

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204824Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW FOR METHOTREXATE INJECTION, NDA 204824

<i>NDA</i>	204824	<i>Submission Date(s)</i>	December 14, 2012
<i>Proposed Brand Name</i>	Otrexup		
<i>Generic Name</i>	Methotrexate injection		
<i>Reviewer</i>	Sheetal Agarwal, Ph.D.		
<i>Team Leaders</i>	Satjit Brar, Pharm.D., Ph.D.		
<i>OCP Division</i>	Division of Clinical Pharmacology-2		
<i>OND Divisions</i>	Division of Pulmonary, Allergy and Rheumatology Products and Division of Topical and Ophthalmic Products		
<i>Sponsor</i>	Antares Pharma		
<i>Submission Type</i>	505(b)(2) NDA referencing NDAs 011719 (Methotrexate Injection, USP) and 008085 (Methotrexate tablets) as well as literature		
<i>Formulation; Strength(s)</i>	Delivers a fixed volume 0.4 mL per injection containing 10, 15, 20, or 25 mg of MTX as a sterile preservative-free solution		
<i>Proposed Indication(s)</i>	For the treatment of rheumatoid arthritis including polyarticular-course juvenile rheumatoid arthritis and moderate to severe psoriasis.		
<i>Proposed Dosing Regimen</i>	<p>Adult Rheumatoid Arthritis: The recommended starting dose for Otrexup is 10 ^{(b)(4)} mg given subcutaneously once weekly.</p> <p>Polyarticular-Course Juvenile Rheumatoid Arthritis: The recommended starting dose for Otrexup is 10 mg/m² given subcutaneously once weekly.</p> <p>Moderate to Severe Psoriasis: The recommended starting dose for Otrexup is 10-25 mg given subcutaneously once weekly.</p>		

TABLE OF CONTENTS

<u>Page Contents/Study Description</u>	<u>Page #</u>
Cover page	1
Table of Contents	2
1.0 Executive Summary	3
1.1 Recommendation	
1.2 Phase 4 Commitment	
1.3 Summary of Important Clinical Pharmacology Findings	
2.0 Clinical Pharmacology Review (Question Based review)	5
2.1 General Attributes/Background	
2.2 General Clinical Pharmacology	
2.3 Intrinsic factors	
3.0 Labeling Recommendations	20
4.0 Appendices	
4.1 Filing review	21

1.0 Executive Summary

1.1 Recommendation:

Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 has reviewed Antares Pharma's NDA 204824 requesting approval of Otrexup, an auto-injector product for methotrexate, and finds the proposed drug product acceptable from a clinical pharmacology perspective.

1.2 Phase 4 commitments:

From a clinical pharmacology perspective, no Phase 4 commitment is applicable to this NDA.

1.3 Summary of important clinical pharmacology findings:

The NDA for Otrexup (methotrexate injection) was submitted under 505(b)(2) regulations referencing literature as well as three previously approved methotrexate products: NDA 011719 (Hospira's methotrexate injection approved August 10, 1959), NDA 008085 (Dava's oral methotrexate tablets approved December 7, 1953) as well as ANDA 40-632 for Methotrexate Preservative-Free Injection from Bedford approved on August 12, 2005. Otrexup is a combination drug-device auto-injector product intended for self-administration of a fixed dose of methotrexate, 10, 15, 20 and 25 mg, as a once weekly administration. Since Otrexup is a combination drug-device auto-injector product, CDRH has been consulted for a review of the device part of this product.

The currently approved and marketed methotrexate products are indicated for neoplastic, rheumatology and psoriasis indications. However, the sponsor's proposed indications do not include neoplastic diseases as Otrexup is intended as a convenience formulation for self or caregiver use in the home setting. The sponsor seeks approval for rheumatoid arthritis (RA) including polyarticular-course juvenile rheumatoid arthritis (pJIA) as well as moderate to severe psoriasis (PsA).

Since the sponsor is seeking the approval of rheumatology as well as psoriasis related indications, the NDA was split into Original 1-Submission (Standard) and the Original 2-Submission (Standard), which are being handled by the clinical divisions, DPARP and DDDP, respectively.

- The Original 1 submission involves the proposed indication of rheumatoid arthritis including polyarticular-course juvenile rheumatoid arthritis.
- The Original 2 submission involves the proposed indication of treatment of moderate to severe psoriasis.

The sponsor included data from two relative BA/BE clinical pharmacology studies in this NDA providing a PK bridge to both previously approved products for methotrexate, i.e., Hospira's methotrexate injection (NDA 011719) and Dava's oral methotrexate tablets (NDA 008085).

- Study MTX-10-001 evaluated the PK of Otrexup as compared to methotrexate injection (NDA 11719). Results indicate that methotrexate C_{max} and AUC, after administration with Otrexup, is similar to the same dose of SC or IM injections of approved parenteral methotrexate product. The 90% CIs of the ratios of the geometric LS means of dose normalized C_{max} and AUC parameters for the test product (Otrexup) were within the bioequivalence range of 80% to 125% when compared to the SC and IM methotrexate injection product. This indicates that, in a clinical setting, whether Otrexup is administered SC or IM, it will lead to systemic methotrexate exposures that are similar to the currently marketed SC or IM parenteral injections of methotrexate.
- Study MTX-10-003 evaluated the PK of Otrexup as compared to methotrexate oral tablets (NDA 008085). Results indicate that methotrexate exposure (AUC) with Otrexup was higher than oral

methotrexate at all dose levels tested (10, 15, 20 and 25 mg). The quantitative differences in systemic exposure between Otrexup and oral methotrexate were not similar across all doses. $AUC_{(0-\infty)}$ was higher for the same methotrexate dose of Otrexup than for oral methotrexate, ranging between ~13% higher (at 15 mg dose) to ~36% higher (at 25 mg dose). This indicates that if patients taking oral methotrexate switch to Otrexup at the same dose, they will exhibit higher systemic exposure of methotrexate. This study also showed that methotrexate exposure with Otrexup is similar when administered in the abdomen or the thigh and both these sites can be used as potential injection sites for Otrexup.

The NDA also includes data from two additional studies. Study MTX-10-002 (open-label safety study) evaluated the ability of RA patients to self-administer Otrexup after training, and Study MTX-10-004 (a device usability study). Primary efficacy and safety support for this NDA comes from several published articles which will be reviewed by Dr. Peter Starke, the medical officer for DPARP and by Dr. Trajkovic, the medical officer for DDDP.

Overall, the sponsor has adequately bridged their product to the approved references with relative BA/BE studies and the NDA is acceptable from a clinical pharmacology perspective.

