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APPLICATION NUMBER:

205776Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205-776
Priority or Standard	Standard
Submit Date(s)	September 9, 2013
Received Date(s)	September 10, 2013
PDUFA Goal Date	July 10, 2014
Division / Office	DDDP in collaboration with DPARP/OND
Reviewer Name(s)	Denise Cook, M.D.
Review Completion Date	June 4, 2014
Established Name	Methotrexate Injection
(Proposed) Trade Name	Rasuvo
Therapeutic Class	Folate analog metabolic inhibitor
Applicant	Medac Pharma, a subsidiary of Medac GmbH
Formulation(s)	Solution for injection in a pre-filled, manually-trigger auto-injector
Dosing Regimen	Subcutaneous injection
Indication(s)	Symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation Rheumatoid Arthritis (RA) Polyarticular Juvenile Idiopathic Arthritis (pJIA) (see separate review by DPARP for latter 2 indications)
Intended Population(s)	Severe recalcitrant disabling psoriasis: adults RA: adults pJIA: 2 years of age and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This application is recommended for approval.

1.2 Risk Benefit Assessment

This is a 505(b)(2) new drug application submitted by Medac Pharma, for a drug/device combination of Methotrexate (MTX) injection, a folate analog metabolic inhibitor, in a presentation consisting of a single-use, single-dose, pre-filled, manually-triggered, "pen" auto-injector intended for subcutaneous (SC) injection. Medac proposes to market multiple dosage strengths from 7.5 mg to 30 mg in 2.5 mg increments. (b) (4) The proposed indications are severe active rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), and severe recalcitrant, disabling psoriasis, where it is to be administered once weekly in the thigh or abdominal wall areas.

The application was submitted on September 10, 2013. The application references two listed drugs for methotrexate: NDA 08-085 for Methotrexate Tablets from Dava Pharmaceuticals and NDA 11-719 for Methotrexate Injection EQ 50 mg base/2mL from Hospira. The proposed Trade Name is Rasuvo, and the PDUFA date is July 10, 2014.

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

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 those of RA, pJIA, and psoriasis, and do not include treatment of neoplastic diseases. Given the

1 *Note*: The current labeling for the oral and parenteral products, which share unified labeling, include IM and SC administration for JRA. Therefore, the proposed SC route for this product does not represent a new route of administration for the JRA indication, although it does represent a new route of administration for adults with RA and psoriasis.

higher dosing used for most of the oncology indications and the fact that this product can only be administered by the subcutaneous route, it is appropriate to limit the indications to the RA, pJIA, and psoriasis indications as proposed by the sponsor rather than broadening the labeling to neoplastic diseases.

The proposed doses (from 7.5 mg to 30 mg in 2.5 mg increments) will cover most of the currently recommended doses for treatment of psoriasis and RA, but will not adequately cover dosing for the entire pJIA population in children, which is dosed by mg/m^2 in doses starting at about 5 mg. Although the oncology indications are not being sought by the applicant, the proposed doses would not adequately cover dosing for these conditions, which extend far higher by the IV route and may require leukovorin rescue. Issues with dosing raised by the limitations imposed by the product will necessitate limitations for use in the Dosing and Administration section of this product.

Because the applicant has proposed RA/pJIA and psoriasis indications, a joint review was conducted, with review of the RA and pJIA indications in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) and review of the (severe) psoriasis indication in the Division of Dermatology and Dental Products (DDDP). This review focuses on the psoriasis indication in DDDP. For discussions of the RA and pJIA indications, please see separate reviews by the Division of Pulmonary, Allergy, and Rheumatology Products.

No clinical trials were performed to support the therapeutic effect, safety, or efficacy using the to-be-marketed product. Support for approval of this application is based on the Agency's previous findings of safety and efficacy for the proposed indications, the literature, 1 bioavailability study in adults MC-MTX.14/PK and an in-use study. The results of the BA study MC-MTX.14/PK support the efficacy of SC dosing in RA and psoriasis patients because, when compared to oral exposure, SC dosing yields higher systemic exposures, particularly after GI absorption is saturated both at 15 mg and above oral doses of 15 mg. Efficacy and safety of MTX administered by the SC route in children with pJIA is already established.

Safety in adults with psoriasis is supported by the long safety record in these patients, safety information when administered by this and other routes at much higher doses for other indications, such as treatment of neoplasms, as well as safety information from the literature when MTX is administered by the SC route to RA patients (see DPARP review). Safety in adults with psoriasis is supported by safety information with IM and IV administration in these patients, where systemic exposure is expected to meet or exceed systemic exposure after SC dosing. The safety of the SC route is further supported by the relative bioavailability study MC-MTX.12/PK where at the highest recommended dose for psoriasis, the systemic exposure of the SC dose was the same or lower than the IM dose.

Specifically, support comes from:

1. The Agency's previous findings of the safety and effectiveness of methotrexate in adults with RA (oral route) and psoriasis (oral, IM and IV routes), and in children with JRA (pJIA) (oral, SC, and IM routes).
2. A BA study (MC-MTX.14/PK) in healthy adults that links the proposed product to the approved oral MTX product and supports the efficacy of SC administration of MTX in adult patients with RA and psoriasis because it showed equal or greater systemic exposure to MTX administered SC from the proposed pen injector product when compared to with orally administered MTX tablets. The higher systemic exposure with SC administration encompasses the known efficacy with oral administration and is supported by substantial safety data with similar or higher systemic exposures when MTX is administered by approved routes and at higher doses, all of which are represented in the labeling of the listed products referenced in the application (see DPARP reviews).
3. Literature data that support the safety and efficacy of SC administration of methotrexate for RA, pJIA, and psoriasis. Of note, the applicant performed a clinical trial (MC-MTX.06) that compared the efficacy and safety of a predecessor MTX subcutaneous product with oral dosing in patients with RA, and the study report was submitted with the application. Because the trial did not evaluate the to-be-marketed product, the study report was submitted to the NDA and considered to be a supportive but not a pivotal study. In this respect, the trial was similar to the other literature reports submitted to the application that support SC administration as an alternative to oral or IM administration of MTX, with higher systemic exposure and minimization of oral toxicity when administered by the SC or IM routes compared with oral administration at similar doses, particularly when the doses are above 15 mg. The safety review of the literature and of the studies provided to this application did not reveal any new safety signals that would require additional labeling beyond those already labeled in the reference products (see DPARP review).
4. An actual use study (MC-MTX.15/HF) to support the labeling for use of the proposed product. The study demonstrated that patients and caregivers could be taught to successfully administer the product and that the device functions appropriately in the patient's hands.

   The applicant also performed a BA study (MC-MTX.12/PK) comparing the proposed product administered SC to the referenced Hospira parenteral product administered IM. However, the study report for this study was not submitted with the application. It was determined prior to filing that this study would not be needed to support review of the submission or approval of the NDA. The results of the study became available during the course of the review of the NDA (submitted on April 30, 2014), and were reviewed. Also, BA study MC-MTX.9/PH which compared the SC route to the parental routes (IM and IV) provided indirect evidence to support the parental routes for the indication in psoriasis. Although not pivotal for approval, these studies added support to the current application in terms of safety because of the direct

comparison of the SC route with the already approved IM route in psoriasis. It was found that because the bioavailability of the SC route was equal to or lower than the IM route, there are no safety concerns with this route of administration.

The Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) is triggered by this application for the indication of psoriasis, for which this is a new route of administration. MTX is already approved in adults for the treatment of "severe recalcitrant disabling psoriasis that is not adequately responsive to other forms of therapy" by the oral, IM, and IV routes. The safety and efficacy of this drug product has not been established for this indication in children because of the unfavorable risk/benefit of methotrexate. Therefore, while the application triggers PREA because it provides for a new route of administration, consistent with the current approval in adults only, the applicant has asked for a full waiver in children 0 to <17 years because of safety reasons under the psoriasis indication. This was discussed with the Pediatric Review Committee (PeRC) on April 2, 2014, and PeRC concurred with the recommendation stated above. However, PeRC did recommend that, since pediatric studies for severe psoriasis will be waived because the risk/benefit does not support studying this population (i.e., due safety concerns), a statement about the risk of use for psoriasis in children should be included in Section 8.4. The Division considered the recommendation from PeRC and concluded that the statement in the labeling concerning the pediatric population is sufficient.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

This is a 505(b)(2) new drug application submitted by Medac Pharma, for Methotrexate (MTX) injection. The drug product is a drug/device combination consisting of a single-use, prefilled, manually-triggered," pen" auto-injector. The device is intended for once weekly subcutaneous (SC) administration in the thigh or abdomen by patients or caregivers in the out-patient setting. The proposed drug product will be supplied in doses ranging from 7.5 to 30 mg in 2.5 mg increments. (b) (4)

Injection is triggered manually by pressure of the thumb on the injection button located at the top of the device. These characteristics make the product sufficiently different from the reference parenteral vial product(s) that the 505(b)(2) route is appropriate.

The application references two listed applications for methotrexate, both of which are listed in the Orange Book as reference listed drugs (RLD) and were the originators for the generic methotrexate products. These include: NDA 08-085 for Methotrexate Tablets from Dava Pharmaceuticals and NDA 11-719 for Methotrexate Injection EQ 50 mg base/2mL from Hospira. The proposed Trade Name for the product is Rasuvo, and the PDUFA date is July 10, 2014.

MTX is a folate analog metabolic inhibitor. Methotrexate Tablets have been marketed since December of 1953 (NDA 08-085, Dava Pharmaceuticals Inc.) when the product was approved for the treatment of acute leukemia in adults. In addition to tablets, MTX was approved in an injection form in 1959 (NDA 11-719; Hospira). Generics are also available. Based on the labeling of the two listed products [the labeling for which is unified], methotrexate is currently approved for the following indications when administered by the oral, intramuscular (IM), intravenous (IV), subcutaneous (SC), intra-arterial (IA), and intrathecal (IT) routes, as shown below:

Indication	Route
Neoplastic diseases	oral, IM, IV, IA, IT
Adults with severe recalcitrant disabling psoriasis that is not adequately responsive to other forms of therapy	oral, IM, IV
Adults with rheumatoid arthritis (RA) who have insufficient therapeutic response to, or are intolerant of, an adequate trial of first line therapy*	oral
Polyarticular-course juvenile rheumatoid arthritis (JRA) who have insufficient therapeutic response to, or are intolerant of, an adequate trial of first line therapy*	oral, IM, SC
* First line therapy for RA and JRA, as defined in the Indications and Usage section of the labels, includes full dose non-steroidal anti-inflammatory agents (NSAIDS).	

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

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 severe forms of RA, pJIA, and psoriasis, and do not include treatment of neoplastic diseases. Given the higher dosing used for most of the oncology indications and the fact that this product can only be administered by the subcutaneous route, it is appropriate to limit the indications to RA, pJIA, and psoriasis as proposed by the sponsor rather than broadening the label to neoplastic diseases.

Because the applicant has proposed both [severe] RA/pJIA and [severe] psoriasis indications, the application was reviewed jointly in the Division of Pulmonary, Allergy,

and Rheumatology Products (DPARP) and the Division of Dermatology and Dental Products (DDDP). This review focuses on the psoriasis indication in DDDP. For discussions of the RA/pJIA indications, please see separate reviews by DPARP.

2.1 Product Information

The proposed product (Figure 1) is drug-device combination consisting of a single-use, single-dose, pre-filled, manually-triggered auto-injector fitted with a 27-gauge, ½ inch needle [full length] that delivers a variable volume (0.15 to 0.6 mL per injection) of a fixed concentration of 50 mg/mL of methotrexate as a sterile, preservative-free solution.

Inactive ingredients include sodium chloride USP (b) (4) sodium hydroxide and hydrochloric acid for pH adjustment, and water for injection USP. (b) (4) Medac proposes that the device will contain the following MTX doses: 7.5,10, 12.5, 15, 17.5, 20, 22.5, 25, 27.5, and 30 mg of MTX. Since the concentration remains the same for all dosage strengths, the fill volumes range from 0.15 mL for the 7.5 mg product up to 0.6 mL for the 30 mg product.

The prefilled syringe is a (b) (4) syringe (manufactured by (b) (4)) that has a 1 mL capacity and is made of Type 1 (b) (4) glass barrel embedded with a stainless steel needle and a (b) (4) rubber plunger stopper. The Physioject™ auto-injector pen device (manufactured by Becton Dickinson, Swindon, United Kingdom) is supplied (b) (4) Note that, throughout the application, Medac calls this device Metroject, which is the European name for the same device.

The needle is protected before use by a yellow needle safety cap, which must be removed in order to activate the device. Activation of the auto-injector is manual via a yellow button at the top of the device. Since activation is much like the use of a click-type pen, this type of device is often referred to as a 'pen' device. The mean "force to fire", i.e., the force required to activate the device, is (b) (4) with the maximum being (b) (4) and exposed needle length is 8 ±2 mm [IR response of 2/25/2014]. After use, a clear plastic safety guard extends over the needle to provide sharps protection. Figure 2 shows a view of a demo device after activation, with the needle guard extended and the cap to the side. Views of the assembled and disassembled parts are shown in Figure 3. [3.2.P.7 Container Closure System]

(b) (4)

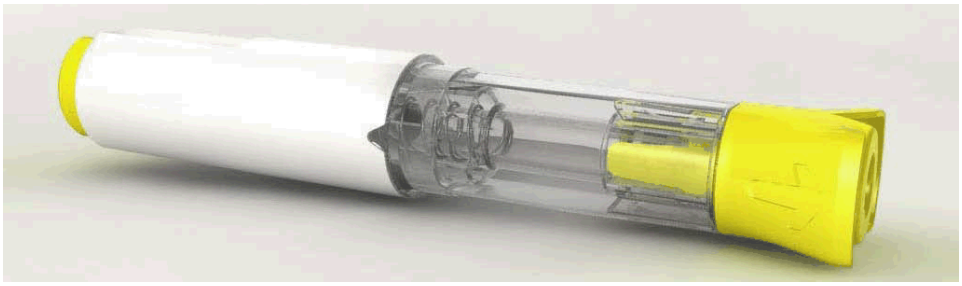


Figure 1. The assembled proposed device

Source: F1, p5; Module 3.2.P.7, BD-Physioject-common-technical-document.pdf

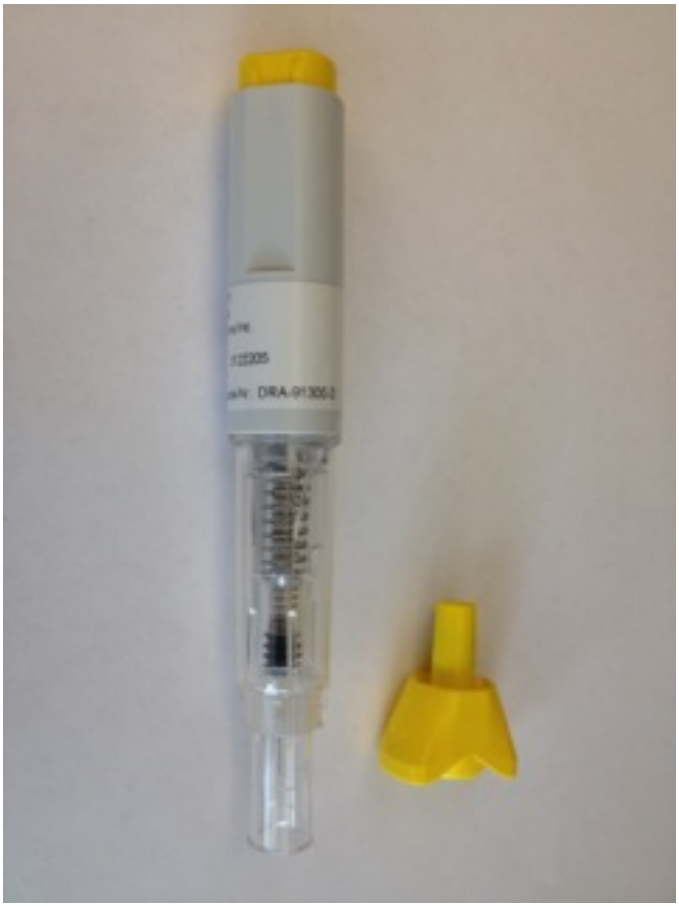
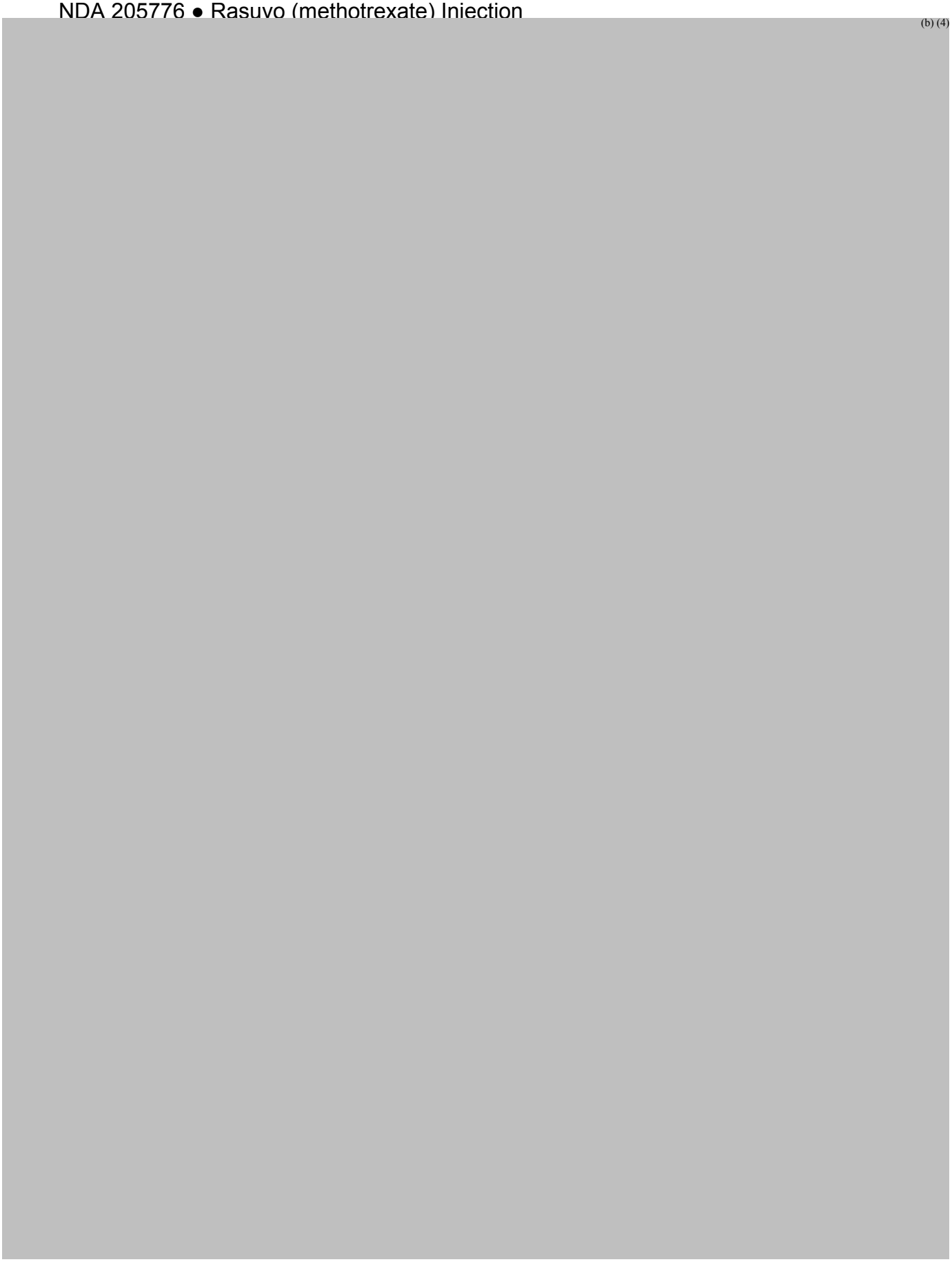


Figure 2. Demo proposed device after activation, with cap off and needle guard in place

(b) (4)



2.2 Tables of Currently Available Treatments for Proposed Indication

There are several products on the market whose indication encompasses the indication of severe psoriasis that has been unresponsive to other treatments. However, a perfect treatment for psoriasis does not exist. Treatments to date do not induce a permanent remission and most often must be given in cyclical or continuous fashion in an effort to circumvent unwanted adverse events in a disease that has to be treated over an individual's lifetime.

