CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204824Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sarah Yim, M.D., Associate Director Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 204824 original-1 (RA) and original-2 (Psoriasis)
Applicant Name	Antares Pharma, Inc.
Date of Submission	December 14, 2012
PDUFA Goal Date	October 14, 2013
Proprietary Name / **Established (USAN) Name**	Otrexup™ / methotrexate injection
Dosage Forms / Strength	Prefilled Syringe in Autoinjector: 10 mg/0.4 mL, 15 mg/0.4 mL, 20 mg/0.4 mL, and 25 mg/0.4 mL
Proposed Indication(s)	1. Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis (original-1) 2. Moderate to Severe Psoriasis (original-2)
Action:	*Approval for RA indication, with revisions to proposed labeling. See Original-2 regarding psoriasis.*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Clinical Review (DPARP) / Clinical Review (DDDP)	Peter Starke, M.D. Snezana Trajkovic, M.D.; Tatiana Oussova, M.D.
Statistical Review	Joan Buenconsejo, Ph.D.
Pharmacology/Toxicology Review	Andrew Goodwin, Ph.D.; Timothy Robison, Ph.D.
CMC Review/ CMC microbiology	Arthur Shaw Ph.D.; Prasad Peri, Ph.D.; Erika Pfeiler, Ph.D.
CDRH Reviews	Jacqueline Ryan, Quynh Nguyen
Clinical Pharmacology Review	Sheetal Agarwal, Ph.D.; Satjit Brar, Pharm.D., Ph.D.
CDTL Review	Sarah Yim, M.D.
OSE/DMEPA	Teresa McMillan, PharmD; Lubna Merchant PharmD, M.S.; Carol Holquist, RPh.
OMP/DMPP	Sharon Williams RN BSN; LaShawn Griffiths, MSHS-PH BSN RN; Shawna Hutchins MPH BSN RN
OPDP	Roberta Szydlo RPh MBA; Puja Shah

OND=Office of New Drugs
DDDP=Division of Dermatology and Dental Products
CMC=Chemistry, Manufacturing, and Controls
CDRH=Center for Devices and Radiological Health
CDTL=Cross Discipline Team Leader
OSE/DMEPA=Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis
OMP/DMPP=Office of Medical Policy/Division of Medical Policy Programs
OPDP=Office of Prescription Drug Promotion

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, although parenteral methotrexate products have been approved for over 50 years.

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, recalcitrant, disabling 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 to severe" psoriasis. To support the new route of administration and indications, 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 provide information on the usability of the autoinjector device and its instructions for use, 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 for psoriasis that differs from the approved listed drugs, this application was administratively split, and the review of the psoriasis indication

was performed and documented separately by reviewers from the Division of Dermatology and Dental Products (DDDP)—see their reviews for "original-2."

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 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 starting doses are specifically mentioned for RA, along with a note that "dosages may be adjusted gradually to achieve an optimal response."

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

[1] Coury FF and ME Weinblatt, Clin Exp Rheumatol 2010; 28 (Suppl 61):S9-S12.
[2] Kremer, J Rheum 1996 (suppl 44) 23:34-37; Visser et al, Ann Rheum Dis 2009 Jul; 68(7):1086-93.

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 should include a relative bioavailability bridge between the subcutaneous and oral routes in addition to the IM route proposed by the sponsor, 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.

3. CMC/Device

Drug substance

Methotrexate is a yellow to orange, (b) (4) insoluble in water. The CMC information for the methotrexate drug substance is covered in drug master file (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 and the CMC review team has determined these to be acceptable.

Drug product

The drug product is formulated by titrating with sodium hydroxide to a neutral pH, (b) (4) methotrexate. There are no novel excipients and no preservatives. 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 and sterility aspects of the drug product manufacturing have been reviewed 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)%, which was determined to be acceptable.

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 CDRH 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 (Human factors study MTX-11-004). These studies are intended to support the conclusion that the device can be used safely if marketed, 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) 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 included two sessions spaced one week apart, to be consistent with the once-weekly dosing interval and to assess the impact of training decay. Seventy-five individuals were recruited, including 17 RA patients, 16 lay caregivers, and 17 healthcare professionals (nurses). The 17 healthcare professionals participated in Session 2 only, but all others participated in both Sessions 1 and 2.

Eighty-one of 83 (98%) of the attempted injections were successful. The CDRH Human Factors Study reviewer 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." DMEPA raised concerns about the "close calls" in the study but deferred to CDRH regarding whether the device design should be modified. I address the "close calls" with respect to their potential ramifications on the safety of the device in Section 8 below.

Facilities review/inspection status

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).

CMC/Device conclusions

The CMC review team and CDRH consultants are of the opinion that there are no CMC or device issues that would preclude approval, and I concur. The concerns raised by DMEPA regarding the use and handling studies would not be expected to pose a significant safety concern (see Section 8 below), and thus do not preclude approval.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology team that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

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). It is well-known that oral bioavailability of MTX drops at high doses.[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.

The clinical pharmacology team finds the NDA acceptable for approval from a clinical pharmacology perspective, and I concur.

6. Clinical Microbiology

I concur with the conclusions reached by the CMC microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

[3] Abolmaali et al., Cancer Chemother Pharmacol, 2013, 71:1115-1130.

7. Clinical/Statistical-Efficacy

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 extrapolated based on exposures that are equal or greater than exposures via the approved oral route of administration.

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) which showed a similar/somewhat higher proportion of patients experiencing American College of Rheumatology (ACR) 20%/50%/70% levels of response with SC administration of MTX compared to the same dose of MTX given orally. Other published literature support a similar conclusion.