2. Question Based Review

2.1 General Attributes/Background:

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

The NDA for Otrexup (auto-injector dispensing methotrexate) was submitted under 505(b)(2) regulations referencing both literature and previously approved methotrexate products. Currently approved NDAs for methotrexate include NDA 011719 (Hospira's methotrexate injection approved on August 10, 1959) and NDA 008085 (Dava's oral methotrexate tablets approved on December 7, 1953). Due to the shortage of Hospira's methotrexate product, the sponsor employed a generic methotrexate product from Bedford (ANDA 40-632, approved on August 12, 2005) in clinical pharmacology studies for this application which is also listed in the Orange Book as a reference listed drug (RLD). Therefore, the application also needed to reference this product.

Otrexup is a combination drug-device auto-injector product delivering a fixed dose of methotrexate at 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.

In this NDA, the sponsor is seeking the approval of several indications; therefore, it includes the Original 1-Submission (Standard) and the Original 2-Submission (Standard), which is being handled by the clinical divisions, DPARP and DDDP, respectively.

- The Original 1 submission involves the proposed indication of rheumatoid arthritis including polyarticular-course juvenile rheumatoid arthritis.
- The Original 2 submission involves the proposed indication of treatment of moderate to severe psoriasis.

The primary difference between the approved methotrexate products and the sponsor's product is that the sponsor's product, Otrexup, is an auto-injector presentation available as fixed doses of 10, 15, 20 and 25 mg methotrexate for once weekly self-administration. Whereas the approved methotrexate products (injection or tablets), can be dosed with much more flexibility (in terms of total dose) and at much higher doses, depending on the patient population and indications, which include several oncology indications.

The sponsor indicates that the intended route of administration of methotrexate through Otrexup is subcutaneous (SC). Since the current approved labeling for methotrexate injection only includes dosing instructions for intramuscular (IM) administration, the SC route of delivery for methotrexate could be considered a new route of delivery for methotrexate. However, the current approved labeling for methotrexate injection does indicate that both, SC and IM administration of methotrexate, may be advantageous over oral route for methotrexate administration (better absorption and fewer gastrointestinal side effects) indicating that methotrexate could be used SC. In addition, the sponsor has provided published information in support of efficacy of methotrexate when administered through the SC route in addition to the IM route. As such, it seems that the SC route of administration for methotrexate is not really a novel route for methotrexate administration and has been frequently employed as a route of delivery in clinical setting for parenteral methotrexate administration. Refer to the clinical review in DARRTS by the medical officers, Dr. Peter Starke, and Dr. Snezana Trajkovic, for a review of literature articles provided in support of safety, efficacy and dosing of the product as proposed to be labeled for the different indications.

At the pre-NDA meeting held for this product on November 2, 2012 (meeting minutes in DARRTS dated 11/28/2012), discussion was primarily related to availability of good quality published information to support all the indications as proposed by the sponsor. Some of the clinical pharmacology related aspects that were discussed at this meeting were: (a) analysis of effect of body weight on methotrexate exposure with sponsor's product, (b) literature search to address dosing in special populations such as renal and hepatic impairment subjects, elderly subjects etc., and (c) product labeling related to the issue of limited choice of doses available if patients were to use sponsor's product vs. other approved methotrexate products. The sponsor has addressed all of discussed aspects in the submission. This reviewer conducted a literature search for any available studies to address some of the factors that may affect exposure such as renal or hepatic impairment etc., however no such published studies that can be used for product labeling were available.

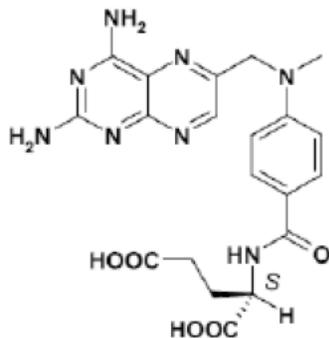
An OSI inspection request was not made for the 2 relative BA studies as the studies were not designed to show bioequivalence between Otrexup and the approved oral and parenteral methotrexate products, rather the studies provided a PK bridge for Otrexup to be linked to the approved products to be able to utilize Agency's summary of findings of safety and efficacy for each of the approved products. In addition, the NDA is a 505(b)(2) referencing literature (in addition to the two previously approved methotrexate products) for clinical/safety assessments and, as such, the relative BA studies were not considered pivotal.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Drug Substance:

The structure of methotrexate as shown below contains (b) (4). *S*-enantiomer of methotrexate for the Antares drug product is supplied by (b) (4), and the morphic form of this methotrexate (b) (4). The content of the *R*-enantiomer in methotrexate is directly controlled with a validated HPLC analysis (b) (4).

Chemical structure of methotrexate:



Molecular Formula: C₂₀H₂₂N₈O₅

Molecular Mass: 454.45 g/mol

Physical Form and Appearance: Yellow to orange, (b) (4)

Solubility: Practically insoluble in water, dichloroethane, ethanol, and diethylether; soluble in dilute acids and alkaline solutions. Upon conversion to the sodium salt, methotrexate becomes freely soluble at pH 7 and above. Solubility of methotrexate at various pH (20°C) is shown below:

pH	Solubility (mg/mL)	Expression of Solubility
7.0	(b) (4)	Freely soluble
7.5		Freely soluble
8.0		Freely soluble
8.5		Freely soluble
9.0		Freely soluble

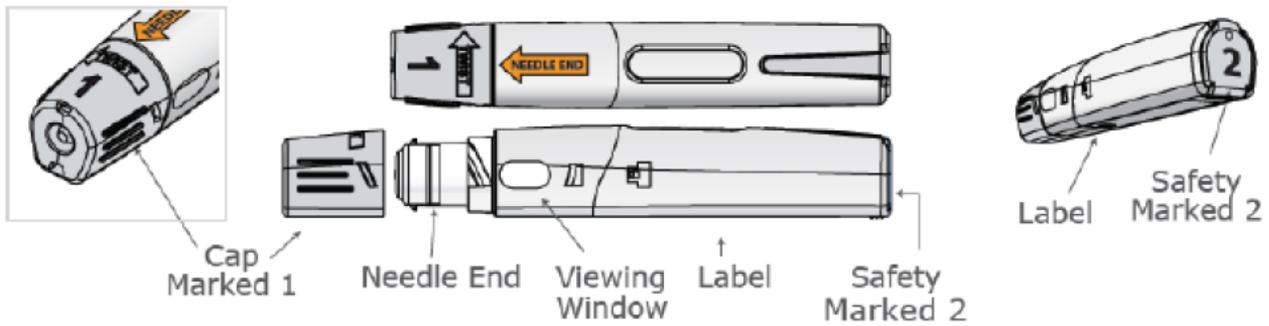
Drug Product:

Each single-use prefilled autoinjector (PFS) contains sterile, preservative-free Methotrexate Injection for subcutaneous administration of a fixed volume of 0.4 mL, yielding final delivered doses of Methotrexate sodium equivalent to 10 mg, 15 mg, 20 mg or 25 mg methotrexate. The drug product is a sterile, preservative-free clear, yellowish solution, with a pH range of (b) (4), and an osmolarity between 230 - 320 mOsmol/L. There is no reconstitution diluent associated with this drug product. Methotrexate injection is contained within a single-dose syringe with a 27-gauge, ½-inch needle with a soft needle shield within an autoinjector, which is equipped with a needle safety guard and safety cap. (b) (4), manufactures Methotrexate Injection and (b) (4) fills the PFS. Assembly of the PFS within the autoinjector is performed by (b) (4).