Table 1
Approved small molecule products for the treatment of Severe Psoriasis in the United States

	Product	NDA	Sponsor	Year of Approval
1	Methotrexate	11-719	Multiple	1971
2	Soriatane	19-821 & ANDAs	Stiefel & others	1996
3	Cyclosporine (Neoral)	50-715 & 50-716	Novartis	1997

Table 2
Approved Biologic Products for the treatment of Severe Psoriasis in the United States

	Product	BLA (sponsor)	Year Approved for Psoriasis	Characteristics	ROA[1]
1	Infliximab (REMICADE®)	103772 (Centocor)	2006	Monoclonal antibody (TNFα inhibitor)	IV
2	Etanercept (ENBREL®)	103795 (Immunex)	2004	Fusion protein (TNFα inhibitor)	SC
3	Adalimumab (HUMIRA®)	125057 (Abbvie)	2008	Monoclonal antibody (TNFα inhibitor)	SC
4	Ustekinumab (STELARA)	125261	2009	Monoclonal antibody (IL-12/IL-23 cytokines)	SC
[1]ROA – route of administration					

Other Therapies – Phototherapy

Phototherapy is usually reserved for moderate to severe psoriasis. Phototherapy involves treatment with UVB alone. Broadband UVB phototherapy has been an effective approach to treatment of moderate to severe psoriasis. In recent years, a shift to narrow band UVB (311-313 nm) has become the most optimal irradiation available today.
Treatment with UVB is time consuming, requiring 2-3 visits/week for treatment for several months and the possibility of experiencing an acute sunburn reaction exists.

Cumulative doses over time can also increase the risk of developing cutaneous skin cancer, particularly squamous cell carcinoma and melanoma.

2.3 Availability of Proposed Active Ingredient in the United States

Methotrexate is available as oral tablets in multiple strengths and as an injectable solution (both preservative-free and with a preservative) in several strengths. Proprietary and generic forms are available. Many of the products are labeled as the sodium salt, which is an incorrect statement.

Additionally, a single-dose auto-injector presentation of MTX for SC administration, Otrexup (NDA 204824, Antares), was approved on October 11, 2103, after submission of this application. However, Otrexup is only available in dosage strengths from 10 to 25 mg in 5 mg increments (i.e., dosage strengths of 10, 15, 20, and 25 mg).

The Orange Book listings for injectable (**Error! Reference source not found.**) and oral (Table 4) MTX products are shown below (*Note*: Otrexup had not yet been listed at the time of the Orange Book query). Two NDA products, NDA 08-085 for MTX tablets from Dava Pharmaceuticals, and NDA 11-719 for injectable MTX from Hospira, are listed as RLDs and are referenced in this application. Referenced products are shown in **bold** font.

Table 3
Orange Book Listing of Methotrexate injectable products as of 9/10/2013

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

Appl No	TE Code	RLD	Dosage Form	Route Strength	Proprietary Name	Applicant
				25MG BASE/ML)	PRESERVATIVE FREE	
A040266	AP	No	INJECTABLE; INJECTION	EQ 1GM BASE/VIAL	METHOTREXATE PRESERVATIVE FREE	FRESENIUS KABI USA
A040263	AP	Yes	INJECTABLE; INJECTION	EQ 250MG BASE/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM	FRESENIUS KABI USA
A040263	AP	Yes	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM	FRESENIUS KABI USA
N011719	**AP**	**Yes**	**INJECTABLE; INJECTION**	**EQ 1GM BASE/40ML (EQ 25MG BASE/ML)**	**METHOTREXATE SODIUM PRESERVATIVE FREE**	**HOSPIRA**
N011719	AP	Yes	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM	HOSPIRA
A040716	AP	Yes	INJECTABLE; INJECTION	EQ 1GM BASE/40ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	MYLAN INSTITUTIONAL
A040768	AP	Yes	INJECTABLE; INJECTION	EQ 250MG BASE/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	MYLAN INSTITUTIONAL
A040767	AP	Yes	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	MYLAN INSTITUTIONAL
A201529	AP	No	INJECTABLE; INJECTION	EQ 100MG BASE/4ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A201530	AP	No	INJECTABLE; INJECTION	EQ 1GM BASE/40ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A201529	AP	No	INJECTABLE; INJECTION	EQ 200MG BASE/8ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A201529	AP	No	INJECTABLE; INJECTION	EQ 250MG BASE/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A201529	AP	No	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A200171	AP	No	INJECTABLE; INJECTION	EQ 100MG BASE/4ML (EQ 25MG BASE/ML)	METHOTREXATE PRESERVATIVE FREE	PHARMACHEMIE BV
A040843	AP	No	INJECTABLE; INJECTION	EQ 1GM BASE/40ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	PHARMACHEMIE BV
A040853	AP	No	INJECTABLE; INJECTION	EQ 250MG/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	PHARMACHEMIE BV
A040850	AP	No	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	PHARMACHEMIE BV

Table 4
Orange Book listing of Methotrexate Oral Products as of 10/21/2013

Appl No	TE Code	RLD	Dosage Form	Route Strength	Proprietary Name	Applicant
A040385		No	TABLET; ORAL	EQ 10MG BASE	TREXALL	BARR
A040385		Yes	TABLET; ORAL	EQ 15MG BASE	TREXALL	BARR
A081099	AB	No	TABLET; ORAL	EQ 2.5MG BASE	METHOTREXATE SODIUM	BARR
A040385		No	TABLET; ORAL	EQ 5MG BASE	TREXALL	BARR
A040385		No	TABLET; ORAL	EQ 7.5MG BASE	TREXALL	BARR
N008085	**AB**	**Yes**	**TABLET; ORAL**	**EQ 2.5MG BASE**	**METHOTREXATE SODIUM**	**DAVA PHARMS INC**
A081235	AB	No	TABLET; ORAL	EQ 2.5MG BASE	METHOTREXATE SODIUM	MYLAN
A040054	AB	No	TABLET; ORAL	EQ 2.5MG BASE	METHOTREXATE SODIUM	ROXANE

2.4 Important Safety Issues With Consideration to Related Drugs

N/A

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A PreIND meeting was held with the applicant on February 27, 2012 to discuss a path forward for their proposed product, methotrexate (MTX) 50 mg/ml, solution for injection, pre-filled syringe sealed in a disposable auto-injector to be administered subcutaneously. This represented a new route of administration for the indication of "symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy". MTX is currently approved for this indication in oral, IM, and IV formulations.
The sponsor proposed a 505(b)(2) route with methotrexate (Hospira) sodium injection (25mg/vial) as a listed drug for the approved parental doses for the psoriasis indication. The sponsor was advised this would be an appropriate listed drug. They were advised that the Division recommends that the relative bioavailability study should also compare the IM route vs the SC route in psoriasis subjects at the 30 mg dose, as that is the dose that is generally not exceeded in the treatment of plaque psoriasis. However, it was subsequently noted at a pre-NDA meeting with the Agency on June 17, 2013, that it would be reasonable to submit a 505(b)(2) NDA based on a relative BA study comparing the proposed product to oral methotrexate to support all of the proposed indications.

2.6 Other Relevant Background Information

2.6.1 Trade Name

With the submission, Medac requested a proposed Trade (Proprietary) Name of (b) (4) for the product. The proposed TN was reviewed by the Office of Medication Error Prevention and Risk Management within the Office of Surveillance and Epidemiology (OSE), but found to be NOT acceptable. On December 20, 2013, Medac then proposed the Trade Name of Rasuvo, which was found to be acceptable. A letter granting the TN was issued by OSE on March 6, 2014.

2.6.2 Pediatric Issues

In the labeling for the listed originator products referenced in this application, Methotrexate is currently approved for the indication of treatment of rheumatoid arthritis when administered by **oral** route; for the indication of JRA (pJIA), when administered by **oral**, **IM** or **SC** routes, and for the indication of severe recalcitrant disabling psoriasis when administered by **oral**, **IM** or **IV** routes. However, another product intended for SC administration, Otrexup, was just approved on October 11, 2013, for the same indications. That application triggered the Pediatric Research Equity Act (PREA, 21 U.S.C. 355c) for the indications of RA and severe psoriasis, for which this is a new route of administration. Because there is another drug-device combination approved for SC use in these indications, this application will not trigger PREA for a new SC route of administration. However, the application will trigger PREA because this new drug-device combination will be available in more doses than Otrexup – therefore it will have a dosing regimen that extends beyond that for Otrexup, i.e., a new dosing regimen that will be reflected in the D&A section (see DPARP review for discussion of RA and pJIA).

Regarding the psoriasis indication, the applicant has asked for a waiver in children 0 to 17 years of safety concerns with use in this population. MTX has the potential for serious toxic reactions (which can be fatal), and the labeling carries a BOXED WARNING for multiple safety concerns. Additionally, as currently worded in the labeling, periodic liver biopsy is recommended during the treatment of patients with psoriasis. As a result, the safety concerns posed by the drug outweigh the potential benefits of treatment in pediatric psoriasis.

Reviewer Comment: *We agree with the sponsor sponsor's request for a waiver in children 0 to 17 years. MTX has been on the market for decades and the safety concerns with the use of this drug product are well elucidated. The Division has concluded that the labeling of methotrexate for pediatric patients is sufficient (see last paragraph section 1.2)*

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

3.2 Compliance with Good Clinical Practices

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

3.3 Financial Disclosures

Financial disclosure forms were submitted and reviewed for the human factors/actual use study, but not for the biopharmaceutical study. The applicant omitted financial certification/disclosure information for study MC-MTX.14/PK, stating that the study was a single-center, Phase 1 PK study, and therefore this information is not required to be submitted. The sponsor also did not submit any financial disclosure forms for study MC-MTX.12/PK, also a single-center, Phase 1 PK study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There were no significant review issues noted in this application noted by either the ONDQA (CMC) reviewer or by the CDRH reviewer. The company has provided stability data and requested (b) (4) expiry dating. The CMC reviewer agrees. The reader is referred to the CMC and CDRH review for full details.

4.2 Clinical Microbiology

No microbiological issues were noted in the application. The drug substance is (b) (4)

Manufacture of the prefilled syringes is performed at Oncotec Pharma Produktion GmbH, (Dessau-Roblau, Germany),.

4.3 Preclinical Pharmacology/Toxicology

The only pharmacology/toxicology information submitted with this application was a local tolerance study that evaluated the proposed methotrexate product in rabbits after a single IV, IM, intra-arterial, paravenous, or SC administration.

Data to support leachables and extractables in the product were reviewed by pharmacology/toxicology team, who came to the conclusion that there are no nonclinical concerns related to the safety qualification of the impurities, leachables, and extractables in the proposed product (see review consult in DARRTS dated 5/30/14)

4.4 Clinical Pharmacology

There was 1 biopharmacology study that was considered pivotal to support a clinical bridge of Medac's prefilled syringe to be administered subcutaneously to the already approved routes of administration, oral, IM, and IV for the psoriasis indication: MC-MTX.14/PK. MC-MTX.9/PH and MC-MTX.12/PK were supportive relative biopharmacology studies.

MC-MTX.14/PK is a single-dose relative bioavailability study that compared systemic methotrexate exposure following SC administration of MTX using the proposed pen injector device with a similar dose following oral (Dava MTX tablets) administration. Bioavailability following SC administration with the pen injector was equal or higher than following oral administration, particularly at dose levels at and above 15 mg. See DPARP medical officer and clinical pharmacology reviews for details of this study (DARRTS 6/2/14) .

.

The clinical biopharmacology reviewer, Dr.Doanh Tran, reviewed the relative biopharmacology study MC-MTX.12/PK which compared the 30 mg dose of the subcutaneous route of administration of Medac's MTX with a 30 mg dose of Hospira's MTX given IM to assure the safety of Medac's MTX at the highest dose recommended dose for psoriasis patients compared to Hospira. See clinical pharmacology review for details of this study (DARRTS 5/8/14). He noted the following in his review of MC-MTX.12/PK:

"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."[3]

[3]Clinical Pharmacology Consults Review for NDA 205776: page 4, DARRTS dated 5/8/14.

In this same review, Dr. Tran also noted that MC-MTX.9/PH was supportive through indirect data comparing the SC route of MTX with the approved routes IM or IV. Although not thoroughly reviewed because of the subsequent submission of study MC-MTX.12/PK, which provided direct evidence, he had the following to say in support of the relative bioequivalence of methotrexate SC to IM and IV:

"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."[4]

4.4.1 Mechanism of Action

N/A. No new information was submitted with this application.

4.4.2 Pharmacodynamics

N/A. No new information was submitted with this application

4.4.3 Pharmacokinetics

See section 4.4

5 Sources of Clinical Data

No clinical trials were performed to support the therapeutic effect, efficacy, or safety of the proposed product. This is a 505(b)(2) application that references NDA 08-085, Dava Pharmaceuticals, Inc for MTX tablets and NDA 11-719, Hospira, Inc for injection. The primary data to support this NDA submission and approval for all of the proposed indications are from the BA study comparing the proposed SC methotrexate product to oral methotrexate (MC-MTX.14/PK) and from the in-use/human factors study [MC-MTX.15/HF (see Table 5)].

[4]Clinical Pharmacology Consults Review for NDA 205776: page 2, DARRTS dated 5/8/14.

The application includes a literature review summarizing the safety and effectiveness of MTX administered via SC administration, a single-dose relative bioavailability study in RA patients that compared the proposed to-be-marketed product with the referenced Dava oral tablets (MC-MTX.14/PK), a single-dose relative bioavailability study in psoriasis patients that compared the proposed to-be-marketed product with the referenced Hospira 10mg/mL and 25 mg/mL for injection via the IM route of administration (MC-MTX.12/PK), and an in-use study (MC-MTX.15/HF).

Several other studies (or study protocols) were submitted to the application, but none were considered as specifically pertinent and none were reviewed. These included several marketing and PK studies that evaluated the proposed product compared with other formulations or devices made by Medac, as well as studies that used predecessor formulations. Datasets were not submitted for any of these studies.

