CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205776Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW FOR METHOTREXATE PRE-FILLED PEN, NDA 205776

NDA	205776	*Submission Date(s)*	September 10, 2013
Proposed Brand Name		Rasuvo	
Generic Name		Methotrexate pre-filled pen 50 mg/mL	
Reviewer		Sheetal Agarwal, Ph.D., RAC	
Team Leaders		Satjit Brar, Pharm.D., Ph.D.	
OCP Division		Division of Clinical Pharmacology-2	
OND Divisions		Division of Pulmonary, Allergy and Rheumatology Products and Division of Topical and Ophthalmic Products	
Sponsor		Medac Pharma, a subsidiary of Medac GmbH US Agent: B&H Consulting Services, Inc	
Submission Type		505(b)(2) NDA referencing NDA 008085 (Methotrexate tablets) as well as literature	
Formulation; Strength(s)		Single-use auto-injector pen delivers fixed doses of 7.5 to 30 mg of methotrexate in 2.5 mg increments	
Proposed Indication(s)		For the treatment of rheumatoid arthritis including polyarticular-course juvenile rheumatoid arthritis and (b) (4) severe psoriasis.	
Proposed Dosing Regimen		Adult Rheumatoid Arthritis: Recommended starting dose is 7.5 mg Polyarticular-Course Juvenile Rheumatoid Arthritis: Recommended starting dose is 10 mg per m^2	

TABLE OF CONTENTS

1.0 Executive Summary

1.1 Recommendation:

Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 has reviewed Medac Pharma's NDA 205-776 requesting approval of Methotrexate pre-filled pen, a single-use, auto-injector product for methotrexate, and finds the proposed drug product acceptable from a clinical pharmacology perspective for the proposed indications of rheumatoid arthritis (RA) including polyarticular-course juvenile rheumatoid arthritis (pJIA).

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 methotrexate (MTX) pre-filled pen 50 mg/mL, was submitted under 505(b)(2) regulations referencing literature as well as the previously approved NDA 008085 (Dava's oral MTX tablets approved December 7, 1953). Methotrexate pre-filled pen 50 mg/mL is a combination drug-device auto-injector product intended for self-administration of a fixed dose of MTX, ranging from 7.5 to 30 mg, as a once weekly administration. Since MTX pre-filled pen 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 MTX products are indicated for neoplastic, rheumatology and psoriasis indications. However, the sponsor's proposed indications do not include neoplastic diseases as MTX pre-filled pen 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 (b) (4) severe psoriasis (PSOR). Since the sponsor is seeking the approval of rheumatology as well as psoriasis related indications, the NDA is being reviewed by two clinical divisions, DPARP and DDDP, respectively. This clinical pharmacology review only pertains to the RA and pJIA indications, a separate clinical pharmacology review for the psoriasis indications is being conducted by Dr. Donny Tran from DDDP.

The sponsor included data from one relative BA/BE clinical pharmacology study (MCMTX.14/PK) in this NDA providing a PK bridge to previously approved oral MTX tablets (NDA 008085). The sponsor also conducted an actual use study that evaluated two doses of MTX administered via the pre-filled pen injector in RA patients, in which they included clinical pharmacology related evaluations related to MTX absorption through 2 different injection sites (abdomen or upper thigh) and PK, in a subset of subjects, across a range of body weights (MC-MTX.15/HF).

Study MCMTX.14/PK compared the systemic exposure of 7.5, 15, 22.5 and 30 mg of MTX dosed orally (using oral MTX tablets, NDA 008085) vs. the same dose administered subcutaneously (SC) using the to-be-marketed MTX pre-filled pen injector in healthy subjects. MTX systemic absorption was higher with SC dosing as compared with oral dosing at all doses. $AUC_{(0\text{-inf})}$ was higher by 33, 46, 50 and 66% for the same methotrexate dose of MTX pre-filled pen than for oral MTX at 7.5, 15, 22.5 and 30 mg doses, respectively. This indicates that if patients taking oral methotrexate switch to MTX pre-filled pen at the same dose, they will exhibit higher systemic exposure of methotrexate. The differences in bioavailability of MTX with Medac's product as compared to the oral tablets will be included in the label. The higher exposure of MTX with sponsor's product (intended to be administered SC) as compared to corresponding doses of oral MTX tablets was expected. This relative BA study only provides a PK bridge to the already

approved oral MTX tablets for the same indications, higher exposure with Medac's pre-filled pen as compared to approved oral MTX tablets ensures its efficacy, with safety coverage provided by published literature for SC administration of MTX in RA at similar doses as well as with much higher doses of MTX administered for other indications, as reviewed by the DPARP clinical reviewer, Dr. Peter Starke in his clinical review of the existing safety and efficacy information for MTX products to support safety and efficacy for Medac's pre-filled pen. In addition, it should be noted that although at the time of pre-submission meetings for this product, the SC route of administration was considered a new route of administration for MTX injectable products (the label for approved products included oral and IM routes of administration), the Agency recently approved a MTX injectable product (Otrexup NDA 204824) for SC administration of MTX for the same indications as those requested by Medac for this product, as such, the SC route is not considered a new route of administration for MTX at the time of review of this NDA.

Study MC-MTX.15/HF evaluated effect of body weight (60-100 kg vs. less than 60 kg and higher than 100 kg) and effect of injection site (abdomen vs. upper thigh) on systemic exposure of MTX when administered SC as MTX pre-filled pen. The PK evaluation was conducted in a subset of 24 patients (out of 104 patients) only. The PK data showed that in subjects weighing more than 100 kg, mean AUC and mean Cmax of MTX decreased by approximately 16% and 33% respectively as compared to 60-100 kg group. In addition, the study showed that while absorption of MTX was higher through abdomen vs. thigh in subjects weighing less than 100 kg, absorption of MTX was higher through thigh vs. abdomen in subjects weighing more than 100 kg. As the number of subjects in each of these categories was too small to make a meaningful conclusion, and since MTX is generally titrated to a therapeutic dose, the differences in MTX absorption across subjects of different weights or through different injection sites are not considered clinically relevant and will not be included in the labeling.

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. Cook, the medical officer for DDDP.

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

An OSI inspection request was made for the relative BA study MCMTX.14/PK, the results from which are pending at the time of writing this review.

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 methotrexate pre-filled pen 50 mg/mL was submitted under 505(b)(2) regulations referencing both literature and the previously approved methotrexate product, NDA 008085 for oral MTX tablets. Currently approved NDAs for methotrexate include the most recently approved Otrexup, an auto-injector MTX product intended to be administered in fixed doses subcutaneously (NDA 204824), NDA 011719 (Hospira's methotrexate injection approved on August 10, 1959) and NDA 008085 (Dava's oral methotrexate tablets approved on December 7, 1953).

Methotrexate pre-filled pen 50 mg/mL is a combination drug-device auto-injector product intended for self-administration of a fixed dose of MTX, ranging from 7.5 to 30 mg, as a once weekly administration. As it is intended to be 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 is being reviewed by DPARP for the RA and pJIA indications and DDDP for the psoriasis indication. At the time of filing the NDA, the DDDP clinical pharmacology reviewer, Dr. Donny Tran requested the sponsor to clarify the status of another relative bioavailability study, study MC-MTX.12/PK, for which the sponsor had included a protocol in the NDA (Dr. Tran's filing review in DARRTS dated 11/8/13). Study MC-MTX.12/PK is a relative bioavailability study comparing MTX exposure from sponsor's product vs. an IM administration of the same dose of Methotrexate Injection, USP 25 mg/mL (Hospira's NDA 011719) in patients with psoriasis. In their response dated 1/16/14, the sponsor indicated that the study report for this trial will be submitted to the Agency in April 2014. This report was submitted to the Agency on April 30, 2014, and was reviewed by Dr. Donny Tran for the psoriasis indication (review in DARRTS dated 5/8/2014). As noted in his review, MTX exposure (AUC values) from the IM administration of MTX injection was comparable to the exposure from sponsor's product at the same dose. The relative BA results comparing the sponsor's product to the IM administration of approved MTX parenteral product were incorporated into the label.

For the indications of RA and pJIA, the sponsor has successfully linked their product to the oral MTX tablets for 505(b)(2) bridging purpose. The oral MTX tablets are approved for the same indications and the same doses as requested by the sponsor for their product. As such, the data from study MC-MTX.12/PK were not reviewed for the DPARP related indications.

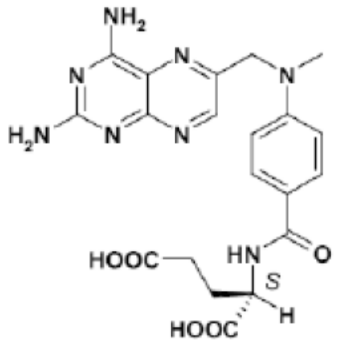
An OSI inspection request was made for the relative BA study MCMTX.14/PK, the results from which are pending at the time of writing this review.

2.1.2 What are the highlights of the chemistry and physico-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 MTX, as shown below, contains one asymmetric carbon atom located in the glutamic acid side chain. *S*-enantiomer of methotrexate for the [redacted] drug product is supplied by [redacted] and the morphic form of this methotrexate resembles the crystalline hydrate form [redacted] The content of the *R*-enantiomer in methotrexate is directly controlled with a validated HPLC analysis and indirectly controlled via optical rotation.