The components and composition of Otrexup are shown below:

Component and Quality Standard	Function	Strength (label claim) 10 mg/0.4 mL		Strength (label claim) 15 mg/0.4 mL		Strength (label claim) 20 mg/0.4 mL		Strength (label claim) 25 mg/0.4 mL	
		Quantity per unit dose	% (wt/wt)						
Methotrexate, USP	Active Ingredient	10 mg	(b) (4)	15 mg	(b) (4)	20 mg	(b) (4)	25 mg	(b) (4)
Sodium Chloride, NF/Ph. Eur.	(b) (4)	1.96 mg		1.60 mg		1.28 mg		0.56 mg	
Sodium Hydroxide, NF/Ph. Eur.	pH Adjustor	pH		pH		pH		pH	
Hydrochloric Acid, NF/Ph. Eur.	pH Adjustor	pH		pH		pH		pH	
Water for Injection, USP/Ph. Eur.	(b) (4)	0.4 mL		0.4 mL		0.4 mL		0.4 mL	

The medical device used for the combination product Otrexup, as shown below, is a single-use disposable grey and white auto-injector that is manufactured by the sponsor, Antares Pharma, Inc. The auto-injector does not seem to require preparation before injection and is suggested to be designed such as to deliver the complete volume of the single-dose PFS. The device is proposed to be discarded after injection. For complete review of the device product, refer to CDRH consult review of this product.



2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action:

- **Malignancy:** As currently labeled, methotrexate inhibits dihydrofolic acid reductase. Dihydrofolates must be reduced to tetrahydrofolates by this enzyme before they can be utilized as carriers of one-carbon groups in the synthesis of purine nucleotides and thymidylate. Therefore, methotrexate interferes with DNA synthesis, repair, and cellular replication. Actively proliferating tissues such as malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa, and cells of the urinary bladder are in general more sensitive to this effect of methotrexate. (b) (4)

[Redacted text block]

[Redacted text block]

Proposed Indications:

- **Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis:** Otrexup™ is indicated for the treatment of rheumatoid arthritis including polyarticular-course juvenile rheumatoid arthritis.
- **Psoriasis:** Otrexup is indicated for treatment of moderate or severe psoriasis.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

Several dosing regimens via different dosing routes in both adult and pediatric populations have been proposed by the sponsor as indicated below.

- **Adult Rheumatoid Arthritis:** The recommended starting dose for Otrexup is 10 (b) (4) mg given

subcutaneously once weekly. Patients requiring doses less than 10 mg per week may not be suitable for treatment with Otrexup. Dosages may be adjusted in 5 mg increments at (b) (4) intervals to achieve optimal clinical response. Therapeutic response usually begins within 3 to 6 weeks and the patient may continue to improve for another 12 weeks or more.

- **Polyarticular-Course Juvenile Rheumatoid Arthritis:** The recommended starting dose for Otrexup is 10 mg/m² given subcutaneously once weekly. Patients requiring doses less than 10 mg per week may not be suitable for treatment with Otrexup. Dosages may be adjusted in 5 mg increments every (b) (4) to achieve optimal clinical response.
- **Moderate to Severe Psoriasis:** The recommended starting dose for Otrexup is 10-25 mg given subcutaneously once weekly. Patients requiring doses less than 10 mg per week may not be suitable for treatment with Otrexup. Dosages may be adjusted in 5 mg increments every (b) (4) to achieve optimal clinical response.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Two clinical pharmacology studies (MTX-10-001 and MTX-10-003) as described below, have been conducted in the support of this 505(b)(2) NDA referencing previously approved oral and parenteral methotrexate products. No clinical safety/efficacy studies with Otrexup were conducted. The NDA references several published studies for establishing safety and efficacy at proposed doses and for proposed indications. In addition to 2 relative BA/BE studies, the NDA also includes data from an open-label safety study (Study MTX-10-002) and a device usability study (Study MTX-10-004).

Study ID	Number of study sites enrolling/ Location	Study start date/ Study completion date	Design and control type/ Development stage	Study and control drugs	Key study objective(s) pertaining to Section 2.7.2	# of subjects Mean : age BMI	Population racial distribution
MTX-10-001	2 clinical sites USA	January 2011/May 2011	Open-label, randomized, 3-way crossover of single doses of 10, 15, 20 or 25 by 3 different methods of administration Phase 2	MTX A) For SC injection with Methotrexate Injection Device B) For SC injection without device C) For IM injection	- Compare the PK of MTX following SC injection using the Methotrexate Injection device to that following SC injection of MTX without the device in adults with RA -Compare the PK of MTX following SC injection using the Methotrexate Injection device to that following IM injection of MTX in adults with RA	38 randomized/36 safety 62.1 years 30.6 kg/m ²	PK/Safety Population White 35 (97.2%) Black 1 (2.8%)

Study ID	Number of study sites enrolling/ Location	Study start date/ Study completion date	Design and control type/ Development stage	Study and control drugs	Key study objective(s) pertaining to Section 2.7.2	# of subjects Mean : age BMI	Population racial distribution
MTX-11-003	3 clinical sites USA	May 2012/ July 2012	Open-label, randomized, 3-way crossover of single doses of 10, 15, 20 or 25 mg by 3 different methods of administration Phase 2	MTX A) Oral MTX B) SC injection of MTX into the abdomen using Methotrexate Injection device C) SC injection into the thigh using Methotrexate Injection device.	-Compare relative bioavailability and other PK parameters of MTX following oral administration to that obtained after SC injection into the abdomen using the Methotrexate Injection device based on $AUC_{[0-t]}$, $AUC_{[0-inf]}$, and (C_{max}) . -Compare relative bioavailability and other PK parameters of MTX following oral administration to that obtained after SC injection into the thigh using the Methotrexate Injection device based on $AUC_{[0-t]}$, $AUC_{[0-inf]}$, and (C_{max}) . -Compare the relative bioavailability and other PK parameters of MTX following SC injection into the abdomen to that obtained after SC injection into the thigh using the Methotrexate Injection device by measuring $AUC_{[0-t]}$, $AUC_{[0-inf]}$, and (C_{max}) .	50 randomized/49 safety 61.4 years 30.7 kg/m ²	BA/Safety Population White 44 (89.9%) Black 5 (10.2%)

2.2.2 What are the known PK characteristics of methotrexate and its metabolites?

The following PK information is obtained from currently approved labels for oral and parenteral methotrexate and is relevant to the populations in which this product will be administered.