5.1 Tables of Studies/Clinical Trials

Table 5
Pivotal Studies

Study	Type	Design	Products	Doses (mg)	N
MC-MTX.14/PK	Relative BA	R, OL, 2-way, SD crossover in healthy adult males Single site in Germany	MTX 2.5 mg Oral Tabs [Dava] MTX 50 mg/mL pre-filled pen SC in abdominal wall	4 dosing levels: 7.5 mg 15 mg 22.5 mg 30 mg	62 (54)** 16 (14) 17 (14) 15 (14) 14 (12)
MC-MTX.15/HF	In-Use	OL, single-arm 2-dose study in patients ≥16y with RA, with PK in a subset of pts ≥21y Five centers in US	MTX 50 mg/mL pre-filled pen SC in abd or upper thigh weekly 2x	15 mg	106 (104)** PK: 24
* These studies used the to-be-marketed 50 mg/mL prefilled pen auto-injector. ** N (n) = Randomized and received study treatment (completed)					

Table 6
Other Studies

Study	Type	Design /Other Info	Products	Doses (mg)	N
Marketing, PK, and Local Tolerability studies using the to-be-marketed formulation / device					
MC-MTX.11/RA	Patient preference and local tolerability	6-week, R, OL, 2-way crossover study in adults 18-75y with RA Multiple centers in Germany	MTX 50 mg/mL pre-filled pen x 3 MTX pre-filled syringe x3	15, 17.5, or 20 mg once weekly SC x3 for each of the two treatments	Protocol only. No study report. Planned = 120
MC-MTX.12/PK*	Relative BA	R, OL, 2-way, SD crossover in adults (18-65y) with mod-to-	MTX 50 mg/mL pre-filled pen SC MTX inj [Hospira]	30 mg single dose SC or IM	34

Study	Type	Design /Other Info	Products	Doses (mg)	N
		severe psoriasis Single site in US	IM		
MC-MTX.13/PK	BE	R, OL, 2-way, SD crossover in healthy Caucasian males Single site in Germany	MTX 50 mg/mL pre-filled pen MTX 50 mg/mL pre-filled syringe	15 mg SC	14 (14)
Studies with other (predecessor) formulations / devices					
MC-MTX.9/PH[#]	Relative BA	R, OL, 2-treatment, 2-way, SD crossover in healthy Caucasian males, 18-45y Single site in Germany	Group 1: MTX pre-filled syringe 50 mg/mL MTX pre-filled syringe 10 mg/mL Group 2: MTX pre-filled syringe 50 mg/mL MTX pre-filled syringe 10 mg/mL	Group 1 (n=12): 15 mg SC 15 mg SC Group 2 (n=12): 15 mg IM 15 mg IM	25
MC-MTX.10/RH	Patient preference and local tolerability	OL, single-arm 2-way MD crossover study in patients with RA, 18-75y Multiple centers in Germany	MTX pre-filled syringe, 10 mg/mL MTX pre-filled syringe, 50 mg/mL	20 mg x3 (injections 1-3) 20 mg x3 (injections 4-6)	132 (131)
Efficacy and Safety (using predecessor formulation / device)					
MC-MTX.6/RH	Efficacy & Safety	6-month, R, DB, DD, MD, AC in adults RA patients 18-75y who were MTX-naïve 29 sites in Germany from 2003 to 2005	MTX pre-filled syringe 10 mg/mL Oral MTX	15 mg SC 15 mg orally	384 (375) 194 (188) 190 (187)

*Reviewed in detail as supportive for the psoriasis indication

#Not reviewed in detail by clinical pharmacology but mentioned in the clin/pharm review as supportive of the SC route when compared to other parenteral routes.

AU = Actual use; HF = Human factors; BA = Bioavailability, BE = Bioequivalence; SD = single-dose; MD = multiple-dose; OL = open-label; R = randomized; DB = double-blind; AC = active-controlled

For all studies except study MC-MTX.6/RH, the numbers in parentheses are the numbers of subjects who completed the study. For study MC-MTX.6/RH, the numbers in parentheses represent the numbers of patients in the efficacy evaluable population.

5.2 Review Strategy

The studies submitted to the application were reviewed along with any applicable literature references for the psoriasis indication.

5.3 Discussion of Individual Studies/Clinical Trials

See clinical pharmacology reviews. See section 6, efficacy summary, section 7, safety summary, and section 2, risk/benefit.

6 Review of Efficacy

Efficacy Summary

There were no efficacy trials submitted with this application. Support for approval of this application is based on the Agency's previous findings of safety and effectiveness of MTX in patients with severe, disabling psoriasis and relative bioavailability study MC-MTX.14/PK that establishes a clinical bridge to the already approved dosages via the oral route of administration for the psoriasis indication and from the in-use/human factors study MC-MTX.15/HF (see Table 5).

The applicant also performed a relative bioavailability study, MC-MTX.12/PK, that compared the proposed product administered SC to the referenced Hospira parental product administered IM. MC-MTX.12/PK provides some secondary support for single-dose safety in the psoriasis indication. Additionally, MC-MTX/9PH provides some secondary support for efficacy of parental routes of administration for the psoriasis indication.

In treating severe, disabling psoriasis, MTX is given in a titratable relative to disease remission and side effects, using the lowest possible dose. Although the labeling does not recommend exceeding 30 mg per week, doses as high as 37.5 mg orally and up to 50 mg parentally have been used.[5] The relative bioavailability studies support the efficacy of MTX given by the subcutaneous route for the treatment of severe disabling psoriasis by demonstrating higher or similar systemic exposures as compared to the oral and parental routes.

There are no well-controlled trials in the literature of patients using subcutaneous methotrexate in psoriasis. However, the sponsor did submit two articles that chronicle the use of SC MTX in patients with psoriasis. The first is a data registry report out of Austria by M. Inziger, et. al, where with a retrospective analysis, the efficacy of methotrexate was compared to the use of fumaric acid esters in patients with moderate-to severe chronic plaque psoriasis. For purposes of support for the efficacy of oral MTX as compared to SC MTX, the analysis did not find a statistically significant difference in those patients who were treated with oral MTX (n=24) or SC MTX (n=48).[6] The second is an article out of the British Journal of Dermatology where 36 subjects had previously tried oral MTX. All were switched to SC MTX for varying reasons, including

5 Bolognia, Jean, et.al: Dermatology Volume 1: page 141, 2003.

6 M Inziger, et.at: Methotrexate vs. fumaric acid esters in moderate-to-severe chronic plaque psoriasis: data registry report on the efficacy under daily life conditions. JEADV 2013, 27, pages 861-866

ineffective control of CPP. Of the 16 subjects who failed to achieve remission with oral MTX, 11 subsequently responded to SC MTX, suggesting either a better bioavailability or more tolerance of the SC as compared to oral (nausea was less severe in 8 of the subjects using SC as compared to oral.[7]

Reviewer's Comment: *While these 2 articles are not well-controlled trials, the analyses support the findings of the relative bioavailability studies for similar efficacy among the various routes of administration of MTX. As no efficacy trials were submitted as part of this NDA, the remainder of this section will be blank.*

6.1 Indication

6.1.1 Methods

N/A

6.1.2 Demographics

N/A

6.1.3 Subject Disposition

N/A

6.1.4 Analysis of Primary Endpoint(s)

N/A

6.1.5 Analysis of Secondary Endpoints(s)

N/A

6.1.6 Other Endpoints

N/A

6.1.7 Subpopulations

N/A

7 Yesudian, P.D., et.al: Effectiveness of subcutaneous methotrexate in chronic plaque psoriasis. British Journal of Dermatology 2012 167 (Suppl. 1), p. 97.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

N/A

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

N/A

6.1.10 Additional Efficacy Issues/Analyses

N/A

7 Review of Safety

Safety Summary

Three BA studies and one actual use study were submitted and reviewed for safety, and no unexpected findings were noted. Review of the literature did not reveal any specific safety concerns with SC dosing beyond those already labeled. The BA study done in psoriasis subjects is reviewed in detail for safety in this review. See MO DPARP review for the overall safety summary (DARRTS dated 6/2/14).

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety of methotrexate 50 mg/mL is evaluated in one relative bioavailability trial in subjects in psoriasis entitled, “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”

7.1.2 Categorization of Adverse Events

Adverse events were summarized by system organ class and preferred term. On review the preferred terms and verbatim terms were consistent. Adverse events were summarized by relationship to study drug and severity.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

N/A

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The target population in this trial was adult subjects with moderate to severe chronic plaque psoriasis. The mean extent of exposure was 8 days. Table 7 delineates the exposure time for the safety analysis set.

Table 7
Extent of Exposure
Safety Analysis Set

	IM/SC[a] N=17	SC/IM[b] N=17	Total N=34
Extent of exposure (days)[c]			
n	17	17	34
Mean (SD)	8.0 (0.00)	8.0 (0.00)	8.0 (0.00)
Median	8.0	8.0	8.0
Q1, Q3	8.0, 8.0	8.0, 8.0	8.0, 8.0
Minimum, maximum	8, 8	8, 8	8, 8
Number of patients who received MTX, n (%)			
IM	17 (100.0)	17 (100.0)	34 (100.0)
SC	17 (100.0)	17 (100.0)	34 (100.0)

Abbreviations: IM, intramuscular; MTX, methotrexate; Q1, quartile 1; Q3, quartile 3; SC, subcutaneous.

[a] IM/SC Sequence: Period 1 – 30 mg of MTX administered as a 1.2-mL IM injection of 25 mg/mL (MTX Hospira PI 2011); Period 2 – 30 mg of MTX administered as a prefilled pen SC injection containing 0.6 mL of 50-mg/mL MTX solution.

[b] SC/IM Sequence: Period 1 – 30 mg of MTX administered as a prefilled pen SC injection containing 0.6 mL of 50-mg/mL MTX solution; Period 2 – 30 mg of MTX administered as a 1.2-mL IM injection of 25 mg/mL (MTX Hospira PI 2011).

[c] Extent of exposure (days) was calculated as Last Dose Date (Period 2 administration date) – First Dose Date (Period 1 administration date) + 1.

Source: NDA 205776: SD#14: Module 5: Clinical Study Report, table 12-1, page 84.

7.2.2 Explorations for Dose Response

N/A

7.2.3 Special Animal and/or In Vitro Testing

N/A

7.2.4 Routine Clinical Testing

The subjects in this trial had a CXR, ECG, and blood collected for HBsAG, anti-HCV, HIV, and hematology, coagulation, and general chemistries at screening. Serum for pregnancy testing was also performed at screening along with a urine sample for a drug screen. On day 1 of Period 1 and of Period 2, a urine sample for a drug screen was collected, and subjects had repeat pregnancy testing as applicable. Testing for clinical laboratory tests was repeated on day 1, day 8 (1st day of Period 2), and day 16 (follow-up visit).

7.2.5 Metabolic, Clearance, and Interaction Workup

N/A

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

N/A

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in the trial.

7.3.2 Nonfatal Serious Adverse Events

There were no nonfatal serious adverse events.

7.3.3 Dropouts and/or Discontinuations

There were no dropouts and/or discontinuations secondary to an adverse event.

7.3.4 Significant Adverse Events

There were four subjects that reported injection site reactions from the subcutaneous administration of MTX. Redness was reported by 1-2 subjects at varying time points within the 1st 2 hours but by 24 hours, no one reported redness at the injection site.

7.3.5 Submission Specific Primary Safety Concerns

None

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 8 lists the adverse events by system organ class during the bioavailability study. The most common adverse event was headache which occurred at >10% in both arms (intramuscular and subcutaneously). Injection site erythema only occurred in subjects administered MTX subcutaneously, occurring in 4 (11.8%) subjects. Gastrointestinal disorders and infections and infestations occurred equally across both arms.

Table 8
Overall Adverse Events
Safety Analysis Set

System Organ Class **Preferred Term**	**IM** **N=34** **N (%)**	**SC** **N=34** **N (%)**
Total number of AEs	8	17
Subjects with at Least 1 Adverse Event	8 (23.5)	14 (41.2)
Nervous System Disorders		
Headache	4 (11.8)	5 (14.7)
General Disorders and Administration Site Conditions		
Injection site erythema	0 (0.0)	4 (11.8)
Gastrointestinal Disorders		
Diarrhea	0 (0)	1 (2.9)
Nausea	1 (2.9)	0 (0.0)
Vomiting	0 (0)	1 (2.9)
Infections and Infestations		
Nasopharyngitis	0 (0)	1 (2.9)
Upper respiratory tract infection	1 (2.9)	0 (0)
Injury, poisoning, and procedural complications		
Limb injury	0 (0)	1 (2.9)
Wound	0(0)	1 (2.9)
Investigations		
Blood triglycerides increased	1 (2.9)	0 (0)
Skin and subcutaneous tissue disorders		
Dermatitis contact	0 (0)	1 (2.9)
Skin lesion	0 (0)	1 (2.9)
Urticaria	0 (0)	1 (2.9)
Respiratory, thoracic, and mediastinal disorders		
Rhinitis allergic	1 (2.9)	(0)
NDA 205776: SD#14: Module 5: Clinical Study Report, table 14.3.1.1, page 198 and table 12-3 page 87		

Reviewer's comment: *Almost twice as many subjects had an adverse reaction to the subcutaneous administration of MTX when compared to IM administration. This can primarily be accounted for by the adverse event of injection site erythema which only occurred in subjects being administered the drug subcutaneously. As stated before,*

this reaction was mild and dissipated by 24 hours post injection and no one discontinued the trial because of this adverse event. There were no other significant differences between the 2 routes of administration and the events that occurred including headache, diarrhea, nausea, vomiting, and various forms of dermatitis are well documented adverse reactions to MTX. All AEs were listed as mild to moderate with the exception of one incidence of headache listed as severe in the IM arm.
The medical officer's review from DPARP of the remainder of the trials, one clinical pharmacology trial and one "use" trial in RA subjects for this application along with his literature review, does not substantiate the adverse reaction of "injection site erythema" as a significant adverse reaction in the subcutaneous route of administration of MTX, as no local intolerability reactions were reported. Thus, in this reviewer's opinion, based on the small number of subjects in this trial, this adverse reaction, does not need to be listed in the labeling of Medac's MTX, Rasuvo.

7.4.2 Laboratory Findings

There were transient minor changes in hematology, urinary, and chemistry parameters over time following IM and SC dosing but none of the changes were clinically meaningful except for 1 subject with an elevated triglyceride level after IM dosing. The subject in question had an elevated triglyceride at screening (2.6668 mmol/L – normal 0-1.6837 mmol/L). At the end of Period 2, on day 8, the subject's triglyceride was 12.8368 mmol/L. This level was obtained 2.5 hours after IM dosing. At a follow-up visit 9 days later, the subject's triglyceride level was 1.9549 mmol/L. This was lower than the subject's screening triglyceride. None of the levels were taken in a fasting state. The increase in triglycerides was determined not to be related to MTX.

Reviewer's Comment: *Hypertriglyceridemia is not an adverse reaction that has been attributed to MTX over its long history of approval (since 1950). I agree that this one adverse event is unlikely to be related to MTX and does not rise to the level of a labeling change.*

7.4.3 Vital Signs

No clinically meaningful changes over time were reported in vital sign measurements.

7.4.4 Electrocardiograms (ECGs)

No clinically meaningful abnormalities related to chest x-rays were reported.

7.4.5 Special Safety Studies/Clinical Trials

N/A

7.4.6 Immunogenicity

N/A

7.5 Other Safety Explorations

Reviewer's Comment: *There were no other safety explorations in the relative bioavailability study. Therefore, the remainder of this section and the next is non-applicable (N/A) and will remain blank.*

7.5.1 Dose Dependency for Adverse Events

N/A

7.5.2 Time Dependency for Adverse Events

N/A

7.5.3 Drug-Demographic Interactions

N/A

7.5.4 Drug-Disease Interactions

N/A

7.5.5 Drug-Drug Interactions

N/A

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

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

7.6.2 Human Reproduction and Pregnancy Data

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

7.6.3 Pediatrics and Assessment of Effects on Growth

No new information is submitted with this NDA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

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

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

Since no specific safety concerns were noted in the review of this product across Divisions, the sponsor was not requested to submit an evaluation of postmarketing safety reports.

9 Appendices

9.1 Literature Review/References

Refer to section 6 of this review (**Efficacy Summary**) and DPARP review (DARRTS 6/2/14).

9.2 Labeling Recommendations

Based on the relative bioavailability study, MC-MTX-12/PK, reviewed in our division for the psoriasis indication, the clinical pharmacology team has placed the following sentence in the labeling under Absorption in the section 12.3:

12.3 Pharmacokinetics
Absorption

After administration of a single dose of 30 mg methotrexate subcutaneously with Rasuvo, the systemic exposure (AUC) of methotrexate from Rasuvo was similar to that of methotrexate administered at the same dose by the intramuscular route.

9.3 Advisory Committee Meeting

No advisory committee meeting was held in association with this drug product.

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

/s/

DENISE COOK
06/04/2014

GORDANA DIGLISIC
06/04/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205-776
Priority or Standard	Standard
Submit Date(s)	September 9, 2013
Received Date(s)	September 10, 2013
PDUFA Goal Date	July 10, 2014
Division / Office	DPARP / OND
Reviewer Name(s)	Peter Starke, MD
Review Completion Date	June 2, 2013
Established Name	Methotrexate Injection
(Proposed) Trade Name	Rasuvo
Therapeutic Class	Folate analog metabolic inhibitor
Applicant	Medac Pharma, a subsidiary of Medac GmbH
Formulation(s)	Solution for injection in a pre-filled, manually-triggered auto-injector
Dosing Regimen	Subcutaneous injection
Proposed Indication(s)	Rheumatoid Arthritis (RA); Polyarticular Juvenile Idiopathic Arthritis (pJIA); Severe Psoriasis [see separate review]
Intended Population(s)	RA: Adults pJIA: 2 years of age and older Severe Psoriasis: Adults

MEDICAL OFFICER REVIEW

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

SUBMISSIONS REVIEWED IN THIS DOCUMENT / OTHER DOCUMENTS

Document Date	CDER Stamp Date	Submission	Comments
Sept. 10, 2013	Sept. 10, 2013	SD-1	Original application
Jan 10, 2014	Jan 10, 2014	SD-3	Safety Update
Jan 16, 2014	Jan 16, 2014	SD-5	Revised labeling
Feb 19, 2014			*Information Request (IR)*
Feb 25, 2014	Feb 25, 2014	SD-7	Response to IR of 2/19/2014
Feb 28, 2014	Feb 28, 2014	SD-8	Additional response to IR of 2/19/2014
March 27, 2014			*Information Request (IR)*
April 3, 2014	April 3, 2014	SD-10	Response to IR of 3/27/2014
April 4, 2014	April 4, 2014	SD-11	Response to IR of 3/27/2014
April 11, 2014			*Information Request (IR)*
April 8, 2014	April 8, 2014	SD-12	Response to IR of 4/11/2014
April 17, 2014	April 17, 2014	SD-13	Additional response to IR of 4/11/2014
April 30, 2014	April 30, 2014	SD-14	CSR for study MC-MTX.12/PK
May 6, 2014	May 6, 2014	SD-15	Updated data listing for MC-MTX.15/HF
May 14, 2014			*Labeling IR*
May 28, 2014		SD-19	Revised labeling

RECOMMENDED REGULATORY ACTION

NDA/Supplements: _X_ Approval

____ Complete Response

Other Action: ____

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of this application.

