinal upset, concerns were raised about the potential for long-term hepatotoxicity due to the observation of elevated liver enzymes, particularly in the psoriasis experience of the 1960's. This led to a multiple-decades' practice of regular liver enzyme tests and intermittent liver biopsies. Liver biopsies fell out of favor in rheumatology practice as it became evident that liver damage was not likely, even with long-term MTX use (e.g. 10 years).[12] However, it is still standard practice to perform liver biopsies in high risk psoriasis patients, as a higher proportion of these patients appear to develop progression of liver damage.[13] Other potential serious toxicities with MTX include myelosuppression and pulmonary toxicity (i.e. pneumonitis). Renal impairment increases the risk of methotrexate toxicity, particularly myelosuppresion.

[10] Average height and weight of US adult: http://www.cdc.gov/nchs/fastats/bodymeas.htm

[11] Visser, et al. Ann Rheum Dis 2009; 68:1086-1093.
[12] Kremer JM. J Rheum 1996; 44:34-37
[13] Barker, et al. J Eur Acad Dermatol Venereol. 2011 Jul; 25(7):758-64.

Based on these concerns, it is standard practice to get baseline liver enzymes, creatinine, complete blood count, and chest x-ray and to screen patients for risk factors such as regular alcohol intake. In addition, 5 mg of folic acid per week is given to reduce the incidence of GI toxicity and bone marrow suppression. Regular monitoring of liver enzymes, creatinine, and blood count is performed for the duration of therapy.[11]

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests**

The safety experience specific to the Antares MTX autoinjector product is limited to three single-dose studies:

- Study MTX-10-001, an open-label single-dose, 3-way crossover PK study comparing systemic MTX exposure following SC administration with the Antares MTX autoinjector, SC administration of approved MTX using needle and syringe, and IM administration of approved MTX using needle and syringe, in a total of 36 patients ≥18 years with RA, who were on MTX treatment for at least 3 months prior to the study. 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.
- Study MTX-11-003, an open-label single-dose 3-way crossover bioavailability study comparing systemic MTX exposure following SC administration with the Antares MTX autoinjector into the thigh or abdomen with the same dose of approved MTX tablets administered orally. This study included 50 patients ≥18 years with RA who were on MTX treatment for at least 3 months prior to the study. One subject experienced an SAE of myocardial infarction that resulted in death. This patient, on MTX 25 mg, was a 79 year old male with a history of RA, hypertension, CHF, MI, and coronary artery disease. One subject, a 72 year old male on MTX 15 mg, experienced an SAE of sick sinus syndrome, which was severe but considered unrelated to study drug and resolved by the end of the study. One subject (on 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.
- Study MTX-11-002 was an open-label, single-dose study that evaluated the ability of adult patients with RA to use the Antares MTX autoinjector device and its instructions, after having received training in the use of the product. Patients were required to have been on MTX for at least 3 months prior to enrollment and were assigned to their same MTX dose in the study. A total of 101 RA patients were enrolled. One patient on 20 mg MTX 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 reported.

Based on these limited single-dose data, no new safety signals were identified.

- **Immunogenicity**

Immunogenicity was not assessed. As a small molecule chemical, MTX has not been, nor would it be expected to be, associated with significant immunogenicity.

- **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)—a Human Factors study. These studies are intended to support the conclusion that the device can be used safely if approved, but are not informative to prescribers and will not be described in labeling.

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 the Antares MTX auto-injector device and its associated instructions after having received training in the use of the product.
Training consisted of standardized verbal instructions, a demonstration of the proper use of the device, and review of the written patient instructions.

After the training and an assessment of the injection site, patients were asked to independently self-administer a single dose of MTX SC via the Antares autoinjector device using the written instructions (IFU) for guidance. All patients (n = 101) 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. No significant safety concerns were observed. However, the Division of Medication Error Prevention and Analysis (DMEPA, Teresa McMillan) reviewed the study results and does not believe the study reflects how a user would perform under "real world" use because there was no decay time between training and self-injection.