Absorption – In adults, oral absorption appears to be dose dependent. Peak serum levels are reached within one to two hours. At doses of 30 mg/m² or less, methotrexate is generally well absorbed with a mean bioavailability of ~60%. The absorption of doses greater than 80 mg/m² is significantly less, possibly due to a saturation effect.

Distribution – After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg.

Metabolism – After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. Methotrexate is partially metabolized by intestinal flora after oral administration.

Half-Life – The terminal half-life reported for methotrexate is approximately 3-10 hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or low dose antineoplastic therapy (less than 30 mg/m²). For patients receiving high doses of methotrexate, the terminal half-life is 8-15 hours.

Excretion – Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Methotrexate has been detected in human breast milk. The highest breast milk to plasma concentration ratio reached was 0.08:1.

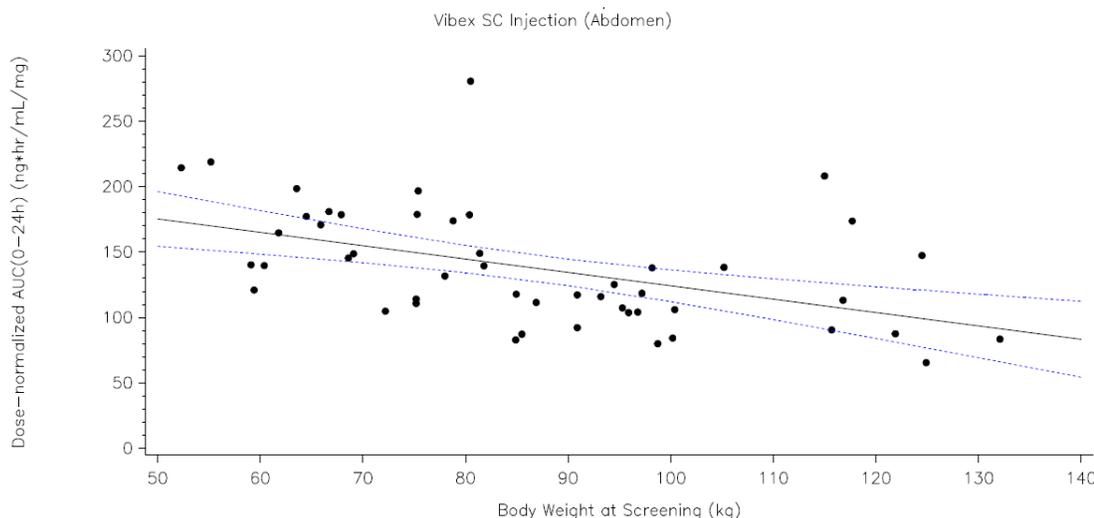
2.3 Intrinsic Factors

2.3.1. Does age, weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

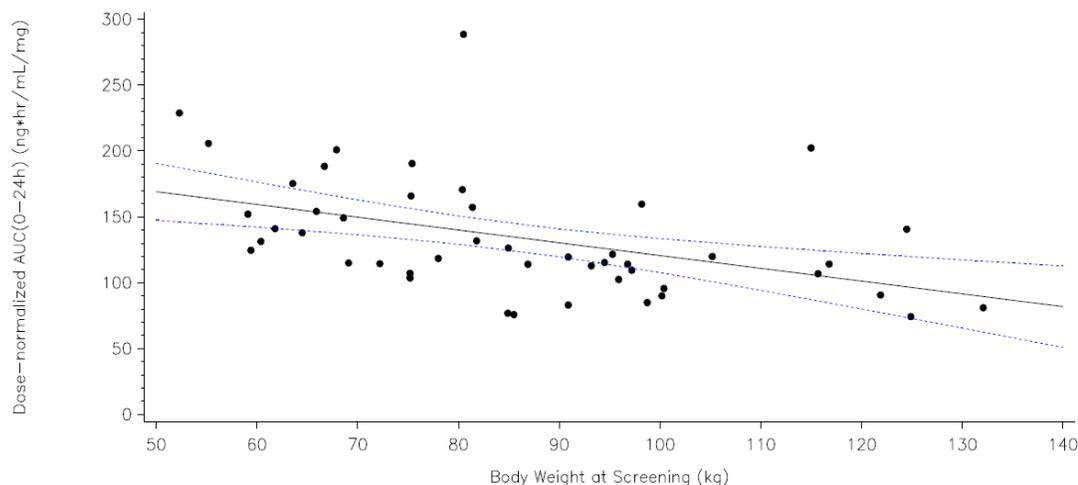
No formal studies were conducted to evaluate effects of intrinsic factors on methotrexate exposure in this NDA.

Body weight: The sponsor analyzed differences in methotrexate exposure, if any, based on body weight in Study MTX-10-003. Compared with the oral administration of methotrexate after 24 hours, the total systemic exposure (AUC 0-24) with Otrexup was about 43% higher for subjects with body weight (BW) < 75 kg, 25% higher for subjects with body weight (BW) ≥ 75 and < 100 kg; and 10% higher for subjects with BW ≥ 100 kg.

A scatter plot of body weight vs. AUC0-24 (Otrexup administered in abdomen) is shown below:



A scatter plot of body weight vs. AUC0-24 (Otrexup administered in thigh) is shown below:



Reviewer's comments: *Although there seems to be a linear correlation between weight and methotrexate systemic exposure, the difference in exposure (AUC) does not seem to be dramatic in subjects at the lower end of the weight range vs. subjects at the higher end of the weight range. Moreover, the methotrexate dose is generally titrated to effect. As such, no specific dosing recommendations need to be made based on the body weight analysis.*

Pediatrics: The addition of an auto-injector to an injectable methotrexate (a drug/device combination) does not trigger PREA, as this change is not considered to be a new dosage form. However, the sponsor's proposed route of administration (SC delivery of methotrexate via Otrexup) for treatment of RA, including pJIA, triggers PREA as the RA indication in the current approved methotrexate products is not labeled for SC dosing. The current approved parenteral methotrexate products are already labeled for SC administration in patients with JRA (pJIA) which is the pediatric counterpart of RA in adults. As such, since this is a 505(b)(2) NDA referencing currently approved and marketed methotrexate products that are already labeled for SC and IM dosing in children, PREA requirements are satisfied and the pediatric assessment is considered complete for children 2 years of age and older. The medical reviewer from DPARP, Dr. Peter Starke recommends that the requested waiver from pediatric assessments in children under 2 years of age is acceptable, as the disease does not exist in this age group. For the psoriasis indication, DDDP indicated that they plan to grant a full waiver of studies in the pediatric population with psoriasis for safety reasons (such as fatal toxic reactions), and will label the product accordingly. The application was discussed at the Pediatric Review Committee (PeRC) meeting on June 4, 2013 and PeRC concurred with the Divisions' recommendations.