1.2 Risk Benefit Assessment

This is a 505(b)(2) new drug application submitted by Medac Pharma, for a drug/device combination of Methotrexate (MTX) injection, a folate analog metabolic inhibitor, in a presentation consisting of a single-use, single-dose, pre-filled, manually-triggered, "pen" auto-injector intended for subcutaneous (SC) injection. Medac proposes to market multiple dosage strengths from 7.5 to 30 mg in 2.5 mg increments. (b) (4) The proposed indications are RA, pJIA, and severe recalcitrant psoriasis, where it is to be administered once weekly in the thigh or abdominal wall areas.

The application was submitted on September 10, 2013. The application references two listed applications for methotrexate: NDA 08-085 for Methotrexate Tablets from Dava Pharmaceuticals and NDA 11-719 for Methotrexate Injection EQ 50 mg base/2mL from Hospira. The proposed Trade Name is Rasuvo, and the PDUFA date is July 10, 2014.

MTX is currently indicated for the treatment of various neoplastic diseases, severe recalcitrant psoriasis, severe active rheumatoid arthritis (RA), and active polyarticular-course juvenile rheumatoid arthritis (JRA), which is now called polyarticular juvenile idiopathic arthritis or pJIA. For the treatment of neoplastic diseases, methotrexate is currently labeled for administration by the oral, intramuscular (IM), intravenous (IV), intrathecal (IT), and intra-arterial (IA) routes; for severe psoriasis by the oral, IM, and IV routes; for RA by the oral route; and for pJIA by the oral, IM and SC routes.[1] The listed originator products were approved in the 1950s, and generics are also available for both oral tablets and parenteral formulations.

This product is intended as a convenience formulation for self or caregiver use in the home setting. Therefore, the applicant's proposed indications are limited to those of RA, pJIA, and psoriasis, and do not include treatment of neoplastic diseases. The proposed doses (from 7.5 mg to 30 mg in 2.5 mg increments) will cover most of the currently recommended doses for treatment of psoriasis, RA, and pJIA. Although the oncology indications are not being sought, the proposed doses would not adequately cover dosing for these conditions, which extend far higher by the IV route and may

1 *Note*: The current labeling for the oral and parenteral products, which share unified labeling, include IM and SC administration for JRA. Therefore, the proposed SC route for this product does not represent a new route of administration for the JRA indication, although it does represent a new route of administration for adults with RA and psoriasis.

require leucovorin rescue. Given the higher dosing used for most of the oncology indications and the fact that this product can only be administered by the subcutaneous route, it is appropriate to limit the indications to the RA, pJIA, and psoriasis indications, as proposed, rather than broadening the label to neoplastic diseases. Issues with dosing raised by the limitations imposed by the product will be addressed by limitations for use in the Dosing and Administration section of this product's prescribing information.

Because the applicant has proposed RA/pJIA and psoriasis indications, a collaborative review was conducted, with review of the RA and pJIA indications in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) and review of the psoriasis indication in the Division of Dermatology and Dental Products (DDDP). This review focuses on the RA and pJIA indications in DPARP. For discussions of the psoriasis indication, please see separate reviews by DDDP.

Support for approval of this application is based on the Agency's previous findings of safety and efficacy of methotrexate for the proposed indications (Dava and Hospira methotrexate products), the literature, a bioavailability study in adults comparing systemic exposure with the proposed product to that from marketed approved oral tablets, and an in-use study. The primary data to support this NDA submission and approval for all of the proposed indications come from the BA study comparing the proposed SC methotrexate product to oral methotrexate (MC-MTX.14/PK). The results of that study support the efficacy of SC dosing in RA and psoriasis patients because, when compared to oral exposure, SC dosing yields higher systemic exposures, particularly after GI absorption is saturated at oral doses greater than or equal to 15 mg. Safety in adults with RA is supported by the extensive safety record in these patients, safety information when administered by this and other routes at much higher doses for other indications, such as treatment of neoplasms, as well as safety information from the literature when MTX is administered by the SC route to RA patients. Safety in adults with psoriasis is supported by safety information with IM and IV administration in these patients, where systemic exposure is expected to meet or exceed systemic exposure after SC dosing. Efficacy and safety of MTX administered by the SC route in children with pJIA is already established.

Specifically, support comes from:

1. The Agency's previous findings of the safety and effectiveness of methotrexate in adults with RA (oral route) and psoriasis (oral, IM and IV routes), and in children with JRA (pJIA) (oral, SC, and IM routes).
2. A relative BA study (MC-MTX.14/PK) in healthy adults that links the proposed product to the approved oral MTX product and supports the efficacy of SC administration of MTX in adult patients with RA and psoriasis because it showed equal or greater systemic exposure to MTX administered SC from the proposed pen injector product when compared to with orally administered MTX tablets. The higher systemic exposure with SC administration encompasses the known efficacy with oral administration and is supported by substantial safety data with similar or higher systemic exposures when MTX is administered by approved routes and at higher

doses, all of which are represented in the labeling of the listed products referenced in the application.

3. Literature data that support the safety and efficacy of SC administration of methotrexate for RA, pJIA, and psoriasis. Of note, the applicant performed a clinical trial (MC-MTX.06) that compared the efficacy and safety of a predecessor MTX subcutaneous product with oral dosing in patients with RA, and the study report was submitted with the application. Because the trial did not evaluate the to-be-marketed product, the study report was submitted to the NDA and considered to be a supportive but not a pivotal study. In this respect, the trial was similar to the other literature reports submitted to the application that support SC administration as an alternative to oral or IM administration of MTX, with higher systemic exposure and minimization of oral toxicity when administered by the SC or IM routes compared with oral administration at similar doses, particularly when the doses are above 15 mg. The safety review of the literature and of the studies provided to this application did not reveal any new safety signals that would require additional labeling beyond those already labeled in the reference products.
4. An actual use study (MC-MTX.15/HF) to support the labeling for use of the proposed product. The study demonstrated that patients and caregivers could be taught to successfully administer the product and that the device functions appropriately in the patient's hands.

Additionally, the applicant performed a BA/BE study (MC-MTX.12/PK) that compared the proposed product administered SC to the referenced Hospira parenteral product administered IM. It was determined prior to filing the application that this study would not be needed to support review of the submission or approval of the NDA. The results of the study became available during the course of the review of the NDA (submitted on April 30, 2014), and were reviewed. The applicant also performed several marketing or PK studies using predecessor products. While the results of several of these studies were submitted to the application, they did not directly support the application and were not reviewed.

The Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) is triggered by this application by the new route of administration for the indications of RA and psoriasis. The addition of a manually-triggered auto-injector makes this a drug/device combination, but does not trigger PREA because this change is not considered a new dosage form. With regard to the RA indication, the reference products are already approved for use (including SC administration) in children with JRA (pJIA), which is considered the pediatric form of RA. Therefore, the PREA requirements for RA are satisfied by the Agency's previous findings of safety and effectiveness of methotrexate for pJIA. The applicant has requested a waiver of studies in children below 2 years of age for RA/pJIA because the disease (pJIA) does not exist below 2 years of age, and this conforms with what the Agency has done in the past for other applications for this indication. With regard to the dermatological indication of treatment of "severe recalcitrant disabling psoriasis that is not adequately responsive to other forms of therapy", methotrexate is approved in adults when administered by oral, IM, or IV routes, but not the SC route. However, the safety and efficacy for this indication has not

been established in children because of the unfavorable risk/benefit of methotrexate. Therefore, while the application triggers PREA because it provides for a new route of administration, consistent with the current approval in adults only, the applicant has asked for a full waiver in children 0 to <17 years because the risk/benefit does not support use in this population. This is acceptable. Both Divisions discussed their recommendations with the Pediatric Review Committee (PeRC) on April 2, 2014, and PeRC concurred with the recommendations stated above. Please refer to Section 2.6.2, Pediatric Issues, for further details.

The application for Rasuvo is the second application the Agency has received for a pre-filled methotrexate auto-injector, the first one being for Otrexup, which was approved on October 12, 2013 (after this NDA was submitted). Otrexup is a fully automatic auto-injector containing methotrexate for SC administration in doses of 10, 15, 20, and 25 mg. It was approved for the same indications sought for this application. As a second application for a methotrexate auto-injector, this product will be the second instance of Physicians Labeling Rule (PLR) labeling for a methotrexate product. While Medac submitted proposed PLR labeling with this application, it is important to recognize that the Agency had already made a considerable effort to convert the PI for MTX to PLR format. The Agency had created a non-product-specific methotrexate PLR label based on the listed reference products and had provided that label to the previous applicant for use as a template for that application. After Medac submitted this application for Rasuvo, the Agency sent Medac the non-product-specific PLR PI template that the Agency had developed, requesting that Medac insert the Rasuvo product-specific information and re-submit the PI. Because of the Agency's efforts related to PLR conversion, and since both applications referenced the same listed drugs, the PI for Rasuvo will be very similar to that of the other product, Otrexup, except with regard to any information that is product-specific. This is intentional on the Agency's part, as both products reference the same listed drugs and the Agency worked independently of the two applicants/applications to create PLR conversions of these listed drugs.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

This is a 505(b)(2) new drug application submitted by Medac Pharma, for Methotrexate (MTX) injection. The drug product is a drug/device combination consisting of a single-use, prefilled, manually-triggered, "pen" auto-injector. The device is intended for once weekly subcutaneous (SC) administration in the thigh or abdomen by patients or caregivers in the out-patient setting. The proposed drug product will be supplied in doses ranging from 7.5 to 30 mg in 2.5 mg increments. (b) (4)

Injection is triggered manually by pressure of the thumb on the injection button located at the top of the device. The new route of administration and the characteristics of the drug-device combination make the product sufficiently different from the reference parenteral vial product that the 505(b)(2) route is appropriate.

The application references two listed applications for methotrexate, both of which are listed in the Orange Book as reference listed drugs (RLD) and were the originators for the generic methotrexate products (see Table 3 and the next paragraph). These include: NDA 08-085 for Methotrexate Tablets from Dava Pharmaceuticals and NDA 11-719 for Methotrexate Injection EQ 50 mg base/2mL from Hospira. The proposed Trade Name for the product is Rasuvo, and the PDUFA date is July 10, 2014.

MTX is a folate analog metabolic inhibitor. Methotrexate Tablets have been marketed since December of 1953 (NDA 08-085, Dava Pharmaceuticals Inc.) when the product was approved for the treatment of acute leukemia in adults. In addition to tablets, MTX was approved in an injection form in 1959 (NDA 11-719; Hospira). Generics are also available. Based on the labeling of the two listed products [the labeling for which is unified], methotrexate is currently approved for the following indications when administered by the oral, intramuscular (IM), intravenous (IV), subcutaneous (SC), intra-arterial (IA), and intrathecal (IT) routes, as shown below:

Indication	Route
Neoplastic diseases	oral, IM, IV, IA, IT
Adults with severe recalcitrant disabling psoriasis that is not adequately responsive to other forms of therapy	oral, IM, IV
Adults with rheumatoid arthritis (RA) who have insufficient therapeutic response to, or are intolerant of, an adequate trial of first line therapy*	oral
Polyarticular-course juvenile rheumatoid arthritis (JRA) who have insufficient therapeutic response to, or are intolerant of, an adequate trial of first line therapy*	oral, IM, SC
* First line therapy for RA and JRA, as defined in the Indications and Usage section of the labels, includes full dose non-steroidal anti-inflammatory agents (NSAIDS).	

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

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

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 severe forms of RA, pJIA, and psoriasis, and do not include treatment of neoplastic diseases. The proposed doses will cover most of the currently recommended doses for treatment of these three indications, but would not adequately cover dosing for these conditions, which extend far higher by the IV route and may require leucovorin rescue. Given the higher dosing used for most of the oncology indications and the fact that this product can only be administered by the subcutaneous route, it is appropriate to limit the indications to RA, pJIA, and psoriasis as proposed by the sponsor rather than including neoplastic diseases indication(s). Issues with dosing raised by the limitations imposed by the product will necessitate limitations for use in the Dosing and Administration section of the PI for this product.

Because the applicant has proposed both [severe] RA/pJIA and [severe] psoriasis indications, the application was reviewed jointly in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) and the Division of Dermatology and Dental Products (DDDP). This review focuses on the RA and JIA indications in DPARP. For a discussion of the psoriasis indication, please see separate reviews by DDDP.

2.1 Product Information

The proposed product (Figure 1) is drug-device combination consisting of a single-use, single-dose, pre-filled, manually-triggered auto-injector fitted with a 27-gauge, ½ inch needle [full length] that delivers a variable volume (0.15 to 0.6 mL per injection) of a fixed concentration of 50 mg/mL of methotrexate as a sterile, preservative-free solution.

Inactive ingredients include sodium chloride USP (b) (4) sodium hydroxide and hydrochloric acid for pH adjustment, and water for injection USP. (b) (4) Medac proposes that the device will contain the following MTX doses: 7.5,10, 12.5, 15, 17.5, 20, 22.5, 25, 27.5, and 30 mg of MTX. Since the concentration remains the same for all dosage strengths, the fill volumes range from 0.15 mL for the 7.5 mg product up to 0.6 mL for the 30 mg product.

The prefilled syringe is a [redacted] syringe (manufactured by [redacted]) that has a 1 mL capacity and is made of Type 1 [redacted] glass barrel embedded with a stainless steel needle and a [redacted] rubber plunger stopper. The Physioject™ auto-injector pen device (manufactured by Becton Dickinson, Swindon, United Kingdom) is supplied [redacted] Note that, throughout the application, Medac calls this device Metroject, which is the European name for the same device. The Physioject device is not 510k cleared, although is used in another approved drug product.

The needle is protected before use by a yellow needle safety cap, which must be removed in order to activate the device. Activation of the auto-injector is manual via a yellow button at the top of the device. Since activation is much like the use of a click-type pen, this type of device is often referred to as a 'pen' device. The mean "force to fire", i.e., the force required to activate the device, is [redacted] with the maximum being [redacted] and exposed needle length is 8 ±2 mm [IR response of 2/25/2014]. After use, a clear plastic safety guard extends over the needle to provide sharps protection. Figure 2 shows a view of a demo device after activation, with the needle guard extended and the cap to the side. Views of the assembled and disassembled parts are shown in Figure 3. [3.2.P.7 Container Closure System]

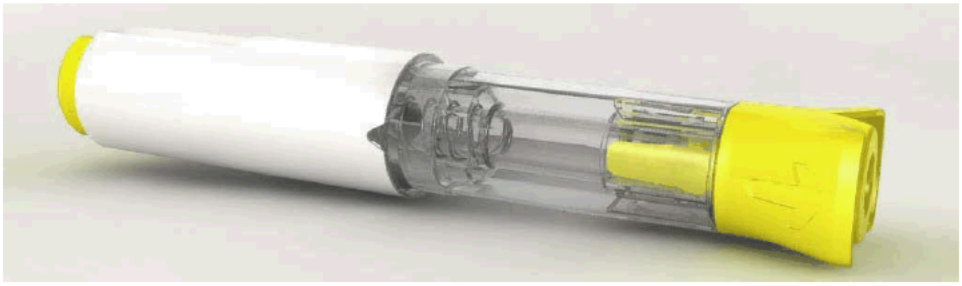


Figure 1. The assembled proposed device

Source: F1, p5; Module 3.2.P.7, BD-Physioject-common-technical-document.pdf

[redacted]