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 Antares MTX auto-injector device and its associated documentation, including the IFU, on-device label, and health care provider (HCP) training script. 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.

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.

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.

Per report, 81 of 83 trials were successful. One patient withdrew the device prematurely from the pad after being startled by the click, and one healthcare professional pointed the needle end of device toward her own hand (although she initially appeared to be overwhelmed by the IFU, and may not have understood the instructions). This person was successfully able to read and understand the IFU and administer the device on the second try.

Dr. Starke expressed a concern regarding the potential safety issue related to the error of holding the device upside down, and wondered whether additional safeguards need to be put into place to prevent similar instances in the clinical setting. DMEPA reviewed the study results and has proposed changes to the IFU to address the 2 failures and "close calls" for the critical tasks. These close calls primarily pertained to holding the device for the required delivery time (n=11), using the device with inadequate force to retract the needle shield (n=10), and confusion regarding the location and removal of the safety cap (n=5). The CDRH Human Factors Reviewer (Quynh Nguyen) reviewed MTX-11-004 and did not identify any concerns with the study, concluding that the "user interface is optimized, and does not require any additional modifications."

- **Safety Conclusions**

Dr. Starke has concluded that there is adequate evidence to support the safety of MTX administered subcutaneously for RA, and I concur. The basis for the conclusion that the subcutaneous route of administration would not negatively impact the safety of methotrexate is the modest increase in exposure observed in relative bioavailability studies (the applicant's and in the literature), in the context of the dosing of methotrexate for RA, which is in the lower end of the therapeutic range. The limited single-dose data derived from study MTX-11-002 would

not be considered adequate evidence of safety of a new route of administration for a chronically administered drug.

Regarding the safety of the device, Dr. Starke and DMEPA expressed concerns that the instructions for use, container labeling, and device itself may not be optimized, in light of the close calls in the human factors study. However, CDRH concluded that the study was acceptable and that modifications to the device were not warranted.

In evaluating the acceptability of the device, I considered the following:

- Methotrexate will not be administered under emergency conditions, thus use of the device does not have to be immediately intuitive.
- Methotrexate is a chronically administered drug. Although some errors may occur when users are unfamiliar with the device, this would be likely with any device, and the potential concerns raised by the "close calls" in the human factors study will not be an issue when patients/providers become familiar with use.
- The human factors study showed a 98% success rate, despite the "close calls".
- The "close call" issues were more likely to result in lack of medication administration, or partial medication administration. Because methotrexate is not an emergency medication, and is not a narrow therapeutic index product, lack of, or partial, administration would not be expected to result in clinically significant concerns.
- The worst case scenario would be an inadvertent needlestick into the hand due to holding the device the wrong way, as was observed in one of the human factors study failures. The device is clearly labeled with a large orange arrow and words to show which end is the needle end, but the potential for human error always exists. In the worst case scenario, no severe or permanent injury would be expected to result from the inadvertent needlestick, due to the limited exposed needle length and fine gauge needle, and the relatively benign characteristics of the MTX parenteral formulation—neutral pH and tonicity, preservative-free, and standard excipients that would not pose a concern even if accidentally administered intra-arterially, or in the tendons or nerves of the hand.
- Although Dr. Starke recommends different coloring to distinguish the live device from the trainer device, this is not considered essential for approval by him or me, as the trainer is not intended for distribution to patients. Therefore confusion is not likely to occur outside of the training setting in the clinic. The concern for confusion will be addressed by prominent labeling on the autoinjector to distinguish the trainer from the live device.
- The device is acceptable from the standpoint of the reviewers from the Center for Devices and Radiological Health and conforms to CDRH standards for similar devices.

Based on these considerations, I am of the opinion that there are no safety concerns with the device that would preclude approval.

- **Notable safety issues (resolved or outstanding)**

See above.

9. Advisory Committee Meeting

An advisory committee meeting was not held for this application. Methotrexate is an approved drug and no issues were identified that would warrant advisory committee input.