2.5 General Biopharmaceutics

2.5.1 What is the relative bioavailability of the proposed test product when compared to the approved reference products?

Otrexup was found to be equivalent in terms of systemic methotrexate exposure (AUC) as well as peak plasma concentration (C_{max}) to both the subcutaneous and intramuscular administrations of approved methotrexate injection (Study MTX-10-001).

Otrexup was not found to be equivalent to the approved oral methotrexate tablets. Whereas systemic exposure of methotrexate with Otrexup increased linearly over a dose range of 10-25 mg, systemic exposure of methotrexate with oral methotrexate tablets leveled off at 15 mg staying similar between 15 through 25 mg of oral methotrexate indicating saturated oral absorption of methotrexate. Otrexup was found to yield similar exposures of methotrexate when administered into the abdomen or the thigh (Study MTX-10-003).

Study MTX-10-001 was a randomized, open-label, multi-center, 3-way crossover design study conducted in subjects with adult RA currently undergoing treatment with methotrexate. The methotrexate treatments in 4 dose groups (10 mg, 15 mg, 20 mg, or 25 mg) were investigated over the course of 3 treatment periods. The 3 treatment periods were each 1-week in duration and individual doses of methotrexate were separated by intervals of at least 7 days for washout. During each treatment period, all subjects received the assigned dose of MTX via 1 of the following 3 treatments:

- SC injection with Otrexup (Treatment A), (b) (4)
- SC injection without device (Treatment B); or
- IM injection (Treatment C).

Study MTX-10-001 showed that the 90% CIs for the test treatment (Otrexup) when administered as the proposed to be marketed device were within 80-125% of the approved parenteral methotrexate product (administered as both intramuscular and subcutaneous injections).

A dose-normalized plasma profile comparison (Otrexup was administered at all 4 doses, 10, 15, 20 and 25 mg) for the 3 treatments is shown below (Figure 1):

Figure 1: Plasma profiles of methotrexate when administered as Otrexup (test product) and as SC or IM injections of the approved parenteral methotrexate (references)

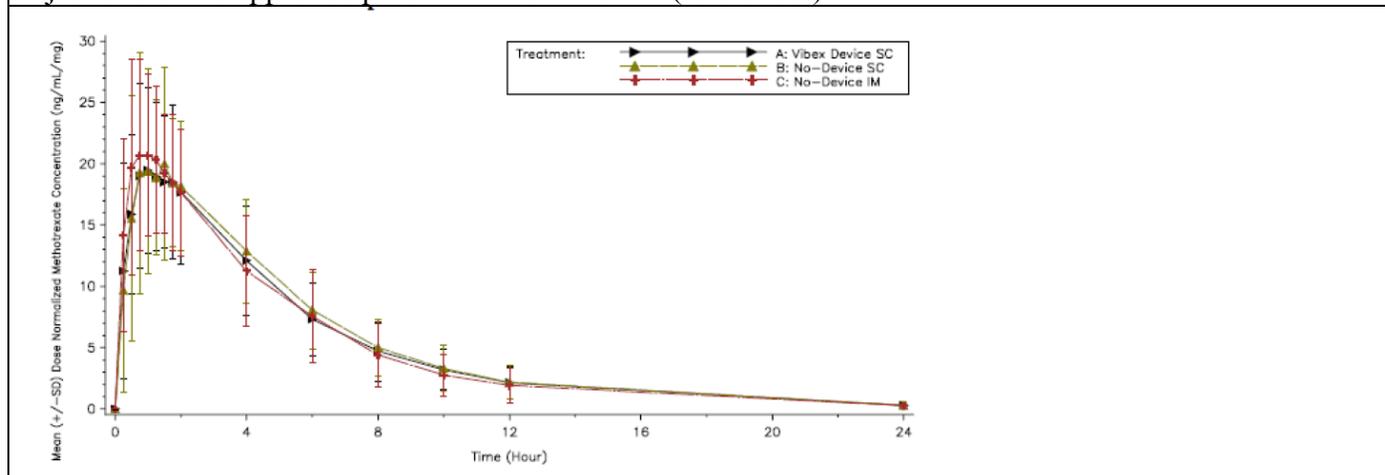


Table 1: BE analysis for the 3 treatments, i.e., Otrexup (test product) and as SC or IM injections of the approved parenteral methotrexate (references)

Dose-Normalized PK Parameter (unit)	SC Injection with Methotrexate Injection Device (Treatment A) (N=36) Geometric LS Mean	SC Injection without Device (Treatment B) (N=36) Geometric LS Mean	Ratio of Geometric LS Mean (%)	90% CI for Ratio (%)	Intra-Subject CV (%)
AUC _{(0-24)/Dose} (ng·hr/mL/mg)	111.30	115.7	96.22	(92.32, 100.28)	10.5
AUC _{(0-inf)/Dose} (ng·hr/mL/mg)	112.6	117.0	96.24	(92.33, 100.31)	10.6
C _{max} /Dose (ng/mL/mg)	20.2	20.9	96.76	(87.93, 106.47)	24.6

Reviewer's comments: Study MTX-10-001 showed that the 90% CIs for the test treatment (Otrexup) when administered as the proposed to be marketed device were within 80-125% of the approved reference treatment (intramuscular or subcutaneous).

Study MTX-10-003 was a randomized, open-label, multi-center, 3 way cross-over study in patients undergoing treatment with methotrexate conducted at 3 sites and approximately 12 weeks in duration. The primary objectives were to compare the relative bioavailability of methotrexate following oral administration vs. Otrexup. Otrexup was administered into 2 different injection sites, i.e., the abdomen and the thigh to compare the relative bioavailability of Otrexup when administered through these 2 sites as possible injection sites for Otrexup. Four dose groups (10 mg, 15 mg, 20 mg and 25 mg) were investigated over 3 treatment periods, each 1 week in duration separated by intervals of at least 7 days for washout. In each treatment period all subjects received the assigned dose of MTX via one of the following 3 treatments:

- Oral MTX (Treatment A)
- SC injection of MTX into the abdomen using the Methotrexate Injection device (Treatment B)
- SC injection of MTX into the thigh using the Methotrexate Injection device (Treatment C)

A dose-normalized plasma profile comparison (Otrexup was administered at all 4 doses, 10, 15, 20 and 25 mg) for the 3 treatments is shown below in Figure 2 and the BE analysis for comparing relative BA of Otrexup vs. oral methotrexate tablets and for comparing relative BA of Otrexup when injected into the abdomen vs. the thigh, is shown below in Tables 2 and 3 respectively:

Figure 2: Plasma profiles of methotrexate when administered as Otrexup (abdomen or thigh) and as oral tablets (reference).