Chemical structure of methotrexate:



Molecular Formula: $C_{20}H_{22}N_8O_5$

Molecular Mass: 454.45 g/mol

Physical Form and Appearance: Yellow to orange, crystalline powder

Solubility: Practically insoluble in water, dichloroethane, ethanol, and diethylether; soluble in dilute acids and alkaline solutions. [redacted] 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	177	Freely soluble
7.5	167	Freely soluble
8.0	166	Freely soluble
8.5	193	Freely soluble
9.0	214	Freely soluble

Drug Product:

The drug product, methotrexate 50 mg/mL solution for injection, is a ready-to-use, pre-filled syringe assembled in a disposable pen (auto-injector) for subcutaneous use (methotrexate 50 mg/mL pre-filled pen). It is intended for single use. The pen is supplied to the patient completely assembled with the pre-filled syringe, which together form a single integral product that is not reusable but discarded in its entirety after single use. As the pre-filled pen does not allow dose adjustment, it is intended to market separate pens with appropriate filling volumes for each required dose. The following fill volumes are intended to be registered by the sponsor:

- pre-filled pen with 0.15 mL solution for injection, equivalent to 7.5 mg methotrexate
- pre-filled pen with 0.20 mL solution for injection, equivalent to 10 mg methotrexate
- pre-filled pen with 0.25 mL solution for injection, equivalent to 12.5 mg methotrexate
- pre-filled pen with 0.30 mL solution for injection, equivalent to 15 mg methotrexate
- pre-filled pen with 0.35 mL solution for injection, equivalent to 17.5 mg methotrexate
- pre-filled pen with 0.40 mL solution for injection, equivalent to 20 mg methotrexate

- pre-filled pen with 0.45 mL solution for injection, equivalent to 22.5 mg methotrexate
- pre-filled pen with 0.50 mL solution for injection, equivalent to 25 mg methotrexate
- pre-filled pen with 0.55 mL solution for injection, equivalent to 27.5 mg methotrexate
- pre-filled pen with 0.60 mL solution for injection, equivalent to 30 mg methotrexate

These fill volumes allow a gradual dose increase by 2.5 mg per week. After assembly of the pen with the pre-filled syringe, the ready-to-use, pre-filled pen is obtained. The pre-filled pen is intended solely for use in the given combination to administer the entire contents of the pre-filled syringe during one subcutaneous injection. The whole system (pre-filled pen) is provided as a single entity to the market, for single-use, and is to be discarded after injection.

The composition of methotrexate 50 mg/mL solution for injection is provided below:

Ingredient	Unit [mg/ml]	Function	Reference to standards
Methotrexate[a]	50	active	USP
Sodium chloride	(b) (4)	(b) (4)	USP
Sodium hydroxide[b]		(b) (4)	NF
		pH adjusting agent	
Hydrochloric acid (b) (4)	*q.s.*	pH adjusting agent	NF
Water for injection	(b) (4)	(b) (4)	USP
(b) (4)			
Total weight of solution	1022.8		
(b) (4)			

The pre-filled pen consists of a glass syringe (Type I (b) (4) glass) with embedded needle. The syringe is further assembled with a device for self-application (pen/auto-injector). The pen is supplied to the manufacturer for further assembly (b) (4) a picture of which is shown below:

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

Mechanism of Action:

- **Malignancy:** As currently labeled, MTX 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. When cellular proliferation in malignant tissues is greater than in most normal tissues, methotrexate may impair malignant growth without irreversible damage to normal tissues.

- **Rheumatoid Arthritis:** As currently labeled, the mechanism of action in rheumatoid arthritis is unknown; it may affect immune function.

- **Psoriasis:** In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in proliferation rates is the basis for the use of methotrexate to control the psoriatic process.

Proposed Indications:

- **Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis:** Methotrexate 50 mg/mL pre-filled pen is indicated for the treatment of rheumatoid arthritis including polyarticular-course juvenile rheumatoid arthritis.

- **Psoriasis:** Methotrexate 50 mg/mL pre-filled pen is indicated for treatment of (b) (4) 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***:* 7.5 mg as a single subcutaneous injection once weekly.
- **Polyarticular-Course Juvenile Rheumatoid Arthritis**: 10 mg/m^2 once weekly.
- (b) (4) **Severe Psoriasis:** 10-25 mg as a single subcutaneous injection once weekly.

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?

Data from 2 studies (design features shown below) had been incorporated in the product labeling by the sponsor at the time of submission of the NDA. Study MC-MTX.14/PK was a single center, open label, randomized, two-period, two-sequence, single dose crossover study in four dose groups to investigate the relative bioavailability of MTX when administered by SC injection as MTX 50 mg/mL pre-filled pen as compared to oral administration in healthy volunteers. No clinical safety/efficacy studies with MTX 50 mg/mL pre-filled pen were conducted. The NDA references several published studies for establishing safety and efficacy at proposed doses and for proposed indications. In addition, the NDA also includes a second study, study MC-MTX.15/HF in patients with RA across a range of body weights when using the MTX 50 mg/mL pre-filled pen for self-administered SC injections in the abdomen and upper thigh.

Study Identifier *Trial status (reference document)*	Design discussed with the FDA	Test product	Control	Trial population	Study design Treatment details	Main purpose of study
Pivotal trials						
MC-MTX.14/ PK *Completed CSR*	yes[1]	MTX 50 mg/ml pre-filled pen s.c.	MTX 2.5 mg tablets, USP (Dava), oral[2]	Healthy subjects (n = 56)	Randomized, 2 period, 2-sequence, single dose crossover study in 4 dose groups (7.5, 15, 22.5, and 30 mg) 2 MTX doses per subject (1x oral, 1x s.c.)	**Relative Bioavailability/PK** relative bioavailability of MTX (plasma concentrations of MTX) after s.c. injection with the MTX 50 mg/ml pre-filled pen compared to oral administration
MC-MTX.15/ HF[3] *Completed CSR*	yes[1]	MTX 50 mg/ml pre-filled pen s.c.	-	RA patients (n =106)	Two MTX doses per patient using s.c. MTX 50 mg/ml pre-filled pen Mean dose 15.74 mg (dose range: 7.5 to 20 mg)	**Handling/ usability/ PK / Safety** 1.) Evaluation of human factors/ usability of MTX 50 mg/ml pre-filled pen for RA patients 2.) Assessment of MTX bioavailability after s.c. injection using the MTX 50 mg/ml pre-filled pen in patients across a range of body weights

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/m^2 or less, methotrexate is generally well absorbed with a mean bioavailability of ~60%. The absorption of doses greater than 80 mg/m^2 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/m^2). 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 MTX exposure in this NDA. However the effect of body weight and different injection sites on MTX absorption was evaluated in a human factors study in RA subjects, i.e., study MC-MTX.15/HF.

Body weight: PK data for MTX across various body weights is shown below in Table 1. The number of subjects in each weight group was 7, 10 and 8 for less than 60 kg, 60-100 kg and more than 100 kg groups, respectively. Within each of these groups, the subjects were administered the test product either into the abdomen or in the upper thigh and the number of subjects in each of these different injection site groups was even smaller (ranging from 3 to 5). As such, interpretation of the PK data generated in this study for meaningful conclusion is challenging. Nevertheless, the data in the different weight groups shows that in subjects weighing more than 100 kg, mean total (AUC) exposure and mean peak (Cmax) exposure of MTX decreased by approximately 16% and 33%, respectively, as compared to 60-100 kg group. This difference in MTX exposure between different weight groups does not seem to be clinically relevant as the difference is almost in the range of observed inter-individual variability for MTX, i.e., 20-40% in the studies conducted by the sponsor. Moreover, since the drug is titrated to effect, subjects may develop tolerance to the drug as they are being titrated. Thus, the small differences in exposure between the different weight groups may not be clinically relevant. As such, the label for this product does not need to include any body weight based dosing recommendations based on PK data generated from this study.

Table 1: GM (CV) of plasma PK parameters of MTX by body weight (Source: Table 11-5 in study report for Study MC-MTX.15/HF

Parameter	<60 kg			60 to 100 kg			>100 kg		
	Abdomen N = 4	Upper Thigh N = 3	Total N = 7	Abdomen N = 5	Upper Thigh N = 5	Total N = 10	Abdomen N = 4	Upper Thigh N = 4	Total N = 8
$AUC_{0\text{-}inf}$ h•ng/mL									
Mean (CV)	2697.90 (31.1)	2391.13 (10.8)	2561.89 (23.6)	2803.99 (21.0)	2092.53 (23.4)	2422.28 (26.2)	1599.23 (39.7)	2584.80 (17.7)	2033.15 (39.0)
$AUC_{0\text{-}t}$ h•ng/mL									
Mean (CV)	2670.54 (30.1)	2351.47 (11.3)	2528.81 (23.1)	2748.07 (21.1)	2073.76 (22.9)	2387.22 (25.8)	1580.31 (38.5)	2528.83 (17.2)	1999.08 (38.0)
C_{max} (ng/mL)									
Mean (CV)	619.14 (36.6)	444.00 (10.6)	536.91 (32.1)	512.19 (16.6)	354.68 (23.6)	426.22 (27.7)	256.87 (26.6)	319.89 (22.1)	286.66 (25.6)

Injection site: Similar to evaluation of effect of body weight, the differences in Cmax and AUC of MTX when the product is administered in the abdomen or the upper thigh (data shown below in Table 2) do not seem to be clinically meaningful as the data is variable and inconsistent across the 3 weight groups for the 2 injection sites.