10. Pediatrics

The following section is largely excerpted from Dr. Starke's clinical review:

Methotrexate is currently approved for the indication of treatment of rheumatoid arthritis when administered by **oral** route; for the indication of "polyarticular-course juvenile rheumatoid arthritis" (now termed polyarticular juvenile idiopathic arthritis, or 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.

Historically, approvals in RA have triggered pediatric study requirements in PJIA under PREA. Studies in PJIA patients under 2 years of age have been typically waived due to the rarity of the diagnosis in children under 2 years, which would make studies infeasible. 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, the clinical team does not believe a waiver applies. 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 is extremely rare in this age group and studies would be impossible or highly impractical.

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.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not applicable.
- **Exclusivity or patent issues**

The applicant submitted the required patent certification with respect to the listed drugs.

The applicant also submitted a request for (b) (4) for Otrexup for reasons of the new route of delivery (subcutaneous) for RA and severe psoriasis. In particular, Antares believes that MTX-11-002 (the single-dose actual use study of the Antares MTX autoinjector) and MTX-11-004 (the simulated-use single-dose human factors study) meet the definition of a new clinical investigation, set forth in 21 CFR 314.108(a).

I do not agree that study MTX-11-002 and study MTX-11-004 were necessary for the approval of the subcutaneous route of administration of methotrexate for rheumatoid arthritis or psoriasis for the following reasons:

- The conclusion regarding the efficacy of subcutaneously administered methotrexate for RA is based on relative bioavailability compared to oral methotrexate.
  - As described in Section 7 above, the basis for the conclusion that the subcutaneous route of administration would not negatively impact the efficacy of methotrexate for RA previously demonstrated with the oral route of administration is the higher exposure observed with subcutaneous administration compared to oral administration. That subcutaneous administration of methotrexate results in higher exposure than oral administration has already been demonstrated in the published literature. The applicant's relative bioavailability study MTX-10-003 confirmed that this was the case for methotrexate administered via their autoinjector device as well.
- The conclusion regarding the safety of subcutaneously administered methotrexate for RA is based on relative bioavailability compared to oral methotrexate and the historical experience with methotrexate over the range of its approved doses.

        - As described in Section 8 above, the basis for the conclusion that the subcutaneous route of administration would not negatively impact the safety of methotrexate is the modest increase in exposure observed in relative bioavailability studies (the applicant's and in the literature), in the context of the dosing of methotrexate for RA, which is in the lower end of the therapeutic range. The limited single-dose data derived from study MTX-11-002 would not be considered essential safety information with respect to subcutaneous administration of methotrexate in RA. As methotrexate is a chronically administered product, a single-dose study would not be considered adequate evidence of safety of a new route of administration.
    - The efficacy and safety of the subcutaneous route of administration for the indication of severe psoriasis may be based entirely on the bioequivalence of subcutaneous and intramuscular administration of methotrexate (demonstrated in study MTX-10-001 and other studies in the literature) and the Agency's previous finding of efficacy and safety of intramuscular administration of methotrexate for severe psoriasis.

In conclusion, while studies MTX-11-002 and MTX-11-004 are utilized in this NDA to support approval of the applicant's proposed autoinjector device, these studies were not necessary to support approval of the subcutaneous route of administration of methotrexate for RA or psoriasis. (b) (4)

- **Financial disclosures**—No issues.
- **DSI audits**—Not performed.

No clinical efficacy trials were submitted in this application. Clinical study site inspections were not requested for the two relative bioavailability (BA) studies, as the studies were not designed to show bioequivalence as a basis for approval and were therefore not considered pivotal.

- **Other outstanding regulatory issues**—None.