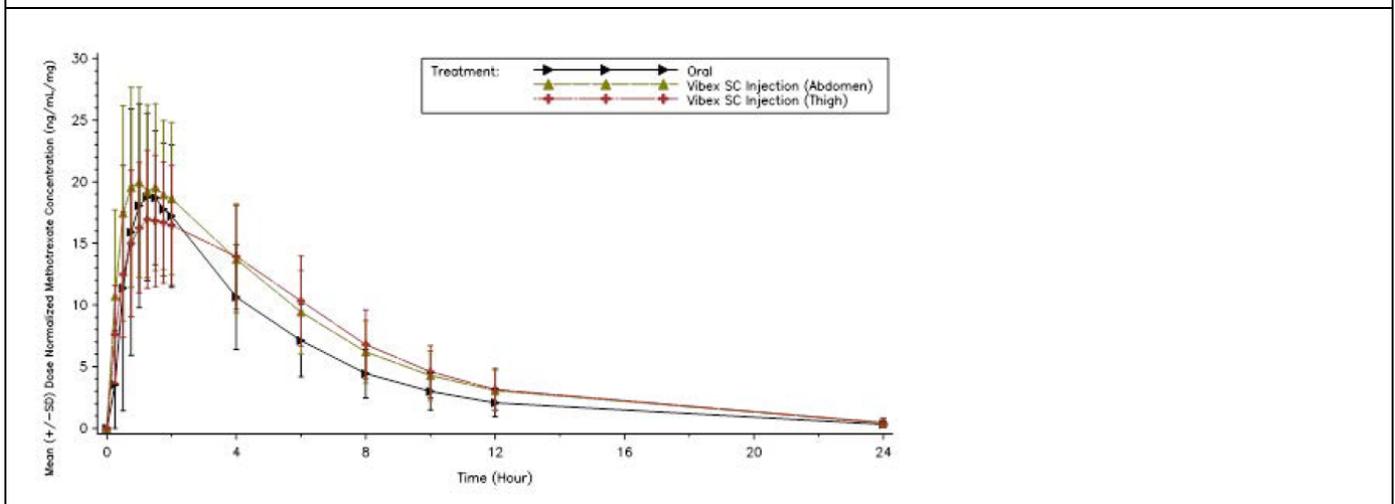


Table 2: BE analysis comparing Otrexup (administered intramuscular or subcutaneous) to oral methotrexate at the 4 doses tested

Dose Level PK Parameter	Methotrexate Injection – SC Injection (Thigh) Treatment C Geometric LS Mean	Oral MTX Treatment A Geometric LS Mean	Ratio of Geometric LS Mean (%)	90% CI for Ratio (%)	Intra-Subject CV (%)
Methotrexate 10 mg					
n	12	12			
AUC ₍₀₋₂₄₎ (ng·hr/mL)	1441.5	1223.7	117.80	(110.5, 125.6)	8.9
AUC _(0-inf) (ng·hr/mL)	1470.3	1246.9	117.91	(110.7, 125.6)	8.9
C _{max} (ng/mL)	178.4	247.2	72.17	(62.6, 83.2)	20.0
Methotrexate 15 mg					
n	12	12			
AUC ₍₀₋₂₄₎ (ng·hr/mL)	1992.7	1752.0	113.74	(106.1, 122.0)	10.0
AUC _(0-inf) (ng·hr/mL)	2040.6	1786.6	114.22	(106.3, 122.7)	10.2
C _{max} (ng/mL)	259.9	349.4	74.38	(68.2, 81.1)	12.4
Methotrexate 20 mg					
n	12	12			
AUC ₍₀₋₂₄₎ (ng·hr/mL)	2542.1	1927.2	131.90	(120.3, 144.6)	13.1
AUC _(0-inf) (ng·hr/mL)	2581.8	1949.7	132.42	(120.7, 145.3)	13.2
C _{max} (ng/mL)	385.7	440.4	87.57	(74.0, 103.6)	24.5
Methotrexate 25 mg					
n	11	11			
AUC ₍₀₋₂₄₎ (ng·hr/mL)	2708.6	1987.8	136.26	(122.2, 152.0)	14.4
AUC _(0-inf) (ng·hr/mL)	2745.3	2012.4	136.42	(122.4, 152.0)	14.3
C _{max} (ng/mL)	395.9	423.5	93.47	(79.06, 110.5)	22.3

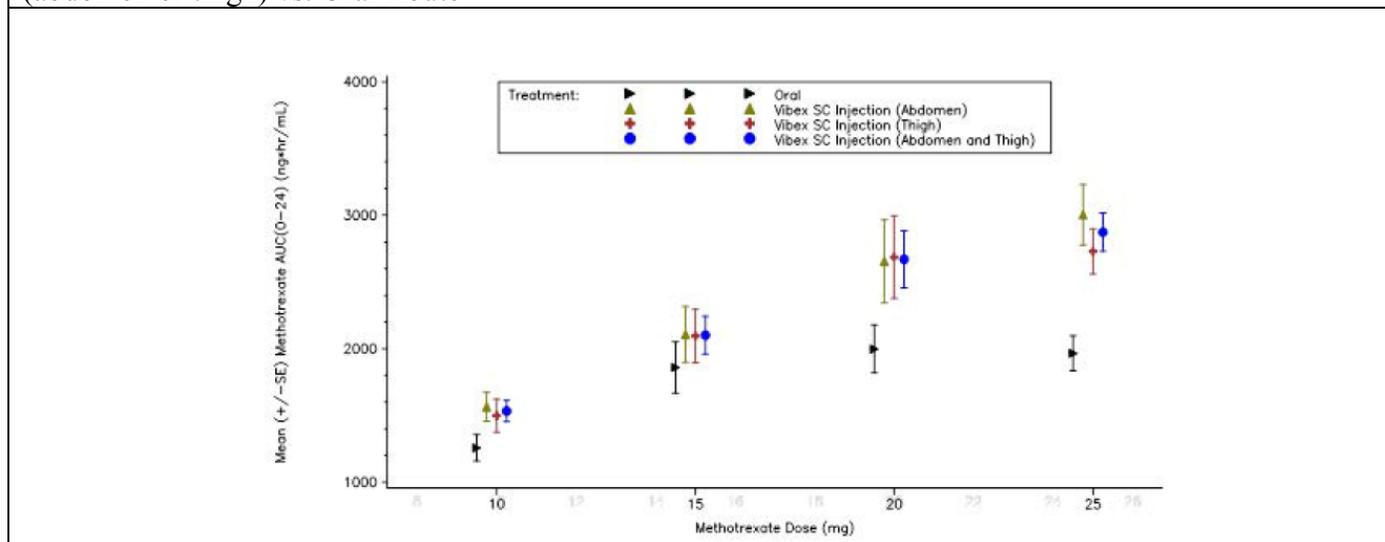
Table 3: BE analysis comparing Otrexup administration into the abdomen or the thigh