Whereas in subjects weighing less than 60 kg and in subjects weighing between 60-100 kg, MTX absorption is higher through the abdomen vs. thigh (Cmax difference: 28%, AUC difference: 11% in subjects less than 60 kg and Cmax difference: 30%, AUC difference: 25% in subjects weighing between 60 to 100 kg), MTX absorption is higher through the thigh than the upper abdomen in subjects weighing more than 100 kg (Cmax difference: 20%, AUC difference: 38%). Based on this PK data, no labeling recommendations based on injection site differences will be made and the subjects will be given the choice to choose between any of these 2 injection sites for their weekly administration.

Table 2: GM (CV) of plasma PK parameters of MTX by injection site (Source: Table 11-5 in study report for Study MC-MTX.15/HF

Parameter	<60 kg			60 to 100 kg			>100 kg		
	Abdomen N = 4	Upper Thigh N = 3	Total N = 7	Abdomen N = 5	Upper Thigh N = 5	Total N = 10	Abdomen N = 4	Upper Thigh N = 4	Total N = 8
$AUC_{0\text{-}inf}$ h•ng/mL									
Mean (CV)	2697.90 (31.1)	2391.13 (10.8)	2561.89 (23.6)	2803.99 (21.0)	2092.53 (23.4)	2422.28 (26.2)	1599.23 (39.7)	2584.80 (17.7)	2033.15 (39.0)
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C_{max} (ng/mL)									
Mean (CV)	619.14 (36.6)	444.00 (10.6)	536.91 (32.1)	512.19 (16.6)	354.68 (23.6)	426.22 (27.7)	256.87 (26.6)	319.89 (22.1)	286.66 (25.6)

2.5 General Biopharmaceutics

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

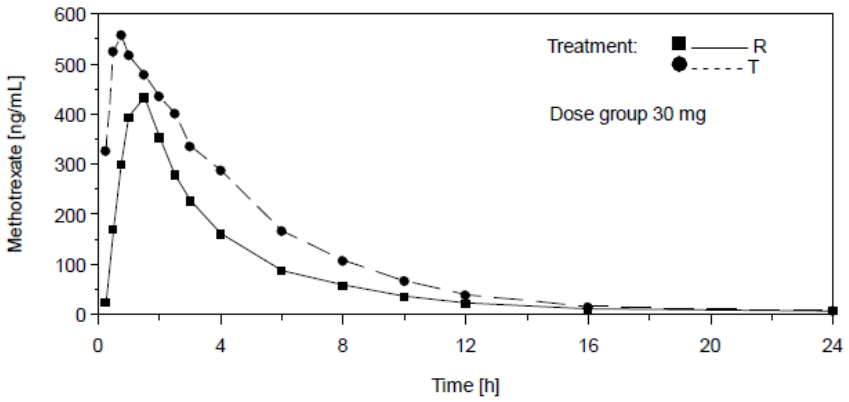
MTX pre-filled pen (intended to be SC administration) was not found to be equivalent in exposure to the approved oral MTX tablets. MTX systemic absorption was higher with SC dosing as compared with oral dosing, at all doses. The relative difference in $AUC_{(0\text{-}inf)}$ between the 2 products increased with an increase in dose, i.e., it was higher by 33, 46, 50 and 66% for the same methotrexate dose of MTX pre-filled pen than for oral MTX at 7.5, 15, 22.5 and 30 mg doses respectively. The higher exposure of MTX with sponsor's product as compared to corresponding doses of oral MTX tablets was expected as the subcutaneous route of administration circumvents first-pass metabolism. This relative BA study only provides a PK bridge to the already approved oral MTX tablets for the same indications, higher exposure with sponsor's product as compared to approved oral MTX tablets ensures efficacy with the sponsor's product. The primary safety and efficacy support for the sponsor's product comes from published literature with SC administration of MTX for several years for the proposed indications of RA and pJIA. Refer to Dr. Peter Starke's clinical review for a review of existing literature to support safety and efficacy for the sponsor's product.

Study MC-MTX.14/PK was a single center, open label, randomized, two-period, two-sequence, single dose crossover study in four dose groups in healthy male and female subjects. The primary objectives were to evaluate the relative BA of MTX based on systemic exposure of MTX when administered by SC injection with an auto-injector as compared to oral administration with doses of 7.5, 15, 22.5, and 30 mg. The SC administrations were made in the abdominal wall. Administrations were separated by a washout phase of at least 1 week. As the study was conducted in healthy volunteers, the subjects were given folinic acid (Calciumfolinat-GRY 15 mg tablets) at 24 and 48 h after each MTX administration to reduce the

severe hematotoxic and gastrotoxic effects of MTX and potassium-sodium-hydrogen citrate (Uralyt-U granulate) a single dose of 7.2 g at 12 h prior to MTX administration and 2.4 or 4.8 g at 4 and 12 h after each MTX administration depending on the obtained pH value, to reduce the nephrotoxic effects of MTX. These drugs are not expected to affect MTX bioavailability.

A plasma profile comparison of MTX pre-filled pen to oral MTX tablets at 30 mg dose (highest dose used in the study) is shown below in Figure 2 as representative of the 4 different doses used and the BE analysis for comparing relative BA of MTX pre-filled pen vs. oral methotrexate tablets at all the 4 doses is shown below in Table 3:

Figure 1: Plasma concentration profile of methotrexate when administered as MTX pre-filled pen (intended for SC administration, administered in abdomen in the study) and as oral tablets (reference)



Source: Figure 14.2.1
Linear concentration scale

Table 3: BE analysis comparing MTX pre-filled pen (abdomen) to oral methotrexate at the 4 doses tested

Parameter	Point estimate T/R [%]	Lower limit 90% CI [%]	Upper limit 90% CI [%]
AUC_{0-t}	135.00	123.04	148.13
$AUC_{0-\infty}$	132.83	121.73	144.95
C_{max}	100.12	91.13	109.99

CI: confidence interval
T: Prefilled pen containing 0.15 mL of the 50 mg/mL methotrexate solution corresponding to 7.5 mg methotrexate (test)
R: Methotrexate tablets USP corresponding to 7.5 mg methotrexate (reference)

Parameter	Point estimate T/R [%]	Lower limit 90% CI [%]	Upper limit 90% CI [%]
AUC_{0-t}	148.59	132.31	166.87
$AUC_{0-\infty}$	145.63	130.06	163.06
C_{max}	129.39	115.44	145.02

CI: confidence interval
T: Prefilled pen containing 0.3 mL of the 50 mg/mL methotrexate solution corresponding to 15 mg methotrexate (test)
R: Methotrexate tablets USP corresponding to 15 mg methotrexate (reference)

Parameter	Point estimate T/R [%]	Lower limit 90% CI [%]	Upper limit 90% CI [%]
AUC_{0-t}	150.57	142.13	159.50
$AUC_{0-\infty}$	150.03	141.81	158.74
C_{max}	130.91	113.78	150.63

CI: confidence interval
T: Prefilled pen containing 0.45 mL of the 50 mg/mL methotrexate solution corresponding to 22.5 mg methotrexate (test)
R: Methotrexate tablets USP corresponding to 22.5 mg methotrexate (reference)

Parameter	Point estimate T/R [%]	Lower limit 90% CI [%]	Upper limit 90% CI [%]
AUC_{0-t}	168.19	137.85	205.21
$AUC_{0-\infty}$	166.04	136.62	201.80
C_{max}	128.00	102.70	159.53

CI: confidence interval
T: Prefilled pen containing 0.6 mL of the 50 mg/mL methotrexate solution corresponding to 30 mg methotrexate (test)
R: Methotrexate tablets USP corresponding to 30 mg methotrexate (reference)

Study MC-MTX.14/PK showed that methotrexate exposure with MTX pre-filled pen is higher than that observed with oral methotrexate tablets. From Table 2, $AUC_{(0\text{-inf})}$ was higher by 33, 46, 50 and 66% for the same methotrexate dose of MTX pre-filled pen than for oral MTX at 7.5, 15, 22.5 and 30 mg doses respectively. These differences in bioavailability between oral methotrexate and MTX pre-filled pen, will be included in the product labeling to inform health care practictioners about the differences in MTX bioavailability between the 2 products.

2.6 Analytical Section

2.6.1 What bioanalytical methods are used to assess methotrexate concentrations?

(b) (4) validated analytical method 003/12-03.ME was employed to measure MTX plasma concentrations in the samples obtained from study MC-MTX.14/PK. The sponsor indicated that, due to an unexpected huge amount of invalid sequences for methotrexate, the analysis of the plasma samples was stopped for a lab investigation. After changing the sample preparation protocol and a new partial validation of the protocol, all samples were re-analyzed and the results of the first measurement were discarded. The reported results were obtained by re-analysis of study samples with the revised method. A brief summary is included in the following table 4:

Table 4: Analytical validation summary for method 003/12-03.ME, for measurement of methotrexate

Short description of the method:	LC-MS/MS
Bioanalytical matrix:	K_3-EDTA human plasma
Analyte:	Methotrexate
Internal standard:	Methotrexate-d3
Calibration range [ng/mL]:	5.000 – 1000.000
QC concentrations [ng/mL]:	12.000, 160.000, 400.000 and 800.000
Between-run accuracy [%]:	−11.25% to −6.07%
Between-run precision [%]:	4.02% and 6.27%

Calibration standards were prepared at seven concentration levels. The overall accuracy for calibration standards used in valid analytical sequences ranged from −3.88% to 3.38% and the precision was between 3.17% and 4.34%. The performance of the method was determined by the analysis of QC samples obtained for valid sequences. The overall accuracy for QC samples used in valid analytical sequences ranged from −11.25% to −6.07% and the overall precision was between 4.02% and 6.27%. Incurred sample re-analysis for methotrexate was performed in 96 study samples from 23 subjects in Period 1 and 25 subjects in Period 2 (2 samples per subject and period). The results for 92 samples (96%) were within ±20% of the original value. Overall, the assay validation criteria including the accuracy and precision parameters are acceptable.