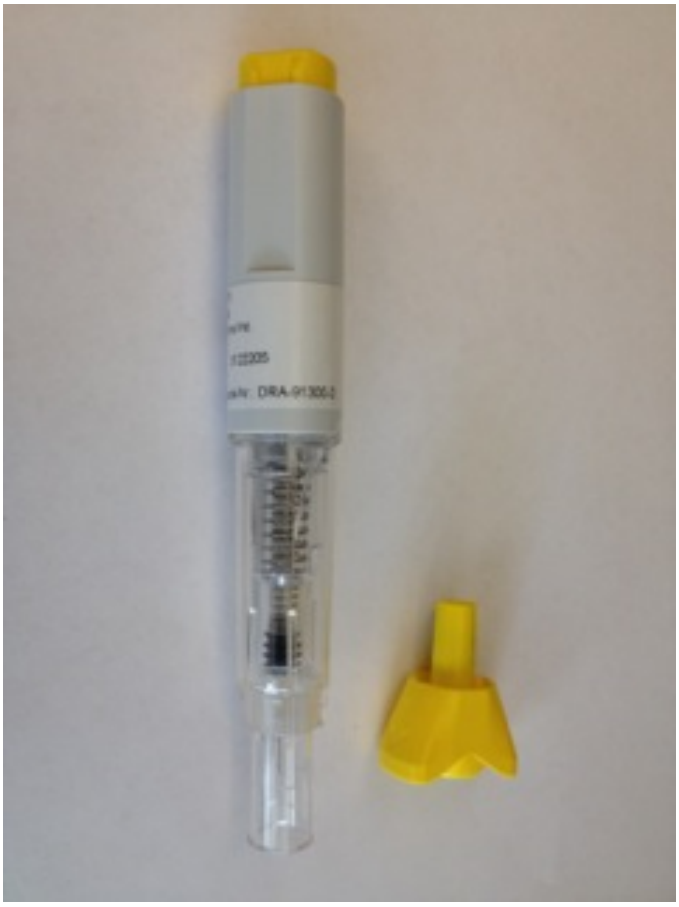
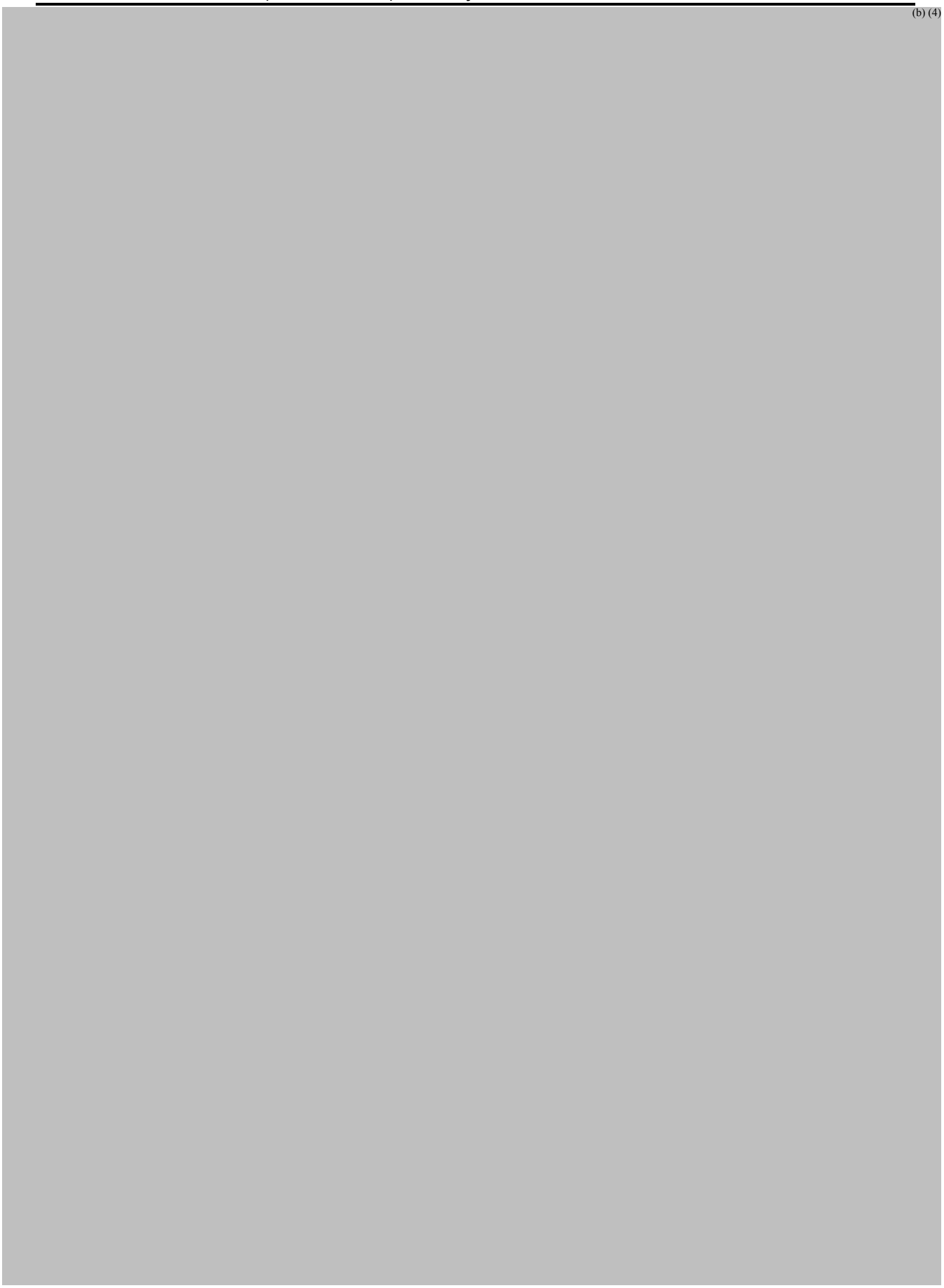


Figure 2. Demo proposed device after activation, with cap off and needle guard in place

(b) (4)



2.2 Tables of Currently Available Treatments for Proposed Indications

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

The labeling for MTX for the treatment of adult rheumatoid arthritis (RA) and polyarticular juvenile rheumatoid arthritis (i.e., pJIA) reflects the treatment paradigms that were in place when the products were approved in the 1950s and over the following 20-30 years, whereas the treatments available these conditions have changed dramatically in the last ~20 years and additional information regarding the use of MTX for these conditions has also become available. As a result, the current labeling for the approved products is quite dated, as well as confusing with respect to the approved routes of administration for each indication. For this reason, an effort is underway within the Agency to update the reference methotrexate PIs to PLR labeling format, and in the process bring the information contained in the labels up to current treatment guidelines and clinical use.

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

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

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

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

	Product	NDA	Sponsor	Year of Approval[2]
1	Sulfasalazine (AZULFIDINE)	7-073	Pfizer	1950
2	Methotrexate sodium (METHOTREXATE SODIUM)	8-085 (PO) 11-719 (IV)	Multiple	1953 1959
3	Hydroxychloroquine (PLAQUENIL)	9-768	Sanofi-Aventis	1955
4	Prednisone	Many ANDAs	Multiple	1955
5	Azathioprine (IMURAN)	16-324	Prometheus Labs	1968
6	Penicillamine (CUPRIMINE)	19-853	Aton	1970
7	Auranofin (RIDAURA)	18-689	Prometheus Labs	1985
8	Cyclosporine (NEORAL) Cyclosporine (SANDIMMUNE)	50-715 50-625	Novartis	1995 1990
9	Leflunomide (ARAVA)	20-905	Sanofi-Aventis	1998
10	Tofacitinib (XELJANZ)	203-214	Pfizer	2012

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

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

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

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

8	Certolizumab Pegol (CIMZIA®)	BLA 125160 (UCB)	2009	Fab fragment conjugated to PEG (TNF inhibitor)	SC
9	Tocilizumab (ACTEMRA®)	125276 (Roche)	2010	Monoclonal antibody (Il-6 receptor inhibitor)	IV
1 Infliximab was originally approved in 1998 for Crohn's Disease and rituximab was originally approved for non-Hodgkin's Lymphoma in 1997. Certolizumab Pegol was originally approved for Crohn's disease in 2008.					

2.3 Availability of Proposed Active Ingredient in the United States

Methotrexate is available as oral tablets in multiple strengths and as an injectable solution (both preservative-free and with a preservative) in several strengths. Proprietary and generic forms are available. Many of the products are labeled as the sodium salt, which is an incorrect statement.

Additionally, a single-dose auto-injector presentation of MTX for SC administration, Otrexup (NDA 204824, Antares), was approved on October 11, 2103, after submission of this application. However, Otrexup is only available in dosage strengths from 10 to 25 mg in 5 mg increments (i.e., dosage strengths of 10, 15, 20, and 25 mg). The indications for Otrexup are the same as those sought for this application, severe active RA and pJIA, and severe recalcitrant psoriasis.

The Orange Book listings for injectable (Table 3) and oral (Table 4) MTX products are shown below (*Note*: Otrexup had not yet been listed at the time of the Orange Book query). Two NDA products, NDA 08-085 for MTX tablets from Dava Pharmaceuticals, and NDA 11-719 for injectable MTX from Hospira, are listed as RLDs and are referenced in this application. Referenced products are shown in **Bold** font.

Table 3. Orange Book listing of Methotrexate injectable products as of 9/10/2013

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

Appl No	TE Code	RLD	Dosage Form	Route Strength	Proprietary Name	Applicant
A090039	AP	No	INJECTABLE; INJECTION	EQ 250MG BASE/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	EBEWE PHARMA
A090039	AP	No	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	EBEWE PHARMA
A040266	AP	No	INJECTABLE; INJECTION	EQ 1GM BASE/VIAL	METHOTREXATE PRESERVATIVE FREE	FRESENIUS KABI USA
A040263	AP	Yes	INJECTABLE; INJECTION	EQ 250MG BASE/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM	FRESENIUS KABI USA
A040263	AP	Yes	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM	FRESENIUS KABI USA
N011719	**AP**	**Yes**	**INJECTABLE; INJECTION**	**EQ 1GM BASE/40ML (EQ 25MG BASE/ML)**	**METHOTREXATE SODIUM PRESERVATIVE FREE**	**HOSPIRA**
N011719	AP	Yes	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM	HOSPIRA
A040716	AP	Yes	INJECTABLE; INJECTION	EQ 1GM BASE/40ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	MYLAN INSTITUTIONAL
A040768	AP	Yes	INJECTABLE; INJECTION	EQ 250MG BASE/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	MYLAN INSTITUTIONAL
A040767	AP	Yes	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	MYLAN INSTITUTIONAL
A201529	AP	No	INJECTABLE; INJECTION	EQ 100MG BASE/4ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A201530	AP	No	INJECTABLE; INJECTION	EQ 1GM BASE/40ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A201529	AP	No	INJECTABLE; INJECTION	EQ 200MG BASE/8ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A201529	AP	No	INJECTABLE; INJECTION	EQ 250MG BASE/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A201529	AP	No	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A200171	AP	No	INJECTABLE; INJECTION	EQ 100MG BASE/4ML (EQ 25MG BASE/ML)	METHOTREXATE PRESERVATIVE FREE	PHARMACHEMIE BV
A040843	AP	No	INJECTABLE; INJECTION	EQ 1GM BASE/40ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	PHARMACHEMIE BV
A040853	AP	No	INJECTABLE; INJECTION	EQ 250MG/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	PHARMACHEMIE BV
A040850	AP	No	INJECTABLE;	EQ 50MG	METHOTREXATE	PHARMACHEMIE

Appl No	TE Code	RLD	Dosage Form	Route Strength	Proprietary Name	Applicant
			INJECTION	BASE/2ML (EQ 25MG BASE/ML)	SODIUM PRESERVATIVE FREE	BV

Table 4. Orange Book listing of Methotrexate oral products as of 10/21/2013

Appl No	TE Code	RLD	Dosage Form	Route Strength	Proprietary Name	Applicant
A040385		No	TABLET; ORAL	EQ 10MG BASE	TREXALL	BARR
A040385		Yes	TABLET; ORAL	EQ 15MG BASE	TREXALL	BARR
A081099	AB	No	TABLET; ORAL	EQ 2.5MG BASE	METHOTREXATE SODIUM	BARR
A040385		No	TABLET; ORAL	EQ 5MG BASE	TREXALL	BARR
A040385		No	TABLET; ORAL	EQ 7.5MG BASE	TREXALL	BARR
N008085	**AB**	**Yes**	**TABLET; ORAL**	**EQ 2.5MG BASE**	**METHOTREXATE SODIUM**	**DAVA PHARMS INC**
A081235	AB	No	TABLET; ORAL	EQ 2.5MG BASE	METHOTREXATE SODIUM	MYLAN
A040054	AB	No	TABLET; ORAL	EQ 2.5MG BASE	METHOTREXATE SODIUM	ROXANE

2.4 Important Safety Issues With Consideration to Related Drugs

NA

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Agency had a number of pre-submission interactions with Medac between 2010 and 2012, including meetings with the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) and the Division of Dermatology and Dental Products (DDDP), to discuss the requirements for an NDA submission. This included a pre-IND meeting with DPARP on 10/14/2010, a pre-IND meeting with DDDP on 2/22/2012, and a pre-NDA meeting with both Divisions on 6/17/2013.

In a pre-IND meeting held between DPARP and the Sponsor on October 14, 2010, the Sponsor proposed the 505(b)(2) application pathway, using methotrexate solution as the reference listed drug. It was noted that methotrexate solution for injection is only approved for the psoriasis, pJIA, and oncology indications. The injectable methotrexate label includes the RA indication when administered with an oral formulation, but the label does not include efficacy, safety, or dosing information for injectable MTX for this indication. DPARP indicated that the Sponsor should consider pursuing the psoriasis indication as well. The Sponsor was told that they would need at least one adequate and well-controlled clinical trial to support SC dosing for an RA indication, although the trial could come from the medical literature.

The Sponsor submitted additional pIND questions on October 31, 2011, and written responses were sent on December 27, 2011. At that time the Sponsor proposed a meta-analysis of all data of MTX in RA, Medac-sponsored clinical trials of MTX using other pre-filled syringes that demonstrate efficacy and safety of MTX administered SC, and PK studies of SC administration of Medac's MTX 50mg/ml solution injection compared to oral administration of the reference listed drug (Rheumatrex tablets from Dava), and one planned pharmacokinetic trial of MTX administered subcutaneously by disposable auto-injector in children and adolescents with JRA. The Agency replied that an efficacy study might not be necessary as evidence to support their 505(b)(2) application could come from published literature. The applicant was informed that an actual use study in RA patients, a human factors study, and a bioavailability study comparing the proposed SC formulation to approved oral MTX would be necessary.

The Division of Dermatology and Dental Products (DDDP) held a teleconference with the Sponsor on February 22, 2010. The Division recommended that a relative BA study be conducted comparing SC with IM administration at the highest recommended dose of 30 mg in psoriasis patients. However, it was subsequently noted at a pre-NDA meeting with the Agency on June 17, 2013, that it would be reasonable to submit a 505(b)(2) NDA based on a relative BA study comparing the proposed product to oral methotrexate to support all of the proposed indications.

At the pre-NDA meeting on June 17, 2013, it was noted that the summary of the development plan in support of a 505(b)(2) NDA submission for MTX was consistent with the advice provided during previous interactions. Therefore, it was felt that the program was generally acceptable to support submission of the sponsor's application. Expectations regarding the NDA content and format were also discussed.

2.6 Other Relevant Background Information

2.6.1 Trade Name

With the submission, Medac requested a proposed Trade (Proprietary) Name (TN) of (b) (4) for the product. The proposed TN was reviewed by the Office of Medication Error Prevention and Risk Management within the Office of Surveillance and Epidemiology (OSE), but found to be NOT acceptable. On December 20, 2013, Medac then proposed the Trade Name of Rasuvo, which was found to be acceptable. A letter granting the TN was issued by OSE on March 6, 2014.

2.6.2 Pediatric Issues

The Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) is triggered by this application by the new route of administration for the indications of RA and psoriasis. The addition of a manually-triggered auto-injector makes this a drug/device combination, but does not trigger PREA because this change is not considered a new dosage form.

Methotrexate is currently approved for the indication of treatment of rheumatoid arthritis when administered by **oral** route; for the indication of JRA (pJIA), when administered by **oral**, **IM** or **SC** routes, and for the indication of severe recalcitrant disabling psoriasis when administered by **oral**, **IM** or **IV** routes.

RA is an adult disease, and pJIA is considered its pediatric counterpart. Pediatric assessments for RA are therefore performed in children with pJIA down to 2 years of age, the lowest age that pJIA can be diagnosed. Therefore, for the RA indication the product will be appropriately labeled via the pJIA indication down to 2 years of age. The applicant has asked for a waiver for children ≤2 years because the necessary studies are impossible or highly impractical, i.e., because the number of patients with JIA is not substantial. This is acceptable and consistent with what the Division has done for other applications for this (these) indication(s).

With regard to the psoriasis indications, the applicant has asked for a waiver in children 0 to 17 years of safety concerns with use in this population. MTX has the potential for serious toxic reactions (which can be fatal), and the labeling carries a BOXED WARNING for multiple safety concerns. Additionally, as currently worded in the labeling, periodic liver biopsy is recommended during the treatment of patients with psoriasis. As a result, the applicant argues that safety concerns posed by the drug outweigh the potential benefits of treatment in pediatric psoriasis. DDDP agrees with granting of a waiver of studies in the pediatric population with psoriasis for safety reasons, and will label the product accordingly. This is consistent with the current labeling and what has been done for other methotrexate applications.

Both Divisions discussed their recommendations with the Pediatric Review Committee (PeRC) on April 2, 2014, and PeRC concurred with the recommendations stated above. However, PeRC did recommend that the language in Section 8.4 reflect the safety concerns that underlie the risk/benefit decision with regard to not labeling for use in children with psoriasis.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

3.2 Compliance with Good Clinical Practices

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

3.3 Financial Disclosures

Financial disclosure forms were submitted and reviewed for the human factors/actual use study, but not for the biopharmaceutical study. The applicant omitted financial certification/disclosure information for study MC-MTX.14/PK, stating that the study was a single-center, Phase 1 PK study, and therefore this information is not required to be submitted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

There were no significant review issues noted in this application noted by either the ONDQA (CMC) reviewer or by the CDRH reviewer. The company has provided stability data and requested (b) (4) expiry dating. Based on the data17 months of expiry dating will be allowed.

As of finalization of this review, facilities inspections had not yet been performed.

Delivered Dose

The applicant provided data sufficient to support that the device adequately and consistently delivers the intended dose. Specifically, the applicant provided dose delivery data for the doses with the smallest and largest fill volumes. Considering that the only differences for the multiple proposed doses is the fill volume, and that data for the dose with the largest and smallest fill volumes were provided, this is considered adequate by the CDRH and ONDQA review teams.

Sharps Protection

During the review, the CDRH reviewer noted that the Physioject has (b) (4) studies to support the sharps protection feature, as outlined in CDRH guidance, had not been submitted. However, in a response dated April 21, 2014 to an IR dated April 8, 2104, the applicant indicated that the in-use study, MC-MTX.15/HF, did contain a question related to proper functioning of the needle shield, and all pens (210/210 injections) functioned appropriately with regard to providing sharps protection after administration of a dose. Further, the applicant noted that BD had conducted a study to evaluate deployment and locking of the needle shield, in which 390 simulated injections were given and all (390/390) cases the needle shield activated automatically. A letter of authorization cross-referencing to the Device Master File in CDRH was provided. Therefore, the issue of sharps protection was satisfied by the cumulative information submitted to or referenced by the application.

Hold Time

The proposed instruction set includes the instruction to hold the injector against the skin for 5 seconds to ensure completion of the injection. However, no specifications were found in the submission with regard to delivery time of the product. This was requested in an IR dated March 27, 2014. On April 4, Medac responded with the results of a testing report that documents that the average ejection (delivery) time is about 2.5 (range 2.24 to 2.54) seconds. Testing was done using ten 30 mg dosage strength devices, since the 30 mg dosage strength has the largest volume proposed to be delivered. Therefore, the 5-second hold instruction is considered adequate for this product.