Dose-Normalized PK Parameter (unit)	Methotrexate Injection – SC Injection (Abdomen) Geometric LS Mean	Methotrexate Injection – SC Injection (Thigh) Geometric LS Mean	Ratio of Geometric LS Mean (%)	90% CI for Ratio (%)	Intra-Subject CV (%)
n	49	47			
AUC ₍₀₋₂₄₎ /Dose (ng·hr/mL/mg)	131.4	129.1	101.82	(99.39, 104.31)	7.0
AUC _(0-inf) /Dose (ng·hr/mL/mg)	133.9	131.4	101.85	(99.41, 104.36)	7.0
C _{max} /Dose (ng/mL/mg)	20.5	17.8	115.63	(108.83, 122.86)	17.7

Reviewer's comments: Study MTX-10-003 showed that methotrexate exposure with Otrexup is higher than that observed with oral methotrexate tablets. As shown in Figure 3 below, systemic exposure of methotrexate (AUC) with Otrexup increases linearly from 10 to 25 mg. However, with oral methotrexate administration, the oral absorption is saturated at 15 mg dose and does not seem to increase with increasing doses. From Table 2, Otrexup leads to higher systemic exposures of methotrexate as compared to oral methotrexate by 17%, 13%, 31% and 36% at 10, 15, 20 and 25 mg doses respectively. These differences in bioavailability between oral methotrexate and Otrexup, will be included in the product labeling. The differences in bioavailability seem to exist due to the fact that methotrexate exposure from oral methotrexate shows a plateau effect starting at 15 mg that is not observed for Otrexup. Differences in oral vs. parenteral absorption mechanisms could be one of the reasons for this difference in exposures between the two routes.

A plot of AUC vs. methotrexate dose (10 through 25 mg) as observed in Study MTX-10-003 is shown below in Figure 3:

Figure 3: Plot of Mean AUC(0-24) (ng·hr/mL) for Methotrexate When Administered as Otrexup (abdomen or thigh) vs. Oral Route



Reviewer's comments: Study MTX-10-003 also showed that Otrexup yields similar methotrexate systemic exposures when administered into abdomen or the thigh and this data will also be incorporated into the product labeling.

2.6 Analytical Section

2.6.1 What bioanalytical methods are used to assess methotrexate concentrations?

Two separate methods were validated for measurement of parent drug, methotrexate only (method MBL-10922M01) or measurement of both parent and metabolite, i.e., methotrexate and 7-hydroxymethotrexate (method MBL-11910M01). In these methods, methotrexate and 7-hydroxy methotrexate was extracted from 0.100 mL of human plasma by protein precipitation prior to LC-MS/MS analysis. A summary of method validations for both these methods is presented below:

Table 4: Analytical validation summary for method MBL-10922M01, for measurement of methotrexate only

Analyte:	Methotrexate
Internal Standard:	Methotrexate- <i>d</i> ₃
Calibration Range:	1 to 1000 ng/mL
Dilution verification	5-fold
Regression Type:	Linear, weighted (1/x ²)
Injection volume:	5 µL
Intraday precision and accuracy	%CV: ≤ 7.2% and %Bias: from -17.4% to -6.7% (for LLOQ) %CV: ≤ 7.0% and %Bias: from -5.9% to 6.5% (for other QC levels)
Inter-day precision and accuracy	%CV: ≤ 8.2% and %Bias: ≤ -10.9% (for LLOQ) %CV: ≤ 5.5% and %Bias: from -3.6% to 2.8% (for other QC levels)
Selectivity	No significant interferences observed
Carry over	No significant carry over observed
Extraction Recovery	58.7% to 61.7% for Methotrexate and 51.3% to 56.2% for the Methotrexate- <i>d</i> ₃
Matrix effect	10.1% to 11.6% for Methotrexate and 11.5% to 14.2% for the Methotrexate- <i>d</i> ₃
Bench-top stability	At least 4 hours at ambient temperature
Freeze/Thaw stability	At least 3 cycles at -20°C and -70°C
Autosampler stability	Approximately 22 hours at ambient temperature
Long-term frozen sample storage stability	At least 104 days at -20°C and -70°C
Stock solution stability	At least 30 days at ~4°C

Table 5: Analytical validation summary for method MBL-11910M01, for measurement of methotrexate and 7-hydroxymethotrexate

Analyte:	Methotrexate
Internal Standard:	Methotrexate- <i>d</i> ₃
Calibration Range:	1 to 1000 ng/mL
Dilution verification	5-fold
Regression Type:	Linear, weighted (1/x ²)
Injection volume:	2, 3, & 5 µL
Intraday precision and accuracy	%CV: ≤ 9.8% and %Bias: from 7.0% to 11.0% (for LLOQ) %CV: ≤ 4.4% and %Bias: from -9.8% to 5.7% (for other QC levels)
Inter-day precision and accuracy	%CV: ≤ 6.9% and %Bias: ≤ 9.0% (for LLOQ) %CV: ≤ 4.0% and %Bias: from -6.4% to 4.7% (for other QC levels)
Carry over	No significant carry over observed
Extraction Recovery	80.7% to 83.8% for Methotrexate and 80.0% to 85.4% for the Methotrexate- <i>d</i> ₃
Matrix effect	-10.3% to 4.4% for Methotrexate and -11.1% to 8.5% for the Methotrexate- <i>d</i> ₃
Bench-top stability	At least 4 hours at room temperature and 17 hours at 4°C
Freeze/Thaw stability	At least 3 cycles at -20°C and -70°C
Autosampler stability	Approximately 45 hours at ambient temperature
Extraction stability	Approximately 119 hours at 4°C
Long-term frozen sample storage stability	At least 131 days at -20°C and -70°C

Analyte:	7-OH Methotrexate
Internal Standard:	Methotrexate- d_3
Calibration Range:	1 to 1000 ng/mL
Dilution verification	5-fold
Regression Type:	Linear, weighted ($1/x^2$)
Injection volume:	2, 3, & 5 μ L
Intraday precision and accuracy	%CV: \leq 10.4% and %Bias: from 4.0% to 7.0% (for LLOQ) %CV: \leq 9.8% and %Bias: from -11.7% to 9.3% (for other QC levels)
Inter-day precision and accuracy	%CV: \leq 8.1% and %Bias: \leq 6.0% (for LLOQ) %CV: \leq 7.5% and %Bias: from -9.6% to 6.0% (for other QC levels)
Carry over	No significant carry over observed
Extraction Recovery	79.2% to 86.0% for 7-OH Methotrexate and 80.0% to 85.4% for the Methotrexate- d_3
Matrix effect	-13.6% to 9.8% for 7-OH Methotrexate and -11.1% to 8.5% for the Methotrexate- d_3
Bench-top stability	At least 4 hours at room temperature and 17 hours at 4°C
Freeze/Thaw stability	At least 3 cycles at -20°C and -70°C
Autosampler stability	Approximately 45 hours at ambient temperature
Extraction stability	Approximately 119 hours at 4°C
Long-term frozen sample storage stability	At least 131 days at -20°C and -70°C