3. Labeling Recommendations

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 edits are recommended:

- Delete from section 2.4, Administration and Handling; (b) (4) and section 17, Patient Counseling Information:

(b) (4)

Rationale: (b) (4) As such, it is recommended that sponsor's proposed statement be deleted.

- Delete from section 12.3, Pharmacokinetics:

(b) (4)

(b) (4)

Rationale: Promotional and excessive, not useful language.

- Add in section 12.3, Pharmacokinetics:

In a relative bioavailability study in healthy subjects, the systemic exposure of methotrexate (AUC) from Rasuvo at doses of 7.5 mg, 15 mg, 22.5 mg, and 30 mg, was higher than that of oral methotrexate administered at the same doses by 35%, 49%, 51%, and 68%, respectively. In a relative bioavailability study in psoriasis patients, the systemic exposure (AUC) of methotrexate from Rasuvo at a dose of 30 mg, was similar to that of methotrexate administered at the same dose by intramuscular route.

Rationale: The differences in bioavailability of MTX from sponsor's product vs. oral MTX tablets and the IM injection are included in the label to inform health care practitioners of the differences in systemic exposure from both the products. The sponsor has evaluated 2 sites of injection for their product, i.e., upper thigh and abdomen, and since significant absorption differences between the 2 sites were not detected, both the sites can be potentially used for injecting the product.

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
06/02/2014

SATJIT S BRAR
06/02/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Division of Clinical Pharmacology 3** **Office of Clinical Pharmacology** **Tracking/Action Sheet for Formal/Informal Consults**

From: **Doanh Tran, R.Ph., Ph.D.**			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 5/7/2014	IND No.: Serial No.: DARRTS No.:	NDA No. **205776**	DATE OF DOCUMENT **9/10/2013**	
NAME OF DRUG **Methotrexate pre-filled pen 50 mg/mL**	PRIORITY CONSIDERATION		Date of informal/Formal Consult: 11/5/2013	

NAME OF THE SPONSOR: Medac Pharma

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☒ OTHER *(SPECIFY BELOW)*: [New NDA]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☒ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☐ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox	☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ See submission cover letter
☐ Micro ☐ Pharmacometrics ☐ Others		☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)		[ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

Please see attached review.

SIGNATURE OF REVIEWER: _____ **SIGNATURE OF TEAM LEADER:**	Date _____ Date _____
CC.: DCP3; TL: None; DD: Bashaw	**Project Manager:**_____ **Date** _____

Clinical Pharmacology Consults Review for NDA 205776

Background: NDA 205776 (methotrexate (MTX) pre-filled pen) was submitted on 9/10/2013 for treatment of rheumatoid arthritis (RA), polyarticular-course juvenile rheumatoid arthritis (JRA), and severe psoriasis. This is a 505(b)(2) NDA referencing Methotrexate for Injection, 10 mg/mL and 25 mg/mL (NDA 11-719, Hospira, Inc.) and Methotrexate Tablets (NDA 08-085, Dava Pharmaceuticals, Inc.). The lead review division is the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). The primary Clinical Pharmacology reviewer for this NDA is Dr. Sheetal Agarwal.

This reviewer was requested to consider whether the available bridging data are adequate to support the psoriasis indication. At time of the initial NDA submission, the applicant provided the results of trial MC-MTX.14/PK evaluating the relative BA of Medac's product with the approved methotrexate oral tablets. The results showed that Cmax and AUC were generally higher with Medac's pre-filled pen given subcutaneously (SC) than those with the oral tablets. This trial is reviewed by Dr. Sheetal Agarwal and will not be discussed further in this review.

There was no direct relative BA comparison data of Medac's pre-filled pen (proposed to be administered SC) and the approved methotrexate injection (approved for administration intramuscularly (IM) or intravenously (IV)) included in the initial NDA. However, there were indirect data that could be reviewed to address the relative BA to the approved methotrexate injection. This reviewer noted the following in the filing memorandum (DARRTS dated 11/8/3013):

> "The NDA does include a supportive PK trial MC-MTX.9/PH that administered a methotrexate pre-filled syringe (i.e., not the proposed pre-filled pen) to assess the effect of the strength of formulation (10 mg/mL and 50 mg/mL). The trial included 2 treatment groups, administering the drug via SC route in one group and via IM route in the other group. The results will be considered during the NDA review to evaluate if there is an effect of formulation strength on absorption (proposed pen is formulated at 50 mg/mL strength and the listed drug is available as 10 mg/mL and 25 mg/mL). In addition, a comparison between the SC and IM routes of administration may be made to support relative BA between these 2 routes. In addition, it appears that the elimination of methotrexate following administration of Medac's pre-filled pen follows linear kinetics with no apparent depot effect and therefore one may assume that the bioavailability of the SC route is less than or equal to the same dose administered via the approved IV route."

During drug development, the sponsor had submitted protocol MC-MTX.12/PK to evaluate the relative BA of Medac's pre-filled pen (given SC) and the approved methotrexate for injection (25 mg/mL, Hospira) given IM. This protocol was also included in the current NDA but no results were provided. An inquiry was made regarding the status of trial MC-MTX.12/PK in the Day-74 letter (DARRTS dated 11/22/2013). As a result, the sponsor submitted the draft study report of trial MC-MTX.12/PK on 4/3/2014 and the final study report on 4/30/2014.

Because trial MC-MTX.12/PK directly addresses the question of relative BA between Medac's pre-filled pen and the listed drug methotrexate injection, it will be the focus of this review. In light of the availability of results from trial MC-MTX.12/PK, a detailed review of supportive PK

trial MC-MTX.9/PH is no longer necessary and thus is not done.

Summary of findings:
Methotrexate is approved for treatment of psoriasis at a dose of 10 – 25 mg once weekly. The same doses can be administered as oral tablets or IM or IV injections (the oral dose can also be administered as 2.5 mg every 12 hours for 3 doses per week). Doses are gradually adjusted to achieve optimal clinical response up to a maximum dose of 30 mg per week. The same recommendation applies among the oral, IM, or IV routes. There appears to be a large range of dose for methotrexate and optimal dosing is titrated based on clinical response.

Medac's MTX pre-filled pen differs from the approved MTX injection in formulation (i.e., higher strength of 50 mg/mL and slight change in the amount of sodium chloride (NaCl) (b) (4)) and route of administration (i.e., SC vs. IM and IV).

The sponsor has provided relative BA data from trial MC-MTX.14/PK which indicate that Medac's pre-filled pen (given SC) results in Cmax and AUC values greater than or equal to that of methotrexate oral tablets. Because the sponsor is proposing to dose Medac's pre-filled pen at the same starting dose of 10 mg/week as approved for the oral tablets, efficacy should be ensured with the higher systemic exposure.

From a safety perspective, we need to ensure that the exposure of Medac's pre-filled pen at a dose of 30 mg (given SC) is not higher than that of the approved methotrexate injection given IM or IV because the approved dose for treatment of psoriasis is recommended not to exceed 30 mg. In addition, relative bioavailability to the approved MTX injection product would aid in the determination of whether a dose adjustment may be needed. The sponsor has provided results of trial MC-MTX.12/PK which compared the bioavailability of a single dose of 30 mg MTX administered as Medac's pre-filled pen (given SC) vs. approved MTX injection given IM. The results showed that Medac's pre-filled pen given SC has similar AUC but about 25% lower Cmax compared to the approved MTX injection given IM (Table 1).

Table 1: Relative bioavailability Medac's prefilled pen injector given SC vs. reference MTX injection given IM (geometric means and CV%, n=34 except where noted otherwise).

Parameter	Medac's pre-filled pen	Listed drug MTX injection	Ratio of Medac/Listed drug	90% CI of the ratio
AUC0-inf (ng*h/mL)	3180 (27.9)	3235 (19.6)[a]	98.10%	90.69 – 106.11%
AUC0-t (ng*h/mL)	3160 (27.9)	3214 (19.3)	98.30%	91.02 – 106.16%
Cmax (ng/mL)	606 (36.1)	808 (37.0)	74.99%	67.55 – 83.25%

[a] n=33

Recommendation:
The available relative bioavailability data are adequate to support bridging of Medac's prefilled

pen to the listed drugs MTX injection and MTX oral tablets for the indication of treatment of severe, recalcitrant, disabling psoriasis. Data from trial MC-MTX.14/PK showed that Medac's pre-filled pen (given SC) has Cmax and AUC values greater than or equal to that of MTX oral tablets (Reviewed by Dr. Sheetal Argawal). The results of trial MC-MTX.12/PK showed that Medac's pre-filled pen given SC has similar AUC and 25% lower Cmax compared to the approved MTX injection given IM. Therefore, there are no safety concerns with respect to systemic exposure of Medac's pre-filled pen relative to the approved MTX injection product.