Needle Length

Medac reports that the exposed needle length for the product is 8 ±2 mm (~0.4 inches). Additionally, the BD Physioject Common Technical Document states that the mean depth of penetration of the needle is between 7.8 to 8.6 mm [using injection volumes of 0.2 and 1.0 mL, respectively]. The results are based on a study performed to support the Physioject in which 40 healthy adults self-injected a total of 8 saline injections each into the thigh or abdomen, 4 with a prefilled syringe (2 x 0.2 mL and 2 x 1.0 mL) and 4 with the prefilled auto-injector (2 x 0.2 mL and 2 x 1.0 mL). Ultrasound was then used to confirm the injection depth. The report states that subjects followed an Instructions for Use (IFU), but does provide the IFU that was used, nor does it specify whether subjects were required to pinch the skin as part of the injection routine. That said, the report states that result results demonstrate that SC administration via the Physioject auto-injector resulted in a similar depth of injection as that achieved by injection using a prefilled syringe (Figure 4), and for almost all subjects that resulted in deposition in the subcutaneous area. [Module 3.2.P.7; BD Physioject Common Technical Document, p10-12]

Based on the above information as well as clinical experience and data in the literature, the exposed needle length of 8 mm is short enough to provide SC injection to the thigh in most adults, and this would be acceptable for most patients without the need for an instruction to pinch the skin in those patients. In a response to an IR, the applicant noted that “in order for the yellow button to be depressed to activate compression of the contained hypodermic barrel, the retractable distal shield needs to retract properly. If the shield does not retract the yellow button cannot be depressed” [p11-12, IR response dated 2/25/2014]. While the exact force necessary to allow this is not provided, at the Agency’s request they provided the mean and maximum “force to fire” or trigger the device, which is between (b) (4) [p10, IR response dated 2/25/2014]. This happens to be similar to other auto-injector products, and will therefore result in compression of the skin at the injection site. The applicant went on to state that many patients who are trained to self-inject with a needle and syringe are already trained in the use of a skin pinch, and while the skin pinch is probably not needed for most patients when the injection site is the upper thigh, a skin pinch can facilitate an injection into the lateral abdomen.

With regard to children, the exposed needle length may be adequate to achieve SC injection into the thigh, but is likely too long for injection into the abdomen, particularly in young children who may be quite thin and have little subcutaneous fat. The applicant corroborated this by stating that in prepubertal children, the overall mean [SD] thickness of the skin plus subcutaneous tissue is 6.58 [2.5] mm in males and 7.55 [3.3] mm in females. Therefore, the needle length of 8 mm may result in IM dosing in some children if a skin pinch is not used [p12, IR response dated 2/25/2014]. The applicant therefore requested to modify the IFU to add the following to statement:

(b) (4)

[p13, IR response dated 2/25/2014]

That said, pinching the skin may difficult for some adults with RA. Therefore, the Instructions for Use of other products were reviewed, and showed that a number of other products approved for RA patients that have an approximately similar needle length and use the same route of administration do include a pinch instruction (Humira, Simponi). However, this instruction is not universal. Of course, inclusion of the instruction is partially dependent upon the needle length for the individual product. For example, Otrexup does not require this instruction because the exposed needle length of 2.5 mm is short enough to ensure SC administration without a pinch.

Based on my review, I recommend inclusion of a skin pinch as an instruction when administering the product to all patients. However, given that some adults with RA may have difficulty with this instruction, it is reasonable to include an optional instruction for adults with RA that the injection may be administered in thigh without pinching if they are not able to pinch the skin.

Figure 4. Ultrasound showing depth of the prefilled syringe and the prefilled syringe in the auto-injector

Source: F2, p11; Module 3.2.P.7, BD-Physioject-common-technical-document.pdf

4.2 Clinical Microbiology

No microbiological issues were noted in the application. The drug substance is (b) (4)

Manufacture of the prefilled syringes is performed at Oncotec Pharma Produktion GmbH, (Dessau-Roblau, Germany).

4.3 Preclinical Pharmacology/Toxicology

No preclinical issues were noted by pharmacology/toxicology review team during the review. The applicant submitted a local tolerance study that evaluated the proposed methotrexate product in rabbits after a single IV, IM, intra-arterial, paravenous, or SC administration. Data to support leachables and extractables in the product were reviewed by pharmacology/toxicology team, who came to the conclusion that there are no nonclinical concerns related to the safety qualification of the impurities, leachables, and extractables in the proposed product.

4.4 Clinical Pharmacology

The clinical pharmacology of this product was assessed in a single-dose relative bioavailability study (MC-MTX.14/PK) that compared systemic methotrexate exposure following SC administration of MTX using the proposed pen injector device with a similar dose following oral (Dava MTX Tablets) administration. Single doses of 7.5, 15, 22.5 and 30 mg were compared in a 2-way crossover design. Bioavailability following SC administration with the pen injector was equal or higher than following oral administration, particularly at dose levels at and above 15 mg. See Section 5.3.1 of this review for details.

4.4.1 Mechanism of Action

NA. No new information was submitted with this application.

4.4.2 Pharmacodynamics

NA. No new information was submitted with this application.

4.4.3 Pharmacokinetics

See Section 5.3.1 of this review for details of the BA study performed for this application.

5 Sources of Clinical Data

The application includes a literature review summarizing the safety and effectiveness of MTC administered via SC administration, a single-dose relative bioavailability study that compared the proposed to-be-marketed product with the referenced Dava oral tablets (MC-MTX.14/PK), and an in-use/human factors study (MC-MTX.15/HF). The clinical program was discussed over several interactions with the Agency.

No clinical trials were performed to support the therapeutic effect, efficacy, or safety of the proposed product. The primary data to support this NDA submission and approval for all of the proposed indications are from the BA study comparing the proposed SC methotrexate product to oral methotrexate (MC-MTX.14/PK) and from the in-use / human factors study (MC-MTX.15/HF). The applicant also performed a BA/BE study (MC-MTX.12/PK) comparing the proposed product administered SC to the referenced Hospira parenteral product administered IM. The results of the study became available during the course of the review of the NDA (submitted on April 30, 2014). It was determined prior to filing the application that lack of this study would not be a filing or review issue, as the BA study (MC-MTX.14/PK) linking the proposed product to the oral formulation is sufficient to support the application for all of the proposed indications. Further, the review clock was not extended when the study results were submitted

because the study was not considered to be pivotal to review of the application. That stated, the study is described in this review and in the labeling because it provides some findings that are helpful (but not required) to label the product.

Several other studies (or study protocols) were submitted to the application, but none were considered as specifically pertinent and none were reviewed. These included several marketing and PK studies that evaluated the proposed product compared with other formulations or devices made by Medac, as well as studies that used predecessor formulations. Datasets were not submitted for any of these studies.

Medac also submitted the final study report (but not the datasets) for a 6-month, randomized, double-blind, double-dummy, active-controlled safety and efficacy trial that they had sponsored in adults with RA. The trial compared SC dosing using a pre-filled syringe [different than the proposed product] with dosing via oral tablets. The results of the trial had also been published by Braun et al. in 2008, although interestingly, the applicant did not include that reference in the literature reference section submitted with the application. Since the overall results are in the public domain, the study report was treated as if it were a published study and reviewed for its overall contribution to the efficacy and safety of SC dosing in patients with RA. The results of the trial support the safety and efficacy of MTX administered SC for treatment of RA.

5.1 Tables of Studies/Clinical Trials

Table 5. Pivotal Studies*

Study	Type	Design	Products	Doses (mg)	N
MC-MTX.14/PK	Relative BA	R, OL, 2-way, SD crossover in healthy adult males Single site in Germany	MTX 2.5 mg Oral Tabs [Dava] MTX 50 mg/mL pre-filled pen SC in abdominal wall	4 dosing levels: 7.5 mg 15 mg 22.5 mg 30 mg	62 (54)** 16 (14) 17 (14) 15 (14) 14 (12)
MC-MTX.15/HF	In-Use	OL, single-arm 2-dose study in patients ≥16y with RA, with PK in a subset of pts ≥21y Five centers in US	MTX 50 mg/mL pre-filled pen SC in abd or upper thigh weekly 2x	15 mg	106 (104)** PK: 24
* These studies used the to-be-marketed 50 mg/mL prefilled pen auto-injector. ** N (n) = Randomized and received study treatment (completed)					

Table 6. Other Studies

Study	Type	Design /Other Info	Products	Doses (mg)	N
Marketing, PK, and Local Tolerability studies using the to-be-marketed formulation / device					
MC-MTX.11/RA	Patient preference and local tolerability	6-week, R, OL, 2-way crossover study in adults 18-75y with RA Multiple centers in Germany	MTX 50 mg/mL pre-filled pen x 3 MTX pre-filled syringe x3	15, 17.5, or 20 mg once weekly SC x3 for each of the two treatments	Protocol only. Planned N = 120

Study	Type	Design /Other Info	Products	Doses (mg)	N
MC-MTX.12/PK	Relative BA	R, OL, 2-way, SD crossover in adults (18-65y) with mod-to-severe psoriasis Single site in US	MTX 50 mg/mL pre-filled pen SC MTX inj [Hospira] IM	30 mg single dose SC or IM	34
MC-MTX.13/PK	BE	R, OL, 2-way, SD crossover in healthy Caucasian males Single site in Germany	MTX 50 mg/mL pre-filled pen MTX 50 mg/mL pre-filled syringe	15 mg SC	14 (14)
Studies with other (predecessor) formulations / devices					
MC-MTX.9/PH	Relative BA	R, OL, 2-treatment, 2-way, SD crossover in healthy Caucasian males, 18-45y Single site in Germany	Group 1: MTX pre-filled syringe 50 mg/mL MTX pre-filled syringe 10 mg/mL Group 2: MTX pre-filled syringe 50 mg/mL MTX pre-filled syringe 10 mg/mL	Group 1 (n=12): 15 mg SC 15 mg SC Group 2 (n=12): 15 mg IM 15 mg IM	25
MC-MTX.10/RH	Patient preference and local tolerability	OL, single-arm 2-way MD crossover study in patients with RA, 18-75y Multiple centers in Germany	MTX pre-filled syringe, 10 mg/mL MTX pre-filled syringe, 50 mg/mL	20 mg x3 (injections 1-3) 20 mg x3 (injections 4-6)	132 (131)
Efficacy and Safety (using predecessor formulation / device)					
MC-MTX.6/RH	Efficacy & Safety	6-month, R, DB, DD, MD, AC in adults RA patients 18-75y who were MTX-naïve 29 sites in Germany from 2003 to 2005	MTX pre-filled syringe 10 mg/mL Oral MTX	15 mg SC 15 mg orally	384 (375) 194 (188) 190 (187)

AU = Actual use; HF = Human factors; BA = Bioavailability, BE = Bioequivalence; SD = single-dose; MD = multiple-dose; OL = open-label; R = randomized; DB = double-blind; AC = active-controlled

For all studies except study MC-MTX.6/RH, the numbers in parentheses are the numbers of subjects who completed the study. For study MC-MTX.6/RH, the numbers in parentheses represent the numbers of patients in the efficacy evaluable population.

5.2 Review Strategy

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

5.3 Discussion of Individual Studies/Clinical Trials

The applicant submitted published literature to support efficacy and safety of SC dosing for JRA and psoriasis, but did not perform any clinical trials for this application. A single clinical pharmacology study and a single use and handling study were performed. Additionally, a BE study and a local tolerability study were conducted.

5.3.1 Clinical Pharmacology Studies

Clinical pharmacology was assessed in a single, open-label, randomized, 2-way crossover study (MC-MTX.14/PK). The applicant also performed a relative bioavailability study (MC-MTX.12/PK) that compared the proposed product administered SC to the referenced Hospira parenteral product administered IM.

5.3.1.1 Study MC-MTX.14/PK

Initiation Date:	June 8, 2012
Completion Date:	August 16, 2012
Investigation Sites:	Until Jan 31, 2013: Dr. med. Wolfgang Timmer After Jan 31, 2013: Dr. med. Sybille Baumann CRS Clinical Research Services Mannheim GmbH Grenadierstrasse 168167, Mannheim, Germany

Study Design

Study MC-MTX.14/PK was open-label, single dose, 2-way crossover (2-treatment, 2-sequence) bioavailability study that compared systemic MTX exposure following SC administration using the proposed pen injector device in the abdominal wall with a similar dose following oral administration in 65 healthy male and female subjects 18-55 years of age. Subjects were randomized to receive 7.5, 15, 22.5 or 30 mg of methotrexate SC or orally followed by a second dose by the alternate route two weeks later. The reference comparator product was Methotrexate 2.5 mg Tablets manufactured by Dava Pharmaceuticals Inc. (NDA 08-085, approved on December 7, 1953), which is listed in the Orange Book as an RLD.

Inclusion criteria included: healthy male and female subjects between 18 and 55 years of age (inclusive) with a body mass index between 18.5 and 30.0 kg/m^2 (inclusive); normal BP, HR, and ECG findings; and no febrile illnesses within 7 days of the first dose. Exclusion criteria included: >10 cigarettes/day; >5 cups of coffee/day; >35 g ethanol consumption/day or >345 g/week; history of alcohol or drug abuse; evidence of active physical disease; history of drug hypersensitivity, asthma, urticaria, or severe allergic diathesis; history of hypersensitivity to any of the medications used in the study; history of chronic gastritis or peptic ulcers; vegetarian; blood donation within 30 days; lab values outside the reference range (including creatinine > ULN, creat clearance <80 mL/min, MCV >98 fL); positive HIV, HbsAg, or Anti-HCV, alcohol breath test, or

barbiturate, amphetamine, benzodiazepine, cocaine, opiates, and cannabis test; any GI complaint within 7 days; use of any medication within 4 weeks; consumption of xanthine containing food or grapefruit juice within 48 hours; WBC<3500 neutrophils and <5000 leukocytes; history or current malignancy; history or current bone marrow, hepatic, or renal impairment; unable to maintain contraception; ulcers of the oral cavity and known active GI ulcer disease; significant leukopenia, thrombocytopenia, or anemia; TB; vaccination with a live vaccine within 3 months, positive serum pregnancy test (females)

Subjects were to be withdrawn for any of the following: AEs that made continuation undesirable; clinically significant teat results; low neutrophil (<1500 on D3 of P1 and <2500 on D-1 of P2), leukocyte (<3000 on D3 of P1 and <4000 on D-1 of P2), or thrombocyte (<75,000) count; AST or ALT>2xULN; creat clearance <80 mL/min; major protocol deviation; non-compliance; withdrawal of consent.

All subjects received the following additional medications:

- 15 mg folinic acid (Calciumfolinat-GRY® 15 mg tablets) at 24 and 48 hours after each methotrexate administration for the reduction of the hematotoxic and gastrotoxic effects of methotrexate
- 7.2 g potassium-sodium hydrogencitrate 12 hours prior to methotrexate administration and 2.4 or 4.8 g at 4 and 12 hours after (depending on the obtained pH value) to reduce the nephrotoxic effects of methotrexate

Results

A total of 65 subjects were enrolled, 62 were treated, and 54 completed two treatments (59 test, 57 reference). Three subjects who had been enrolled were discontinued from the study prior to treatment because they had an exclusion criterion. Another 8 subjects discontinued after administration of the first methotrexate dose due to the following reasons: private reasons (n=2), test result(s) meeting removal criteria (n=3), test result(s) (n=2), adverse event making continuation of the study undesirable (n=1).

The study population was primarily male (male = 48, female = 14) and white (59 white, 1 Hispanic, 1 Asian, 1 Black).

A total of 80 TEAEs were reported by 35 of the 62 subjects (56.5%). Most were considered mild in intensity (63 mild, 17 moderate, 0 severe), and most (75 of 80 events) were considered to be drug-related. There were no deaths and no SAEs. Three subjects discontinued the study due to an AE: 1 because the event made the continuation of the study undesirable, and 2 because the TEAE fulfilled a withdrawal criterion. All TEAEs resolved without treatment except for 2 TEAEs (headache and sore throat), which were treated with medication (paracetamol). As expected, GI AEs were reported more frequently in subjects after oral dosing than after SC dosing.

PK parameters are shown in Table 7, and shown graphically in Figure 5 through Figure 8. The results show that bioavailability was higher following SC administration with the proposed device than following oral administration, particularly at higher dose levels at which a plateau of systemic exposure is reached.