Reviewer's comments: *The assay validation criteria including the accuracy and precision parameters are acceptable.*

3. Labeling Recommendations

The sponsor's proposed label was significantly modified by the Agency. Since the label is still undergoing several changes, the reader is requested to see the final approved label after the approval of the drug product. From a Clinical Pharmacology perspective, the following labeling language is recommended to be included in section 12.3 (Clinical Pharmacology/Pharmacokinetics) in addition to the standard language that will be borrowed from the listed drugs.

Recommended language to be added in section 12.3, Pharmacokinetics:

'In relative bioavailability studies in healthy subjects, systemic exposure of methotrexate was found to be similar between Otrexup and intramuscular or subcutaneous administration of methotrexate injection at the same dose, however systemic exposure of methotrexate was higher with Otrexup as compared to oral administration of methotrexate at the same dose. The systemic exposure of methotrexate from Otrexup at doses of 10, 15, 20 and 25 mg was higher than that of oral methotrexate by 17, 13, 31 and 36%, respectively. Methotrexate systemic absorption from Otrexup was similar when administered into the abdomen or thigh.'

4. Appendices

4.1 Filing Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
Information	Information	Information	Information	
NDA/BLA Number	NDA 204824	Proposed Brand Name	Otrexup™ (b) (4)	
OCP Division (I, II, III, IV, V)	II	Generic Name	Methotrexate auto-injector	
Medical Division	DPARP	Drug Class	Folate analog metabolic inhibitor	
OCP Reviewer	Sheetal Agarwal	Proposed Indication(s)	(b) (4) Severe psoriasis, not adequately responsive to other forms of therapy Rheumatoid arthritis (RA) and polyarticular-course juvenile rheumatoid arthritis (JRA)	
OCP Team Leader	Suresh Doddapaneni	Dosage Form	Single-use, single-dose, pre-filled, auto-injector	
Date of Submission	December 14, 2012	Dosing Regimen	Variable, titrated to effect. Autoinjector delivers fixed volume of 0.4 mL yielding final delivered doses of 10, 15, 20, or 25 mg for once weekly subcutaneous administration.	
Estimated Due Date of OCP Review	September 09, 2013	Route of Administration	Methotrexate is approved for oral, IM, IV, and intrathecal administration	
Medical Division Due Date		Sponsor	Antares Pharma	
PDUFA Due Date	Friday, October 11, 2013	Priority Classification	S	
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies to be reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X	2	2	Includes MTX-11-003 (relative bioavailability of autoinjector vs. oral) and MTX-10-001 (relative bioavailability of autoinjector vs. sc and im)
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1	1	Analytical Assay Method
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA 204824

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	1	1		Pediatric Plan
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -	X	2	2	Relative bioavailability of autoinjector vs. oral) and relative bioavailability of autoinjector vs. sc and im products
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	4	4		

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction	x			

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA 204824

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

	information?				
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA 204824

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

None.

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

None.

Additional comments: In addition to 2 relative BA studies, sponsor has conducted 2 additional studies, a single-dose safety study (MTX-10-002) and a device usability study (MTX-10-004). The sponsor has also summarized information available in literature for safety and efficacy of subcutaneous administration of methotrexate, as the sc route is not an approved route of administration in the current approved labels for methotrexate products. Since the sponsor is requesting for a new route of administration for methotrexate, the application triggers PREA and the sponsor has submitted a pediatric plan requesting full waiver from conducting pediatric studies citing several reasons which on a preliminary review were found to be reasonable by the reviewing medical officer, Dr. Peter Starke.

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA 204824

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

/s/

SHEETAL S AGARWAL
02/01/2013

SURESH DODDAPANENI
02/01/2013

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

/s/

SHEETAL S AGARWAL
09/03/2013

SATJIT S BRAR
09/03/2013

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	NDA 204824	Proposed Brand Name	Otrexup™ (b) (4)
OCP Division (I, II, III, IV, V)	II	Generic Name	Methotrexate auto-injector
Medical Division	DPARP	Drug Class	Folate analog metabolic inhibitor
OCP Reviewer	Sheetal Agarwal	Proposed Indication(s)	(b) (4) Severe psoriasis, not adequately responsive to other forms of therapy Rheumatoid arthritis (RA) and polyarticular-course juvenile rheumatoid arthritis (JRA)
OCP Team Leader	Suresh Doddapaneni	Dosage Form	Single-use, single-dose, pre-filled, auto-injector
Date of Submission	December 14, 2012	Dosing Regimen	Variable, titrated to effect. Autoinjector delivers fixed volume of 0.4 mL yielding final delivered doses of 10, 15, 20, or 25 mg for once weekly subcutaneous administration.
Estimated Due Date of OCP Review	September 09, 2013	Route of Administration	Methotrexate is approved for oral, IM, IV, and intrathecal administration
Medical Division Due Date		Sponsor	Antares Pharma
PDUFA Due Date	Friday, October 11, 2013	Priority Classification	S

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies to be reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X	2	2	Includes MTX-11-003 (relative bioavailability of autoinjector vs. oral) and MTX-10-001 (relative bioavailability of autoinjector vs. sc and im)
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1	1	Analytical Assay Method
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:		1	1	Pediatric Plan
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -	X	2	2	Relative bioavailability of autoinjector vs. oral) and relative bioavailability of autoinjector vs. sc and im products
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4	4	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction	x			

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA 204824

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	information?				
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

None.

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

None.

Additional comments: In addition to 2 relative BA studies, sponsor has conducted 2 additional studies, a single-dose safety study (MTX-10-002) and a device usability study (MTX-10-004). The sponsor has also summarized information available in literature for safety and efficacy of subcutaneous administration of methotrexate, as the sc route is not an approved route of administration in the current approved labels for methotrexate products. Since the sponsor is requesting for a new route of administration for methotrexate, the application triggers PREA and the sponsor has submitted a pediatric plan requesting full waiver from conducting pediatric studies citing several reasons which on a preliminary review were found to be reasonable by the reviewing medical officer, Dr. Peter Starke.

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

/s/

SHEETAL S AGARWAL
02/01/2013

SURESH DODDAPANENI
02/01/2013