Individual trial review of trial MC-MTX.12/PK:

Title: Relative Bioavailability of Methotrexate 50 mg/mL Administered Subcutaneously by a Disposable Autoinjector (Metoject® prefilled pen) Compared with Intramuscular Administration of the United States-Reference Listed Drug Methotrexate Injection (USP 25 mg/mL [Hospira]) in Patients with Psoriasis

Study center(s): The study was conducted at 2 study sites in the United States as follows:

- Site 00001: Douglas S. Denham, DO, Clinical Trials of Texas, Inc, San Antonio, TX 78229 USA.
- Site 00002: Terry M. Jones, MD, J & S Studies, Inc, College Station, TX 77845 USA.

Studied period (5 months):
Date of first patient, first visit: 06 May 2013
Date of last patient, last visit: 08 October 2013

Objectives:
Primary Objective:

- To determine the relative bioavailability of methotrexate (MTX) based on the parent compound MTX when administered by subcutaneous (SC) injection with a prefilled pen (50 mg/mL) as compared with intramuscular (IM) administration (25 mg/mL)

Secondary Objectives:

- To assess the pharmacokinetic (PK) characteristics of MTX (50 mg/mL) when administered by SC injection with a prefilled pen compared with IM administration of the parent reference compound MTX (25 mg/mL)
- To evaluate the safety of MTX after both routes of administration
- To evaluate the local tolerability of both routes of administration

Methodology:
The study comprised a 2-center, single dose, 2-period, 2-treatment, open-label, randomized crossover design to determine the bioavailability of MTX administered as an IM injection (reference article: MTX Injection, USP manufactured by Hospira, Inc) and as an SC injection from a prefilled pen (test article: Metoject prefilled pen).

For each of the 2 periods, patients were admitted to the clinical research unit the evening prior to dosing. Eligible patients were randomly assigned to receive each of the following treatments in a crossover fashion:

- A single dose of 30 mg of MTX administered as an IM injection of 1.2 mL of 25-mg/mL MTX solution
- A single dose of 30 mg of MTX administered as an SC injection using a prefilled pen (Metoject Pen) containing 0.6 mL of 50-mg/mL MTX solution

Even though the drug products are administered as IM or SC injection, the trial required subjects

to fast for at least 10 hours prior to dosing. Subjects continued to fast for 4 hours after dosing. Water was allowed 1 hour before and 1 hour after dosing. All subjects received 5 mg folic acid immediately following the 24-hour PK sampling.

IM injections were administered on the upper thigh, upper arm, or upper buttock. SC injections were administered on the thigh or abdomen. Specifically, IM injection locations for patients in the IM/SC sequence group included the upper arm (4 patients [23.5%]) and the upper buttock (13 patients [76.5%]). IM injection locations for patients in the SC/IM sequence group included the upper arm (8 patients [47.1%]) the upper buttock (8 patients [47.1%]), and the upper thigh (1 patient [5.9%].

For SC injection locations, in the IM/SC sequence group, 7 patients (41.2%) received MTX by SC administration in the abdomen, and 10 patients (58.8%) received MTX by SC administration in the thigh. In the SC/IM sequence group, 7 patients (41.2%) received MTX by SC administration in the abdomen, and 10 patients (58.8%) received MTX by SC administration in the thigh.

Study drug was administered by the investigator or a qualified designee. For each treatment period, patients were confined to the clinical research unit until 24 hours after dosing. Blood samples were collected for PK analysis for 24 hours after dosing. Physical examinations, vital sign measurements, 12 lead electrocardiograms, and clinical laboratory evaluations were performed at screening and at selected times. Patients were monitored for adverse events (AEs), including local tolerability assessments at the injection site, throughout the study.

A washout period of 7 days separated dosing between the 2 periods.

The final study visit was performed 7 (± 2) days after administration of the last dose of study drug in Period 2. Patients were discharged from the study after completion of this visit.

Number of patients (planned and analyzed):
A total of 18 patients were enrolled into the IM/SC treatment sequence group, and a total of 17 patients were enrolled into the SC/IM treatment sequence group, for an overall total of 35 patients included in the all enrolled analysis set. One patient (ID 10034, randomized to IM/SC treatment group) was screened and randomized but discontinued from the study prior to dosing on Day 1 of Period 1. Overall, 34 patients were included in the safety analysis set and also in the PK analysis set.

Diagnosis and main criteria for inclusion:
The patient population included adult (18 – 65 years of age) male and female patients with moderate to severe psoriasis. If a patient was currently receiving MTX for the treatment of psoriasis and his or her diagnosis of moderate to severe psoriasis from a dermatologist was available at screening, Physician's Global Assessment scoring was not necessary. However, if a patient was not currently receiving MTX for the treatment of psoriasis, at screening the patient's psoriasis was evaluated using Physician's Global Assessment scoring. Patients with moderate, moderate to severe, or severe psoriasis were eligible for study participation.

Test product, dose and mode of administration, batch number(s):
A single lot/batch (K110548BA) of prefilled pens, filled with 30 mg of 0.6-mL MTX (50 mg/mL) solution (Metoject Pen), was used in the study.

Reference therapy, dose and mode of administration, batch number(s):
A single lot/batch (Z124437AA) of MTX injection, USP (MTX Hospira), 25 mg/mL, 2-mL vials, was used in the study.

Pharmacokinetics samplings and analysis:
During each period, blood samples (4.0 mL) for the determination of MTX plasma concentrations were collected before dosing (between 2 hours and up to 30 minutes before the study drug administration) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours after dosing. The acceptable windows for the collection times were ± 2 minutes for samples scheduled from 0.25 to 4 hours after dosing and ± 5 minutes for samples scheduled from 6 to 24 hours after dosing.

The relative bioavailability of MTX administered subcutaneously was assessed using an analysis of variance (ANOVA), fitting a linear mixed-effect model on the natural logtransformed AUC0-t, AUC0-inf, and Cmax with sequence, treatment, and period as fixed effects and patient nested within sequence as a random effect.

Assay validation:
A liquid chromatography-mass spectrometry (LC/MS) method was used for the determination of the MTX concentration in the patient plasma samples. Bioanalysis of MTX concentrations was performed by (b) (4) The assay was adequately validated with a range of 1 – 1000 ng/mL. Precision and accuracy was within acceptable limits of ±15% (±20 at lower limit of quantitation). Storage stability at -20 ºC was demonstrated for 449 days (study samples were stored at -20 ºC for up to 183 days). 111 samples (10.2% of all samples) were reassayed for incurred samples reanalysis and 107 (96.4%) were within ±20% acceptance limit.

Results:

Pharmacokinetics Results:
Mean plasma concentrations of MTX following both IM injection of the reference product and SC injection of Medac's pre-filled pen in patients with psoriasis increased rapidly and reached the maximum concentration at a median Tmax of 0.5 and 0.75 hour, respectively (Figure 1). Mean plasma MTX levels declined mono-exponentially (Figure 2). Mean total exposure (AUC0-t or AUC0-inf) of MTX was similar following injection of 30 mg of MTX using either products in patients with psoriasis. However, mean peak exposure (Cmax) of MTX was lower following SC injection of Medac's pre-filled pen compared with IM injection of the reference product. The mean elimination half-life ($t_{1/2}$) of MTX for both treatments was similar and ranged from 3.20 to 3.31 hours (Table 2).

Figure 1: Mean plasma concentration of MTX versus time by treatment (linear scale). Closed circles = IM injection of reference product, open squares = SC injection of Medac's product.

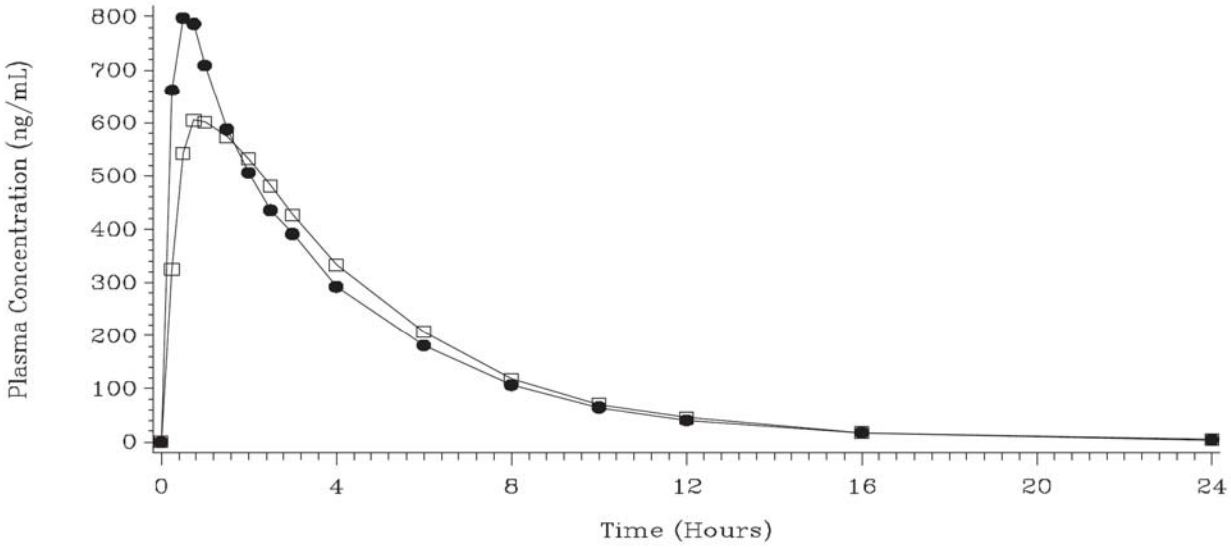


Figure 2: Mean plasma concentration of MTX versus time by treatment (semiLogarithmic scale). Closed circles = IM injection of reference product, open squares = SC injection of Medac's product.