Table 7. MC-MTX.14/PK, Geometric Means and Comparisons by Dose Level, PK pop

Parameter	Dose Group	Geometric Mean CV[%])		Point Est T/R (%)	90-% CI
		Test	Reference		
AUC $_{0-t}$ [h•ng/mL]	7.5 mg	782.73 (9.78)	579.79 (21.79)	135.00	123.04,148.13
	15 mg	1594.84 (11.79)	1073.32 (30.26)	148.59	132.31, 166.87
	22.5 mg	2272.55 (10.80)	1509.34 (13.64)	150.57	142.13, 159.50
	30 mg	2824.72 (12.79)	1679.47 (42.27)	168.19	137.85, 205.21
AUC $_{0-inf}$ [h•ng/mL]	7.5 mg	816.31 (9.75)	614.54 (21.11)	132.83	121.73, 144.95
	15 mg	1632.11 (11.56)	1120.75 (30.47)	145.63	130.06, 163.06
	22.5 mg	2317.95 (10.70)	1544.96 (13.31)	150.03	141.81, 158.74
	30 mg	2866.00 (12.58)	1726.10 (41.05)	166.04	136.62, 201.80
Cmax [ng/mL]	7.5 mg	185.99 (15.55)	185.77 (23.43)	100.12	91.13, 109.99
	15 mg	392.00 (27.06)	302.96 (31.25)	129.39	115.44, 145.02
	22.5 mg	512.71 (21.16)	391.64 (20.46)	130.91	113.78, 150.63
	30 mg	576.26 (19.43)	450.20 (40.31)	128.00	102.70, 159.53

CI: confidence interval

T: Prefilled pen containing 0.15, 0.3, 0.45, and 0.6 mL of the 50 mg/mL methotrexate solution corresponding to 7.5, 15, 22.5, and 30 mg methotrexate

R: Methotrexate tablets USP corresponding to 7.5, 15, 22.5, and 30 mg methotrexate

Source: p5; mc-mtx14pk-report-body-1.pdf

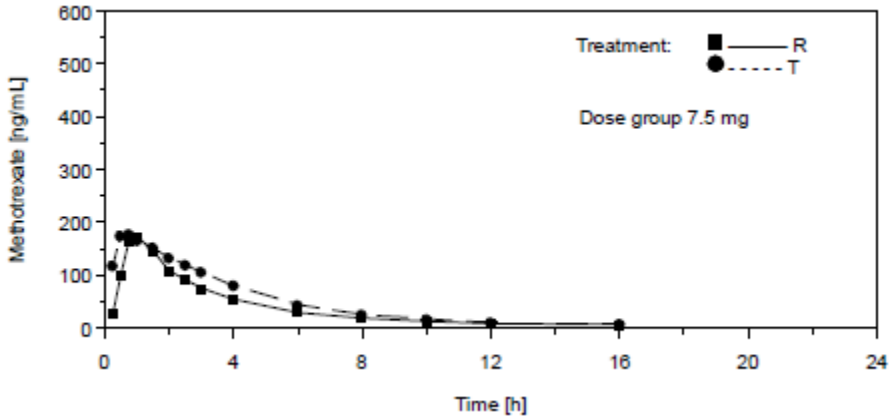


Figure 5. MC-MTX.14/PK, Geometric Mean MTX concentration vs time, by treatment, linear scale, PK pop, MTX 7.5 mg dose group

R (reference) =Methotrexate tablets; T (test) =Methotrexate prefilled pen

Source: F11-1, p69; mc-mtx14pk-report-body-1.pdf

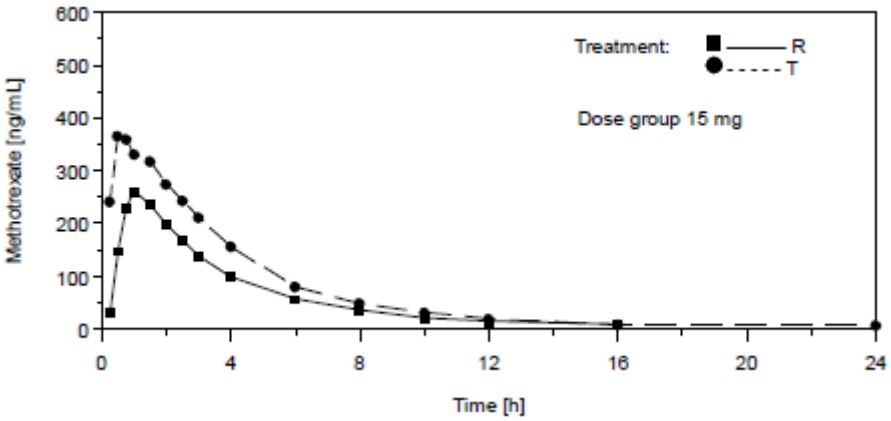


Figure 6. MC-MTX.14/PK, Geometric mean MTX concentration vs time, by treatment, linear scale, PK pop, MTX 15 mg dose group

R (reference) =Methotrexate tablets; T (test) =Methotrexate prefilled pen
Source: F11-3, p73; mc-mtx14pk-report-body-1.pdf

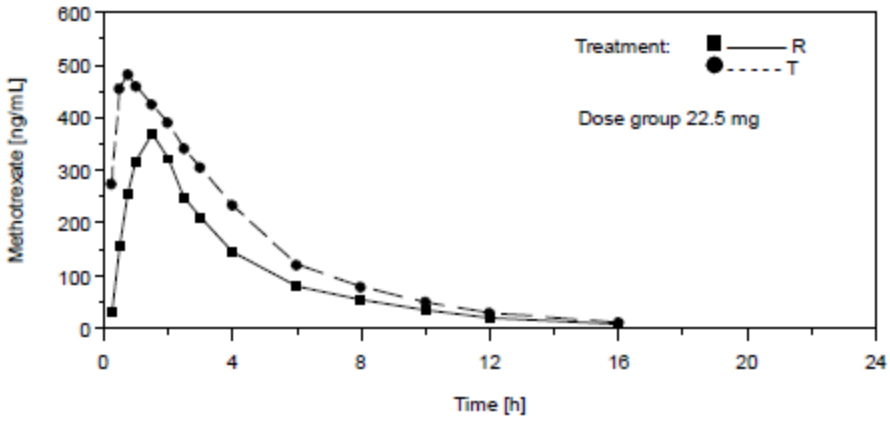


Figure 7. MC-MTX.14/PK, Geometric mean MTX concentration vs time, by treatment, linear scale, PK pop, MTX 22.5 mg dose group

R (reference) =Methotrexate tablets; T (test) =Methotrexate prefilled pen
Source: F11-5, p77; mc-mtx14pk-report-body-1.pdf

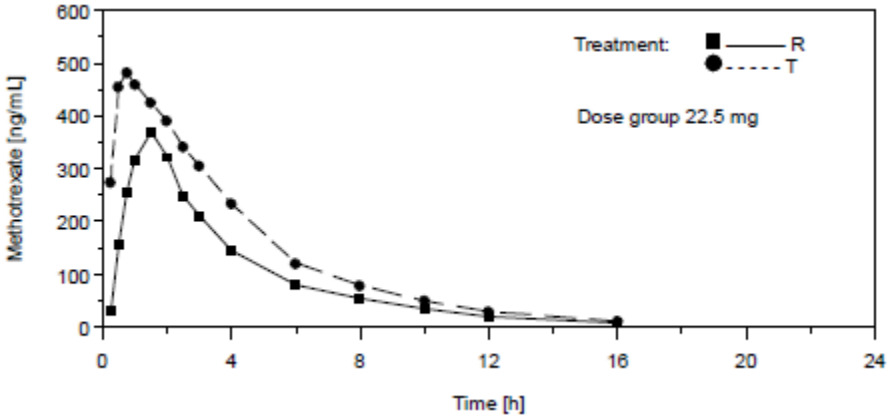


Figure 8. MC-MTX.14/PK, Geometric mean MTX concentration vs time, by treatment, linear scale, PK pop, MTX 30 mg dose group

Source: F11-7, p81; mc-mtx14pk-report-body-1.pdf

Conclusion

In this open-label PK study, subcutaneous dosing was associated with a linear increase in systemic exposure with progressively higher doses, whereas oral dosing with progressively higher doses was associated with non-linear systemic exposure resulting in a relative plateau of exposure at doses above 15 mg orally. AUC_{0-t} test/reference ratios (90% CIs) for the 7.5, 15, 22.5, and 30 mg doses were 135% (123%; 148%), 149% (132%; 167%), 151% (142%; 160%), and 168% (138%; 205%), respectively. This finding was not unexpected, given the known limitations of oral methotrexate dosing with progressively higher doses imposed by saturation of gut absorption.

Given this phenomenon, systemic dosing (IM, IV, or SC routes) provides a viable alternative approach to increasing oral doses of MTX above 15 mg without the resultant increases in GI side effects associated with higher oral dosing.

5.3.1.2 Study MC-MTX.12/PK

Initiation Date:	May 6, 2013
Completion Date:	October 8, 2013
Investigation Sites:	2 sites in the United States: Site 1: Douglas S. Denham, DO, Clinical Trials of Texas, Inc, San Antonio, TX 78229 Site 2: Terry M. Jones, MD, J & S Studies, Inc, College Station, TX 77845

Design

This was a single dose, 2-period, 2-treatment, open-label, randomized crossover study to determine the relative bioavailability of 30 mg of MTX administered an SC injection from the proposed to-be-marketed product compared with the same dose of MTX

administered as an IM injection using the reference Hospira injectable product. The study enrolled a total of 35 otherwise healthy adults 18 to 65 years of age with moderate to severe psoriasis who either were on methotrexate or were eligible for MTX treatment based on a dermatologist's diagnosis and a Physician's Global Assessment score.

Study drug was administered by the investigator or designee, and patients were confined to the clinical research unit for 24 hours after dosing. To match the normal methotrexate treatment interval, the study used a washout period of 7 days between treatments. Blood for PK assessments was obtained 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. Safety assessments included monitoring for adverse events, physical examinations, vital signs, 12-lead ECGs, and clinical laboratory evaluations.

Results

Following SC injection, the median Tmax occurred at 0.75 hours after injection, whereas the median Tmax following IM injection was at 0.50 hours after injection. Following SC injection, Cmax was approximately 25% lower than after IM injection. However, based on the AUCs the relative bioavailability was equivalent following both treatments (the 90% CIs for the geometric LS means ratios of AUC_{0-t}, and AUC_{0-inf} were within the range of 80% to 125%).

There were no deaths, SAEs, or AEs leading to discontinuation. Following IM administration, 8 patients (23.5%) reported an AE, and no patient reported an injection site reaction. Two patients (5.9%) reported moderate AEs of headaches, and 1 patient (2.9%) reported a severe AE of headache. Following SC administration, 14 patients (41.2%) reported an AE, including four patients (11.8%) who 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. AEs included: 5 patients (14.7%) with moderate AEs (2 headache, 1 limb injury, 1 wound, 1contact dermatitis, and 1 urticaria).

Conclusion

In this open-label relative bioavailability study, subcutaneous dosing of 30 mg of methotrexate using the proposed product was bioequivalent to intramuscular dosing of 30 mg of methotrexate using an injectable approved reference product (Hospira), based on AUC evaluations. However, Cmax and Tmax were not bioequivalent, with an earlier Tmax and higher Cmax after IM exposure than after SC exposure using the proposed to-be-marketed product.

5.3.2 Device Usability Study

A single device usability / human factors / PK 'in-use' study was performed to evaluate the ability of patients to follow the instruction set and use the device, to assess the

pharmacokinetics across a range of body weights, and to assess device robustness (MC-MTX.15/HF).

5.3.2.1 Study MC-MTX.15/HF

Study Design

Study MC-MTX.15/HF was an actual use and PK study in patients with RA. The listed objectives included to: 1) evaluate the human factors and usability of the proposed drug product, including a label comprehension assessment and evaluation of device robustness, and 2) to assess the pharmacokinetics of MTX across a range of body weights when a SC dose is administered in either the abdomen or the thigh. It was a multicenter, open-label, single-dose, study that was conducted at 5 clinical sites in the United States between October and January of 2012. The report states that the protocol was reviewed by the (b) (4) was conducted in accord with the ICH tripartite (E6) and applicable Good Clinical Practice guidelines, and appropriate informed consent was obtained prior to initiation of any study procedures.

Enrollment criteria included otherwise healthy RA patients who were at least 16 years of age, have been diagnosed with RA based on the European league Against Rheumatism / American College of Rheumatology 2010 or American College of Rheumatology 1987 revised criteria, and either were candidates for MTX therapy or on 10-20 mg of MTX per week orally or SC off-label, along with standard of care folic acid treatment. The study excluded: Females who were pregnant, trying to become pregnant, breast feeding, or sexually active but not using a highly effective means of birth control during and for at least 6 months after the study; Males who had a female partner of childbearing potential and either not had a vasectomy or was not using a condom and/or cervical cap / diaphragm with spermacide during and for at least 6 months after the study. The PK subset included only patients over 21 years of age.

The study is stated in the application to have evaluated the proposed to be marketed 50 mg/mL prefilled pen device, although the actual study report uses the term 'Metroject®' to describe the prefilled pen, which is the name used during the clinical development program for this product [Response dated Feb 25, 2104, to IR dated Feb 19, 2014]. The study used lot K110547BA of prefilled pens, filled with 0.3 mL of MTX (50 mg/mL) solution (i.e., a dose of 15 mg of MTX was administered). [p46-48]

The study included a screening visit, a training visit on Day 1, a testing / PK visit on Day 8-10, and a follow up / PK visit on Day 9-11. Training (Day 1) consisted of a group or individual training session that reviewed the proper technique for using the prefilled pen using the Patient IFU. Training was provided in the physician's office or clinic by a healthcare professional (i.e., nurse, physician, or pharmacist) to ensure proper understanding of the Patient IFU. The protocol does not comment upon whether the verbal instructions were standardized. Each patient was also provided a copy of the IFU for reference. Comparison shows that the written IFU that was provided to patients was very similar, although not identical, to the proposed IFU submitted with the

application. After training, the patient was asked to perform a self-injection with the healthcare professional available to answer any questions and provide assistance. No testing was performed at this visit. While the study report states that label comprehension was included in the protocol, the label comprehension questionnaire (a check-off list of whether the patient was able to follow the directions and administer an injection) was completed by the healthcare professional who provided the training, and not by the patient, included the following:

- Was the patient trained on the use of the Metoject?
- Did the patient review the Metoject instructions for use?
- Did the patient understand the Metoject instructions for use?
- Did the patient have questions related to the use of the Metoject?
- Were all patient questions related to the Metoject able to be answered?
- Did the patient perform a self-injection using the Metoject?
- Did the patient need assistance to perform the injection?
- Did the patient have any difficulties using the pen?
- Did the patient experience any AEs at this visit?

From the questions listed, it is clear that this was not a true label comprehension evaluation.

To assess how well patients retained the information from the training visit (Visit 1, Day 1), at Visit 2 on Day 8 to 10 patients were tested via a written examination followed by human factors observation of the patient performing a self-injection without provision of assistance or training from the healthcare professional. PK was also evaluated before and after dosing in a subset of approximately 24 patients. In this subset, patients were randomized to abdominal or thigh injection and stratified by body weight (under 60 kg, 60 to 100 kg, and over 100 kg). A follow-up visit was performed the following day to assess for AEs and draw blood for additional PK analysis in the PK subgroup. [p42, 48, 50-1]

On the written examination, a passing score was 80%, i.e., 8 correct answers out of the 10 questions, although the study report also notes that a single re-test was permitted without specifying how this would be performed.

During the human factors testing session, the patient was asked to perform all use steps under direct observation, including specific tasks that were to assess those user-device interactions considered “to pose the highest risk of injury or harm to patients and to assess for usability difficulties or use errors.” Data on performance (time on task, successful completion rates) and subjective measures (ease-of-use ratings, open-ended responses) were collected. The previously identified risks included: appropriate skin-pinch to assure that the injection was administered into the SC area, post-injection dwell interval of at least 5 seconds to assure medication delivery without leakage, post-injection visual confirmation of full movement of the plunger, device handling and

disposal in a manner to avoid unnecessary exposure to MTX by other individuals (due to the cytotoxicity of MTX). The study report states that the actions observed and assessed included the following. Of note, one of the four identified risks, visual inspection to confirm full movement of the plunger, was not included in the specific task list.

- Examining sterile container for expiration date and product identity
- Opening the product package
- Performing visual checks
- Removing the protective end cap
- Selecting and preparing the injection site (upper thigh or abdomen)
- Performing the skin pinch, pressing the prefilled pen against the skin and pushing the injection button
- Self-injecting the drug and holding the prefilled pen for about 5 seconds
- Properly disposing of the pen after use. [p57]

Following the injection, patients completed a subjective questionnaire to assess the ease or difficulty with use of the pen device. Questions included:

- Did you have any difficulty using this device? If yes, please explain.
- What is your impression of using the prefilled pen overall?
- What were the 3 things you liked best about the prefilled pen?
- What were the 3 things you liked least about the prefilled pen?
- What would you change about the prefilled pen, the packaging, any other components or the instructions for use?
- On a scale of 1 to 10, with 1 indicating very difficult and 10 indicating very easy, how would you rate the ease of using the prefilled pen, overall?
- Do you have any final comments or observations about working with the prefilled pen?

Used pens were checked to see if they were intact with all pieces remaining as one unit; if there was any fluid left by checking the transparent control zone; if the needle was intact, bent or broken; and if the protective shield had moved into place to cover the needle.

Results

A total of 106 RA patients were enrolled, and 104 completed the study, 12 in the 21-40 year age range, 53 in the 41-60 year age range, and 41 in the >60 year age range. Most (n=8, 92.5%) had been taking methotrexate in the past, of whom most (89) had been taking MTX by the oral route, 2 by the IM route, and 7 by the SC route. Educational level was at least high school degree or higher for 90% of the patients, 74%

of patients were female, 88% were White, and 93% were taking MTX (mean dose 15,7 mg, 84% but the oral route) at the time of enrollment. About half of the patients had used a prefilled pen before.

Essentially all patients (98%) were able to complete the written exam with an 80% pass rate for each question, and perform a successful SC self-injection of study drug. The study report, however, focused on the subject's subjective interpretation of ease of use for each of the tasks rather than on the objective assessment of the task completion.

A total of 210 injections were documented over the course of the study. Upon inspection, all (210/210) pens were found to be intact after use, with all pieces remaining as one unit. Of particular note, after all of the injections the protective needle shield was noted to have completely moved back into place, completely covering the needle. Along with an additional simulated use study in which the needle shield activated automatically in all (390/390) cases, this satisfies the Agency's concerns that the sharps protection feature incorporated into the device be adequately tested (see the CDRH Guidance for Sharps Injury Protection features at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071755.pdf).