Therefore, I concur that there is adequate information to support a conclusion that the subcutaneous route of administration of MTX would also be efficacious for RA (i.e., the efficacy of orally administered MTX can be extrapolated to apply to subcutaneously administered MTX).

8. Safety

The experience with MTX across all the approved indications covers a much wider range of doses than those utilized in RA, which by convention does not typically exceed 30 mg/week.[4] The toxicity of MTX across its therapeutic range is well known, with the most common toxicities being gastrointestinal (worse with oral administration), and less common but serious toxicities including myelosuppression, pneumonitis, nephrotoxicity and possible long-term hepatotoxicity (primarily liver enzyme elevations). These serious toxicities are uncommon at the doses used for RA, and are ameliorated by the use of folic acid supplementation[5], which is standard practice. Doses for neoplastic indications are up to an order of magnitude higher than those used for RA (i.e. 20 to 30 grams for the treatment of osteosarcoma, which requires leucovorin rescue). Subcutaneous administration of MTX for RA would be limited to doses at the low end of the MTX therapeutic range, and a 36% higher exposure would not be expected to result in significant additional toxicities.

The safety experience specific to the Antares MTX autoinjector product is limited to three single-dose studies in a total of 187 patients with RA—MTX-10-001 (relative BA study), MTX-11-003 (relative BA study), and MTX-11-002 (single-dose evaluation of device and instructions for use). Based on these limited single-dose data, no new safety signals were identified, but alone, these data would not be considered adequate evidence of safety for a new route of administration for a chronically administered drug.

[4] Visser, et al. Ann Rheum Dis 2009; 68:1086-1093.
[5] Shea B, et al. Cochrane Database of Systematic Reviews 2013, Issue 5

Nevertheless, I concur that there is adequate safety information to support the safety of subcutaneously administered MTX, because of the modest increase in exposure associated with the SC route of administration observed in relative bioavailability studies, in the context of the dosing of methotrexate for RA, which is in the lower end of the therapeutic range.

Regarding the safety of the device, potential concerns were raised by some members of the review team related to the results of studies MTX-11-002 and MTX-11-004 (described in Section 3, above). 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 and errors related to unfamiliarity with the device will not be an ongoing concern.
- The human factors study (MTX-11-004) showed a 98% success rate, despite the "close calls". Close calls primarily pertained to holding the device for the required delivery time, using the device with inadequate force to retract the needle shield, and confusion regarding the location and removal of the safety cap.
- The "close calls" 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. In this 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 local tolerability of MTX parenteral formulations.
- Concerns regarding potential confusion of the trainer and live devices can and will be addressed by prominent labeling on the trainer 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 its approval.

- ***Final labeling recommendations***

See Section 12 below.

- ***REMS***

The safety profile of oral and parenteral methotrexate is well known. No risk evaluation/management strategies are warranted on the basis of this submission.

- ***PMRs and PMCs***

Consideration was being given to a postmarketing commitment for device color changes to distinguish the live device from the trainer device, because this was consistent with the Division's approach to other device/trainer products (i.e., epinephrine). However, after further internal discussion, the team was in agreement that clearly identifying the trainer with labeling was acceptable. Therefore, no postmarketing commitments or postmarketing requirements are warranted.

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

Methotrexate is currently approved for the indication of treatment of rheumatoid arthritis when administered by **oral** route and 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. The application triggers the Pediatric Research Equity Act (PREA, 21 U.S.C. 355c) for the RA indication because the route of administration (subcutaneous) is new for this 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. Because methotrexate is already labeled for subcutaneous use in PJIA patients, the PREA requirement associated with the RA approval regarding PJIA patients ages 2 to 17 years is considered as fulfilled. Studies in PJIA patients under 2 will be waived due to studies being impossible or highly impractical due to the rarity of the diagnosis in this age group. 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. This plan was discussed with the Pediatric Review Committee (PeRC) on June 4, and PeRC concurred.

11. Other Relevant Regulatory 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 for the following reasons:

- The conclusion regarding the efficacy of subcutaneously administered methotrexate for RA is based on relative bioavailability compared to oral methotrexate.
  - The efficacy for subcutaneously administered methotrexate may be extrapolated based on the known efficacy of orally administered methotrexate, due to the higher exposure observed with subcutaneous administration compared to oral administration. This relative exposure information is available in the literature, as well as from study MTX-10-003.
- 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.
  - 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.

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

12. Labeling

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

The Antares MTX autoinjector product is 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). However, Antares' label would be the first MTX label in PLR format. After internal discussions which included OND management, SEALD, and affected review divisions, it was determined that the information needed to update the MTX 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. However, a comprehensive update of the content of the parenteral MTX label would not be possible in the timeframe of this NDA cycle. Thus, the approach agreed-upon internally was to create the Antares MTX label from the content of the currently approved parenteral MTX labels but converted into PLR format, (b) (4) . Limited data pertaining to the pharmacokinetics of Otrexup will be included 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. Limited information specific to the Otrexup autoinjector will also be included in Section 2 Dosage and Administration. The neoplastic disease indications will also be excluded from the Antares MTX label because the format and doses are not suitable for those indications. A teleconference was held with Antares on September 19, 2013, at which Antares expressed understanding with the Agency's approach to the Otrexup label.

- ***Carton and immediate container labels***

No outstanding or unresolved issues.

- ***Patient labeling/Medication guide***

No outstanding or unresolved issues. Methotrexate does not have a medication guide.

13. Decision/Action/Risk Benefit Assessment

- ***Regulatory Action***

This action on this NDA will be approval.

- ***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 Mitigation Strategies***

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

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

No postmarketing requirements or commitments are warranted.

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/s/

SARAH K YIM
10/11/2013