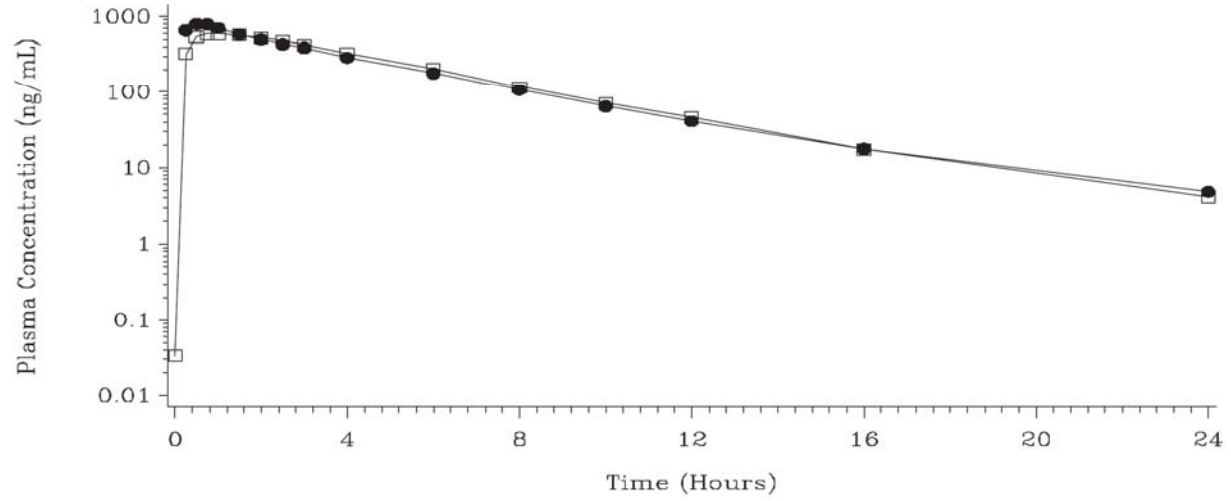


Table 2: Geometric mean (CV%) plasma pharmacokinetic parameters of MTX

Parameter	IM[a] (N = 34)	SC[b] (N = 34)
AUC_{0-t} (ng•h/mL)	3214.29 (19.3)	3159.65 (27.9)
AUC_{0-inf} (ng•h/mL)	3234.96 (19.6)[c]	3179.81 (27.9)
C_{max} (ng/mL)	807.80 (37.0)	605.79 (36.1)
T_{max} (h)[d]	0.50 (0.25, 1.50)	0.75 (0.50, 2.50)
AI (1/h)	0.25 (28.9)[c]	0.19 (21.2)
CL/F (L/h)	9.27 (19.6)[c]	9.43 (27.9)
V_d/F (L)	44.25 (25.8)[c]	43.59 (33.4)
MRT (h)	4.13 (19.3)[c]	4.52 (16.3)
λz (K_{el}) (1/h)	0.2096 (19.7)[c]	0.2164 (17.6)
$t_{1/2}$ (h)	3.31 (19.7)[c]	3.20 (17.6)

Abbreviations: AI, absorption index; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; AUC_{0-t} calculated using the linear trapezoid rule, area under the plasma concentration versus time curve from time zero to the last measureable concentration; C_{max}, maximum observed plasma MTX concentration directly from plasma concentration time curve; CL/F, apparent clearance of MTX; CV%, percent coefficient of variation; h, hour(s); IM, intramuscular; λz (Kel), elimination rate; MRT, mean residence time from time zero extrapolated to infinity; MTX, methotrexate; SC, subcutaneous; $t_{1/2}$, terminal half-life of MTX; T_{max}, time to reach the observed maximum (peak) concentration; V_d/F, apparent volume of distribution of MTX based upon the terminal phase.

[a] IM: Single dose of 30 mg MTX administered as a 1.2-mL IM injection (Hospira, Inc, 25 mg/mL).

[b] SC: Single dose of 30 mg MTX administered as an SC injection using a prefilled pen containing 0.6 mL of 50-mg/mL MTX solution.

[c] n = 33; some parameters could not be estimated for Patient Number 10009 due to a poor regression fit (R-squared <0.80) to the patient's terminal phase concentration data.

[d] For T_{max}, the median (minimum, maximum) values are presented.

Relative bioavailability:

The 90% CIs for the geometric LS means ratios of AUC0-t and AUC0-inf for MTX in the comparison of Medac's pre-filled pen SC injection with the reference drug IM injection were within the range of 80% to 125%, indicating equivalence of MTX total exposure following the administration of Medac's pre-filled pen versus the reference drug (Table 3). Consistent with the statistical analysis, a comparison of intra-individual AUC showed similar values for the 2 treatments except for one subject (Figure 3).

The 90% CI for the geometric LS means ratios of Cmax for MTX in the comparison of Medac's pre-filled pen SC injection with the reference drug IM injection were 67.55% to 83.25% with a point estimate of 74.99%, indicating a lower peak exposure of MTX following Medac's pre-filled pen administration versus administration of the reference drug (Table 3). A comparison of intra-individual Cmax values showed that, while some subjects had higher Cmax values, the majority of the subjects had lower Cmax value following administration of Medac's pre-filled pen (Figure 4).

A reanalysis of the BE statistics using Phoenix software by this reviewer showed similar results

as reported by sponsor. Therefore, only results reported by sponsor are shown below.

Table 3: Relative bioavailability of Medac's prefilled pen injector given SC vs. reference MTX injection given IM.

Parameter	Treatment[a]	N	Geometric LS Means	Treatment Comparison	Ratio (%) of Geometric LS Means	90% Confidence Interval of the Ratio
$AUC_{0\text{-}inf}$ (ng•h/mL)	IM	33	3241.44	SC/IM	98.10	90.69 – 106.11
	SC	34	3179.81			
$AUC_{0\text{-}t}$ (ng•h/mL)	IM	34	3214.29	SC/IM	98.30	91.02 – 106.16
	SC	34	3159.65			
C_{max} (ng/mL)	IM	34	807.80	SC/IM	74.99	67.55 – 83.25
	SC	34	605.79			

Abbreviations: $AUC_{0\text{-}inf}$, area under the plasma concentration versus time curve from time zero extrapolated to infinity; $AUC_{0\text{-}t}$, area under the plasma concentration versus time curve from time zero to the last measureable concentration, calculated using the linear trapezoid rule.; C_{max}, maximum observed MTX plasma concentration directly from plasma concentration time curve; IM, intramuscular; LS, least squares; MTX, methotrexate; PK, pharmacokinetic; SC, subcutaneous.

[a] IM = Single dose of 30 mg MTX administered as a 1.2-mL IM injection (Hospira, Inc, 25 mg/mL). SC = Single dose of 30 mg MTX administered as an SC injection using a prefilled pen containing 0.6 mL of 50-mg/mL MTX solution.

Note: An analysis of variance was performed by fitting a linear mixed-effect model on the natural log-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} with sequence, treatment, and period as fixed effects and patient nested within sequence as a random effect.

*Reviewer's Note: The geometric mean for the $AUC_{0\text{-}inf}$ IM group in Table 3 is different than the geometric mean reported in Table 2 (AUC of 3241 vs. 3235 ng*h/mL). The dataset for this parameter has one missing value (subject 10009) and the minor difference in calculated geometric means appears to be due to the way the BE analysis software take into account the 1 missing value.*

Figure 3: Comparison of intra-individual AUC_{0-t} (SC=Medac's pre-filled pen, IM=reference drug)