12. Labeling

- **Proprietary name**—reviewed and determined to be acceptable as Otrexup.
- **Physician labeling**

The Antares MTX autoinjector product is essentially a parenteral MTX formulation, like the currently approved parenteral MTX formulations, only packaged for subcutaneous injection. The parenteral MTX formulations are also labeled for subcutaneous use (albeit only directly mentioned for the polyarticular course juvenile idiopathic arthritis indication). In determining the appropriate approach for the Antares MTX label, which would be the first MTX label in the Physician's Labeling Rule (PLR) format, the Division held multiple internal meetings with other Agency stakeholders in this process, to include the Division of Oncology Products 2—the home division of the MTX products; also the Study Endpoints and Labeling Development

team (Dr. Anne Marie Trentacosti), and the Division of Dermatology and Dental Products. Office of Drug Evaluation 2 Director Dr. Curtis Rosebraugh and Office of New Drugs Director Dr. John Jenkins were also briefed and provided feedback on the most appropriate approach.

The group agreed that it is difficult to justify labeling this product very differently from other parenteral MTX products. The applicant's primary data to support approval of their product is relative bioavailability data to approved oral MTX and approved parenteral MTX. The bulk of the efficacy and safety information in this NDA is derived from the published literature on MTX and the Agency's previous finding of efficacy and safety of oral and parenteral MTX, and is not specific to Antares' MTX product. Therefore the bulk of the information that would be utilized to update the label would be based on publically available information not owned by Antares, would be applicable to all parenteral MTX products, and should be in all parenteral MTX labels. Additionally, the proposed label submitted by the applicant was not a comprehensive update of the parenteral MTX label, and would not have been sufficient to serve as a model for PLR conversion of the approved parenteral MTX labels. The review team felt that a PLR label with fully updated content would require much additional effort and would not be possible within the timeframe of this NDA cycle.

Therefore the group determined the most appropriate path forward at this time would be to create the Antares MTX label from the content of the currently approved parenteral MTX labels converted into PLR format. The primary exceptions to this will be the addition of the BA/BE results for Otrexup in Section 12.3 Pharmacokinetics and information in Section 2 Dosage and Administration advising prescribers to consider the differences in bioavailability between oral and subcutaneously administered MTX. Additionally, the neoplastic disease indications were removed from the indications section, as Antares' MTX autoinjector is not designed to accommodate the doses and routes of administration currently approved for MTX in the neoplastic diseases. However, unless a given toxicity was clearly only applicable to the neoplastic disease setting, safety information remained in the label, even if likely derived from cancer studies.

(b) (4)

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review.**

See above. Labeling negotiations are ongoing with the applicant at the time of this review.

- **Carton and immediate container labels**

Revisions were recommended by DMEPA and negotiations are ongoing at the time of this review.

- **Patient labeling/Medication guide**

Revisions for patient information sheet and instructions for use were recommended by DMEPA and Division of Medical Policy Programs patient labeling team. Negotiations are ongoing at the time of this review. Methotrexate does not have a medication guide.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of this application, provided that agreement can be reached on revisions to the proposed labeling.

- **Risk Benefit Assessment**

The risk-benefit of the SC route of administration of MTX is favorable for RA. This is based on a modest increase in exposure with SC administration relative to oral administration that allows for extrapolation of the efficacy of oral MTX for RA. The safety of SC administration for RA is also based on the modest increase in exposure with SC administration relative to the conventionally used doses for RA, which are on the low end of the approved therapeutic dose range of MTX. The increase in exposure associated with SC administration would not be expected to have a clinically significant impact on the safety profile of MTX in RA.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

Postmarketing risk evaluation and management strategies are not warranted on the basis of this submission.

- **Recommendation for other Postmarketing Requirements and Commitments**

Dr. Starke recommended different coloring to distinguish the live device from the trainer device, consistent with other device/trainer products in this Division. However, this is not considered essential for approval by him or me, as the trainer is not intended for distribution to patients. The applicant was requested to consider implementing distinguishing colors and internal discussion is ongoing regarding whether this rises to the level of a postmarketing commitment. No postmarketing requirements are warranted.

- **Recommended Comments to Applicant**

Not applicable.

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

/s/

SARAH K YIM
09/19/2013