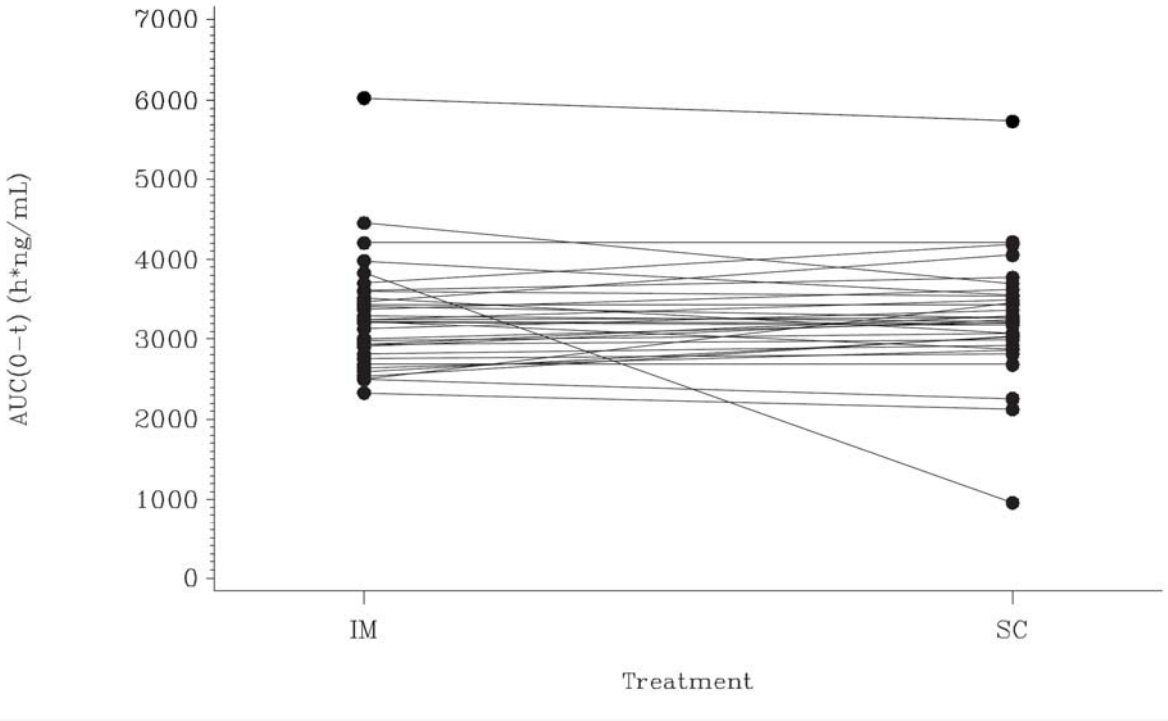
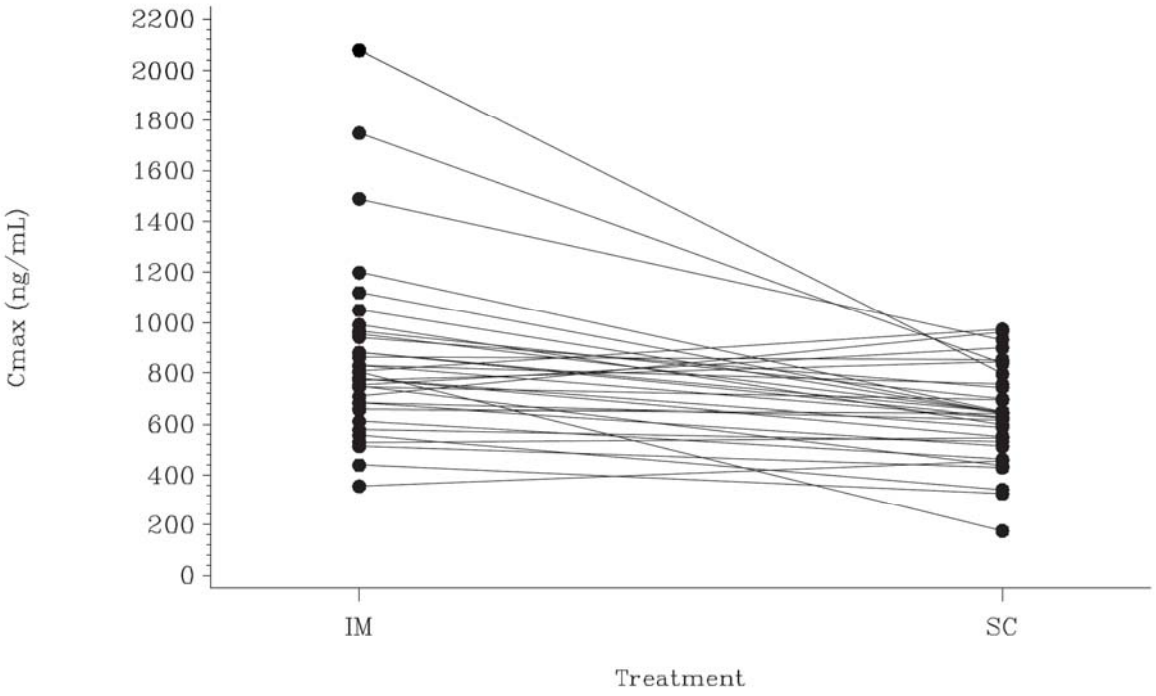


Figure 4 Comparison of intra-individual Cmax (SC=Medac's pre-filled pen, IM=reference drug)



Safety Results:

A summary of safety results as provided by sponsor is shown below. This reviewer has not reviewed details of the safety results. Please see review by the Medical Officer for more details and review conclusions.

- Following IM administration, 8 patients (23.5%) reported an AE. No patient reported an injection site reaction. Five patients (14.7%) reported AEs that were considered by the investigator to be related to MTX. Regarding severity, 2 patients (5.9%) reported moderate AEs (both headaches); and 1 patient (2.9%) reported a severe AE (headache).
- Following SC administration, 14 patients (41.2%) reported an AE. Four patients (11.8%) reported injection site reactions. Redness was reported at the injection site by 1 to 2 patients at varying time points up to 2 hours after dosing; no patients reported redness 24 hours after dosing, and there were no reports of pain, itching, hematoma, or swelling at any time point assessed after SC injection. Ten patients (29.4%) reported AEs that were considered by the investigator to be related to MTX. Regarding severity, 5 patients (14.7%) reported moderate AEs (headache [2 patients], limb injury [1 patient], wound [1 patient], contact dermatitis [1 patient], and urticarial [1 patient]). There were no severe AEs reported following SC administration.
- No SAEs, deaths, ADEs, UADEs, or AEs leading to discontinuation were reported following IM or SC administration.
- No clinically meaningful treatment-related trends were observed in any laboratory parameters, vital sign measurements, physical examinations, ECG parameters, or chest x-ray findings.

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/s/

DOANH C TRAN
05/07/2014

HAE YOUNG AHN
05/08/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Division of Clinical Pharmacology 3** **Office of Clinical Pharmacology** **Tracking/Action Sheet for Formal/Informal Consults**

From: **Doanh Tran, R.Ph., Ph.D.**			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 11/7/2013	IND No.: Serial No.: DARRTS No.:	NDA No. **205776**	DATE OF DOCUMENT **9/10/2013**	
NAME OF DRUG **Methotrexate pre-filled pen 50 mg/mL**	PRIORITY CONSIDERATION		Date of informal/Formal Consult: 11/5/2013	

NAME OF THE SPONSOR: Medac Pharma

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☒ OTHER *(SPECIFY BELOW):* [New NDA]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated) ☐ E-mail comments to: ☐Medical ☐Chemist ☐Pharm-Tox ☐Micro ☐Pharmacometrics ☐Others (Check as appropriate and attach e-mail)	☐ Oral communication with Name: [ ] ☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ Formal Review/Memo (attached) ☒ See comments below ☐ See submission cover letter ☐ OTHER *(SPECIFY BELOW)*: [ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

Background: NDA 205776 was submitted on 9/10/2013 for treatment of rheumatoid arthritis (RA), polyarticular-course juvenile rheumatoid arthritis (JRA), and severe psoriasis. This is a 505(b)(2) NDA referencing Methotrexate for Injection, 10 mg/mL and 25 mg/mL (NDA 11-719, Hospira, Inc.) and Methotrexate Tablets (NDA 08-085, Dava Pharmaceuticals, Inc.). The lead review division is the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). The primary Clinical Pharmacology reviewer for this NDA is Dr. Sheetal Agarwal. Dr. Agarwal has completed the Clinical Pharmacology filing review and determined that it is fileable from a DPARP's perspective. This reviewer was requested to consider whether the available bridging data is adequate to support the psoriasis indication. Since Dr. Agarwal has already addressed other aspects of a filing review (See Clinical Pharmacology filing memorandum in DARRTS, dated 11/7/2013), this review memorandum will only address the specific question related to relative bioavailability (BA) bridging of the proposed methotrexate pre-filled pen 50 mg/mL to the listed drugs.

Available relative BA data in the NDA:

The sponsor provided results of trial MC-MTX.14/PK. This trial evaluated the relative BA of Medac's product with the approved methotrexate oral tablets. The results showed that Cmax and AUC were generally higher with

Medac's pre-filled pen given subcutaneously (SC) compared to the oral tablets. The sponsor considers this to be the pivotal relative BA data supporting the NDA.

There was no relative BA comparison of Medac's pre-filled pen (proposed to be administered SC) and the approved methotrexate injection (approved for administration intramuscularly (IM) or intravenously (IV)). During the IND stage, the sponsor had submitted protocol MC-MTX.12/PK to evaluate the relative BA of Medac's pre-filled pen (given SC) and the approved methotrexate for injection (25 mg/mL) given IM. This protocol was also included in the current NDA. However, there was no study report or any reference to its results or whether the study was conducted.

Reviewer's comments:
Methotrexate is approved for treatment of psoriasis at a dose of 10 – 25 mg once weekly. The same doses can be administered as oral tablets or IM or IV injections (the oral dose can also be administered as 2.5 mg every 12 hours for 3 doses per week). Doses are gradually adjusted to achieve optimal clinical response up to a maximum dose of 30 mg per week. The same recommendation applies among the oral, IM, or IV routes. There appears to be a large range of dose for methotrexate and optimal dosing is titrated based on clinical response.

The sponsor has provided relative BA data from trial MC-MTX.14/PK which indicate that Medac's pre-filled pen (given SC) results in Cmax and AUC values greater than or equal to that of methotrexate oral tablets. Because the sponsor is proposing to dose Medac's pre-filled pen at the same starting dose of 10 mg/week as approved for the oral tablets, efficacy should be ensured with the higher systemic exposure.

From a safety perspective, we need to ensure that the exposure of Medac's pre-filled pen at a dose of 30 mg (given SC) is not higher than that of the approved methotrexate injection given IM or IV. The sponsor previously proposed trial MC-MTX.12/PK, which would have addressed this issue directly. However, the results were not included in this NDA. The NDA does include a supportive PK trial MC-MTX.9/PH that administered a methotrexate pre-filled syringe (i.e., not the proposed pre-filled pen) to assess the effect of the strength of formulation (10 mg/mL and 50 mg/mL). The trial included 2 treatment groups, administering the drug via SC route in one group and via IM route in the other group. The results will be considered during the NDA review to evaluate if there is an effect of formulation strength on absorption (proposed pen is formulated at 50 mg/mL strength and the listed drug is available as 10 mg/mL and 25 mg/mL). In addition, a comparison between the SC and IM routes of administration may be made to support relative BA between these 2 routes. In addition, it appears that the elimination of methotrexate following administration of Medac's pre-filled pen follows linear kinetics with no apparent depot effect and therefore one may assume that the bioavailability of the SC route is less than or equal to the same dose administered via the approved IV route. This indirect method of relative BA assessment in the absence of results from trial MC-MTX.12/PK is not ideal and will be considered in more details during NDA review.

Recommendation:
This reviewer recommends that NDA 205776 be accepted for filing from a clinical pharmacology perspective.

Comments to be sent to sponsor:
1. You have provided relative bioavailability trial protocol MC-MTX-12/PK in the NDA. However, a study report for this trial was not provided. Clarify the status of this trial.
2. Provide raw pharmacokinetic data for trial MC-MTX.9/PH in SAS Transport (.xpt) format.
3. For trial MC-MTX.9/PH: Provide analysis of relative bioavailability (Cmax and AUC) between the subcutaneous (SC) route and the intramuscular (IM) route. The analysis should be stratified by formulation strengths (i.e., 10 mg/mL and 50 mg/mL) as well as based on pooled data from both strengths. Also, provide detailed formulation composition information for the drug products used in this trial.

SIGNATURE OF REVIEWER: _____	Date _____
SIGNATURE OF TEAM LEADER: _____	Date _____
CC.: DCP3; TL: None; DD: Bashaw	**Project Manager:**_____ **Date** _____

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/s/

DOANH C TRAN
11/08/2013

HAE YOUNG AHN
11/08/2013

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 205776**	**Proposed Brand Name**	**TBD**
OCP Division	**II**	**Generic Name**	**Methotrexate pre-filled pen 50mg/mL**
Medical Division	**DPARP**	**Drug Class**	**Folate analog metabolic inhibitor**
OCP Reviewer	**Sheetal Agarwal**	**Proposed Indication(s)**	**Rheumatoid arthritis (RA) and polyarticular-course juvenile rheumatoid arthritis (JRA)**
OCP Team Leader	**Satjit Brar**	**Dosage Form**	**Single-use, single-dose, pre-filled, manually triggered injector**
Date of Submission	**September 10, 2013**	**Dosing Regimen**	**Variable depending on indication, titrated to effect. Delivers fixed doses of 7.5 to 30 mg of methotrexate in 2.5 mg increments**
Estimated Due Date of OCP Review	**June 5, 2014**	**Route of Administration**	**Intended for once weekly subcutaneous administration. (27 gauge needle, ½ inch needle length)**
Medical Division Due Date		**Sponsor**	**Medac Pharma (US agent: B&H Consulting Services, Inc.)**
PDUFA Due Date	**July 10, 2014**	**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 MCMTX.14/PK (relative bioavailability of pen vs. oral) and MCMTX.15/ HF (Actual Use Study) which includes PK assessments for effect of body weight and different injection sites on methotrexate absorption.**
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:				

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multiple dose:				
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**	**1**	**1**	**Relative bioavailability of sponsor's product (pen) vs. marketed and approved methotrexate oral tablets**
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	

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

2	Has the applicant provided metabolism and drug-drug interaction information?	x			
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.

Reviewer's comments: This NDA is a 505(b)(2) NDA submitted by Medac Pharma, for a drug/device combination of Methotrexate (MTX) Injection as a pen injector. The NDA references previously approved and currently marketed MTX products, Methotrexate for Injection (NDA 11-719, Hospira) and Methotrexate Tablets (NDA 8-085, Dava). The NDA has been submitted to DPARP for the RA and pJIA indications as well as to DDDP for psoriasis indication. This review pertains only to the DPARP indications.

The proposed product is a single-use auto-injector pen containing from 7.5 to 30 mg of MTX in 2.5 mg increments, and intended for subcutaneous (SC) injection. The product includes a single dose, pre-filled glass syringe with a 27-gauge, ½ inch needle that delivers a fixed volume of sterile preservative-free MTX solution at a concentration of 50 mg/mL, varying the fill volume from 0.15 to 0.60 mL depending upon the dose in the syringe. The injection is manually triggered by a button at the opposite end from the needle.

Several pre-submission meetings have been held for this product with the sponsor where relative BA assessments that may be needed to bridge this product to the approved MTX products for (505)(b)(2) purpose have been discussed extensively. The NDA submission includes the following clinical pharmacology/clinical data:

- 2 studies conducted by the sponsor:
  - MC-MTX.14/PK: Open label relative BA study (in healthy adults) to link systemic exposure of Medac's product (intended for SC administration) with that of approved and marketed methotrexate oral tablets
    - The higher exposure observed with SC administration implies that efficacy is assured for the proposed indications, with safety covered by clinical experience with much higher doses and systemic exposures that are already included in the labeling (see clinical filing review in DARRTS dated 11/6/2013 by Dr. Peter Starke)
  - MC-MTX.15/HF: Open label Human Factors study that included administration of 2 doses of methotrexate in RA patients
    - Stated to have included label comprehension, human factors, usability, device durability, and PK in a subset of patients across a range of body weights as well as assessment of methotrexate exposure when administered SC in thigh or abdomen
- Review of the literature summarizing the efficacy and safety of SC administration
- A pediatric study plan
  - Waiver of pediatric studies below 2 years of age because the necessary studies are impossible or highly impractical, i.e., the product is not likely to be used in a substantial number of patients in this age group.

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

Regarding pediatric studies for this product: The proposed SC dosing administration route for methotrexate was not indicated as an approved route of administration in the previously approved labels for methotrexe products (oral tablets and parenteral methotrexate), that are listed as references by the sponsor, however, the labels for these products did include some language related to SC dosing of methotrexate to indicate that parenteral routes (including IM and SC) may have beneficial effects in terms of GI tolerability over oral dosing. However, on October 11, 2013 (after Agency received Medac's NDA) the Agency approved methotrexate fixed-dose autoinjector product Otrexup (NDA 204824) which includes SC dosing for RA, pJIA, and psoriasis indications based on supporting clinical trial information provided from literature. Therefore, although initially believed (pre-NDA submission) that this product will trigger PREA due to the new route of administration (SC), at this time, this product does not trigger PREA as we recently approved another MTX product, Otrexup, to be administered SC. However, as the dosage form itself is different from any of the currently approved products (delivers doses ranging from 7.5 to 30 mg as fixed doses), PREA may still be triggered due to difference in 'dosing regimen'. This has not been confirmed at the time of the filing meeting. For recently approved Otrexup, the following is indicated in its approval letter regarding pediatric studies: '*We are waiving the pediatric study requirement for ages 0 through 2 years because pJIA is extremely rare in this age group and studies would be impossible or highly impractical. This product is appropriately labeled for use in pJIA patients ages 2 to 17 years. Therefore, no additional studies are needed in this pediatric group.*' The same principles will probably apply to Medac's product as well.

OSI inspection request: At the filing meeting held on 11/5/2013, the need for an OSI inspection for the relative BA study MC-MTX.14/PK was discussed. It was determined that an OSI inspection request should be made for this study due to the following reasons:

1. The study showed that Medac's product yields higher systemic exposure of methotrexate (MTX) as compared to that of the oral tablets at all the 4 doses employed. At 30 mg dose, the difference in systemic exposure was about 68%. The sponsor has not provided a PK bridge to the approved parenteral MTX product (NDA 11-719 Hospira), as such, it is unknown whether IM or SC administration with the approved parenteral MTX product would have yielded similar exposure as that of Medac's product at the same dose.
2. To be able to justify including the PK data from the relative BA study comparing Medac's product to the oral MTX tablets in Medac's product labeling (if approved), and in the absence of a relative BA assessment comparing Medac's product to approved parenteral MTX, the review team decided that it was best to ensure that the study conducted by Medac was done in the right manner including using US approved products as well as using appropriate analytical assay methodology. The study does not seem to have been conducted under an IND and was conducted in Germany in healthy subjects (patient population is recommended for a toxic drug like MTX).

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/s/

SHEETAL S AGARWAL
11/06/2013

SATJIT S BRAR
11/07/2013