That stated, not all of the devices functioned appropriately. One pen was reported to have a bent needle, and fluid was noted to be deposited in the wall of the control shield of a second pen. The pen with the bent needle was noted to have a "slight bend" post injection. However, it was also noted that the injection was successful (full dose administered with no fluid left in the product), the needle was not broken, the pen was otherwise intact, and the shield had appropriately moved into place. Therefore, no further evaluation of the product was performed. Medac noted that the fluid noted to be on the wall of the control shield of one pen was due to a patient having prematurely lifted the pen from the skin rather than due to a device failure. [IR response dated Feb 25, 2014]

Some patients did not adequately complete an injection, four at the first visit and two (different patients) at the second. All four patients with incomplete injections at the first visit had lifted the pen too early. The reasons given for the two patients who had incomplete injections on the second were nervousness with being observed and not used to an injection. As noted above, for one patient, lifting the pen early resulted in deposition of on the wall of transparent control shield. While listed in the study report as a potential device malfunction, Medac noted [IR response dated Feb 25, 2014] that this was reclassified as a human factors issue and not a device malfunction. The applicant argues that of the incomplete injections can be dealt with by adequate training, and I agree.

There were No SAEs. Three AEs were reported: 1 diarrhea, 1 toothache, and 1 upper respiratory tract infection. Local reactions do not appear to have been recorded.

Plasma levels were lower for the first 4 hours after SC administration in patients who weighed >100 kg compared with patients who weighed <100 kg. In patients weighing <100 kg, mean plasma concentrations after SC administration in the abdomen were higher than plasma concentrations after administration in the upper thigh, whereas in

patients weighing >100 kg mean plasma concentrations after SC administration in the abdomen were lower than after administration in the upper thigh. These differences are likely not clinically significant.

Conclusion

This in-use study conducted in RA patients appears to confirm that patients can learn to use the proposed pen injector device and perform a successful injection after a training demonstration based on the proposed IFU. Further, it appears to show that patients can adequately retain the learned information and appropriately use the device one week later. Most participants were able to satisfactorily answer written questions about important aspects of the IFU one week after the initial training session and were able to complete the second injection without any major difficulties being noted. However, some participants encountered difficulties (i.e., removing the auto-injector prior to the 5 second hold time and not pinching the skin) and required assistance (i.e., assistance with holding the pen, skin, or shirt) to complete the injection, both on the first training day and at the second visit 8-10 days later. However, those participants who encountered difficulties at Visit 1 did not report issues at Visit 2 and vice versa. Further, most of the difficulties encountered by participants were of a similar nature to those noted for other auto-injector devices, so it does not appear that they are not unique to this product. Finally, all of these difficulties should be able to be overcome by adequate training and experience with the product. Therefore, overall the study supports approval of the drug product.

It should be noted, however, that the study design did have some weaknesses and limitations. Specifics of the training scenario were not provided in the study report. When requested, the applicant responded that the IFU was followed but a training script was not provided. The so-called 'label comprehension' evaluation that was part of the study was inadequate because it tested the trainer's evaluation of the patient rather than the patient's actual comprehension of the IFU. Additionally, the 'human factors' evaluation did not fully test all of the critical steps that had been identified in the IFU. Further, the results as presented in the study report portray the patient's subjective evaluation of the steps rather than an objective assessment of whether any of the critical steps were missed. Responses to the Agency's IR about the study results did help to clarify which steps were missed by specific patients, helping to resolve some of these issues. Despite these limitations, there is a significant amount of experience with the use of similar pen injection devices to deliver SC or IM medications across a number of indications, especially for chronically used medications, such that overall the study does support use of the device by patients.

From a clinical perspective, one of the main reasons for a study such as this is to assure that any problems with use of the device would be reported and investigated for cause. Previously, the Agency had recommended that device reliability and robustness data be collected after actual use in at least 100 patients. This study appears to satisfy that recommendation, with the exception that the root cause of the one pen with a bent needle was not evaluated. As a result, the study is adequate to support use and handling of the device as well as sharps protection and labeling for use, although it does

not necessarily provide data to fully assess whether the product is adequately designed, an issue that is generally addressed as part of the CMC and CDRH reviews.

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed this study and concurred that despite the limitations the study does support approval of the device. They recommended some labeling comments, which were conveyed to the sponsor and incorporated into the labeling.

It should be noted that the therapeutic effect (i.e., efficacy and safety) of the proposed drug product was not evaluated in this study. Therefore, it did not provide clinical efficacy or safety data and will not be described as a clinical study in the PI.

5.3.3 Local Tolerability Study

Study MC-MTX.13/PK was performed in Germany when Medac developed the formulation to be marketed in the United States. The study compared 15 mg doses in healthy adult Caucasian males injected with the to-be-marketed 50 mg/mL prefilled pen device and a similar 50 mg/mL formulation delivered by prefilled syringe. Results showed bioequivalence between the two formulation/devices. The study also included an assessment of local tolerability immediately and at 2, 24, and 48 hours after in injection. There were no significant differences in local reactions between the two treatment groups, although two subjects had a hematoma at the injection site, one after each of the two formulation/devices tested.

6 Review of Efficacy

6.1 Efficacy Summary

Support for approval of this application is based on the Agency's previous findings of safety and effectiveness of MTX in patients with RA and JRA [and psoriasis], published literature to support efficacy and safety of SC dosing for RA [and psoriasis], and a bioavailability study (MC-MTX.14/PK) that supports the effectiveness of SC MTX by demonstrating higher systemic exposure dose for dose when MTX is administered SC than orally, particularly as doses that extend above 15 mg. Efficacy and safety of SC administration of MTX has already been demonstrated in patients with JRA [pJIA], as the listed reference product(s) are already labeled for SC use for this indication. Support for the safety for the RA indication comes from labeling for the reference product(s) for treatment of neoplastic diseases where it is used at much higher doses and systemic exposures than for the proposed indications and from a large body of literature that includes clinical trials in which SC dosing has been evaluated. The published literature to support efficacy and safety of SC dosing for RA and pJIA, including the literature that was submitted to the application, was reviewed. The literature supports both the efficacy and safety of SC administration as an alternative to oral or IM administration of MTX, with higher systemic exposure and potential improvements in efficacy when administered SC or IM vs orally in similar doses,

particularly in doses above 15 mg. At least one of these trials was conducted by the applicant, although the trial used a different formulation of SC MTX. Overall, the data support the use of the proposed product as a convenience alternative to using a needle and syringe for at-home self or caregiver injection of methotrexate for both the RA and pJIA indications. Please refer to the reviews from the Division of Dermatology and Dental Products for discussion of the psoriasis indication.

6.2 Indications

This section reviews the support use of the proposed product for the RA and pJIA indications. The sponsor has previously conducted a safety and efficacy trial in adults with RA that evaluated a different formulation of MTX in a prefilled syringe. They have also provided literature that supports the use of MTX for RA. Additionally, although the SC route is already approved for the treatment of pJIA, the applicant has submitted published pediatric literature to support the SC route of administration in patients with pJIA.

6.2.1 Rheumatoid Arthritis (RA)

6.2.1.1 Background

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

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

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

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

6.2.1.2 Medac's Safety and Efficacy Trial

Medac submitted the final study report for a Phase IV, 6-month, randomized, double-blind, double-dummy, multi-center, active-controlled safety and efficacy trial that they had sponsored in Germany between 2003 and 2005. The trial compared SC dosing using a pre-filled syringe that is different than the proposed product, with dosing via oral tablets, in adults with RA. The study report was submitted to this application, but no datasets were submitted. The results of the trial had also been published by Braun et al. in 2008, although interestingly, the applicant did not include that reference in the literature reference section submitted with the application.

A total of 384 patients (190 oral group, 194 SC group) 18 to 75 years were randomized in this trial, from which efficacy data were available in 375 patients and safety data in 381 patients. Patients had to have active rheumatoid arthritis as defined by a DAS28 ≥4, who had never been treated with methotrexate and who were familiar with SC self-administration through a confirmed practice phase.

6.2.1.3 Literature Review

The applicant summarized the literature with respect to SC MTX treatment of RA and other rheumatic diseases, as well as the literature with respect to IM MTX treatment. Additionally, I performed a review of the available literature for SC MTX treatment. I found two randomized controlled trials [Braun 2008, Parker 2004] and multiple other studies and clinical reports. Dosages of SC MTX ranged from 5 mg to 30 mg once a week. Most studies were 6 to 12 months in duration. The MTX SC use literature is summarized below.

Arthur AB, et al, 1999

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

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

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

Arthur V, et al, 2001 and 2002

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

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

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

Bakker et al, 2010

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

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

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

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

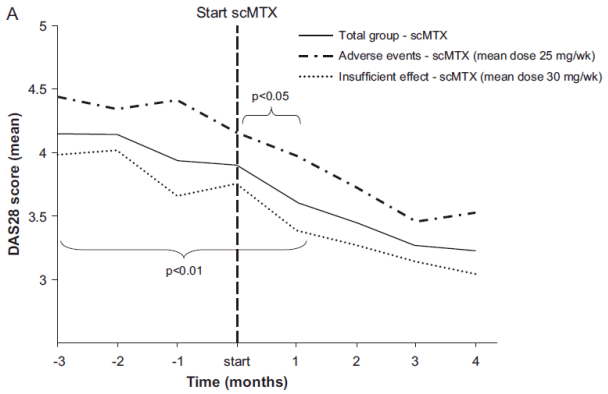


Figure 9. Bakker et al, 2010. DAS28 for patients switched to SC MTX.

Braun et al, 2008

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

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

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

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

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

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

Tolerability was similar between treatments. Overall, 66% of SC MTX–treated patients reported an adverse event during the study, compared with 62% of oral MTX–treated patients. Similar percentages had SAEs. AEs of moderate severity with at least 3% incidence are shown in Table 8.

Table 8. Braun 2008. AEs of moderate severity with at least 3% incidence

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

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

Griffin & Erkeller-Yuksel, 2004

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

Hameed et al, 2010

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

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

Muller-Ladner et al, 2010

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

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

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

Parker et al, 2004

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

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

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

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

Stamp et al, 2011

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

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

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

Thornton et al, 2008

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

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

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

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

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

6.2.1.3 Discussion

The applicant has submitted bioavailability data and published literature to support the SC route of administration in patients with RA. My review of the data presented supports the proposed dosing administered by the SC route for these patients. Further, my review of these data does not reveal any specific safety concerns with this route of administration beyond those already labeled. Study MC-MTX.14/PK showed higher bioavailability with SC dosing than with oral doses, particularly above 15 mg. These data are consistent with clinical results of published studies, including two randomized controlled trials [Braun 2008, Parker 2004] and multiple other studies and clinical reports, suggesting equal or greater efficacy with SC dosing and no increase in safety concerns.

Parenterally administered MTX is also recommended for the treatment of RA in essentially all published treatment guidelines, including those from the American College of Rheumatology (ACR). [Singh, 2012] The updated ACR guideline recommends MTX as either first line monotherapy or in combination with other DMARDs prior to resorting to biologic DMARDS. DMARDs are now recommended for both early and established disease. Although the ACR guideline does not include recommendations with regard to the route of administration, SC administration is recommended by all of the other guidelines. [Pavy et al, 2006; Visser et al, 2009; Visser & van der Heijde, 2009; Verstappen & Hyrich, 2010; Ataman et al, 2011; da Mota et al, 2012]

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

6.2.2 Polyarticular Juvenile Idiopathic Arthritis (pJIA)

The SC route of administration is already approved for pJIA. That said, the applicant submitted data to further support the subcutaneous route of administration for this indication.

6.2.2.1 Background and Terminology

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

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

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

- systemic (sJIA). This form, formerly called systemic JRA (sJRA), is characterized by fever, arthritis, salmon pink rash, lymph node involvement, and internal organ involvement.
- oligoarticular JIA (oJIA). Formerly called pauciarticular-course JRA, this form was renamed to distinguish it from the polyarticular form. It affects 4 or fewer joints in the first 6 months.
- polyarticular JIA (pJIA). This form, formerly called polyarticular-course JRA, affects 5 or more joints in the first 6 months. It is subdivided into rheumatoid factor (RF) positive and RF negative subtypes.

- enthesitis-related arthritis. Enthesitis is the point at which a ligament, tendon, or joint capsule attaches to the bone. This form includes juvenile ankylosing spondylitis and arthritis associated with inflammatory bowel disease.
- psoriatic arthritis, i.e., arthritis associated with psoriasis.
- undifferentiated arthritis.

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

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

First line treatment of JIA typically involves use of nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, naproxen, and naproxen sodium [aspirin is an NSAID, but typically is not used for this condition]. If NSAIDS do not relieve the symptoms, so-called disease-modifying anti-rheumatic drugs (DMARDs) are used. MTX is considered to be a DMARD, along with biologic agents. However, MTX is currently approved only for the treatment of "polyarticular-course JRA who have an insufficient therapeutic response to NSAIDS." Clinical guidelines for the treatment of JIA include MTX as part of the treatment regimen for other forms of JIA when arthritis is active (e.g., systemic JIA with active arthritis) or when disease activity is high (e.g., oligoarticular JIA with high disease activity) [Beukelman 2011], and it is clear from the literature that MTX is used in this fashion in the clinical setting. However, the applicant has not requested expansion beyond pJIA to other JIA subtypes.

6.2.2.2 Discussion

Although the SC route is already approved for the treatment of pJIA, the applicant has submitted additional published pediatric literature to support the SC route of administration in patients with pJIA. My review of the data supports the proposed dosing administered by the SC route for pJIA. Further, my review of these data does not reveal any specific safety concerns with this route of administration in children

beyond those already labeled. Results of published studies suggest equal or greater efficacy with SC dosing than oral dosing with no increase in safety concerns. [Arthur 2001; Ravelli 1998; Ruperto 2004; Tukova 2010; Wallace 2012]

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

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

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

It should be noted that MTX doses for patients with pJIA are often lower than the lowest proposed dose of 7.5 mg weekly, which corresponds (based on a dose of 10 mg/m^2) to a BSA of 0.75 and a weight of about 18 kg (40 lb) (Figure 11). Assuming average height for weight, the 7.5 mg dose corresponds to 50th percentile for boys and girls of around 5 years of age (Figure 10). Since pJIA is considered to begin around 2 years of age, the lowest starting dose of 7.5 mg for this product will therefore not be sufficient to allow for use in all pediatric patients. Based on the CDC growth charts (Figure 10), the lowest weight would likely be about 10 kg, which corresponds to a BSA (Figure 11) of 0.47 m^2, and a dose of 5 mg. Corresponding weights for standardized doses of 5, 7.5, 10, and 12.5 mg in children are shown in Table 9, using a dose of 10 mg/m^2 and assuming an average height for weight. However, since PREA (triggered by the new route for RA) is satisfied by the fact that MTX is already labeled as safe and effective in children 2 years of age and older with pJIA when administered by the SC route, no additional doses are required under PREA

Medac has requested a waiver of PK studies in children of all ages, and a waiver of PK studies in children is appropriate from an ethical perspective because the information is available from data in adults. Medac has also requested a waiver of pediatric studies for RA/pJIA below 2 years of age because the disease is rare in this age range. This is appropriate and acceptable. The pediatric assessment will therefore be considered to

be complete for 2 years of age and older, and a waiver will be granted from birth to 2 years of age because the disease does not exist in this age range.

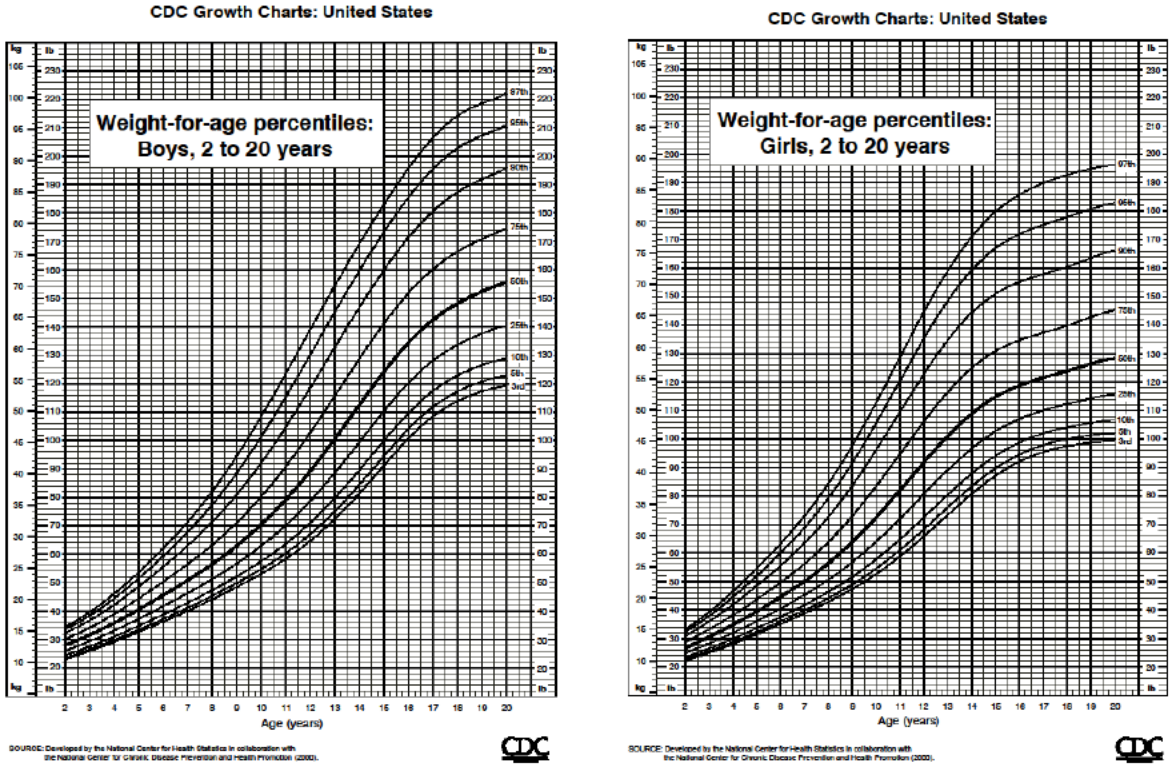


Figure 10. CDC growth charts for boys and girls 2-20 years of age

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

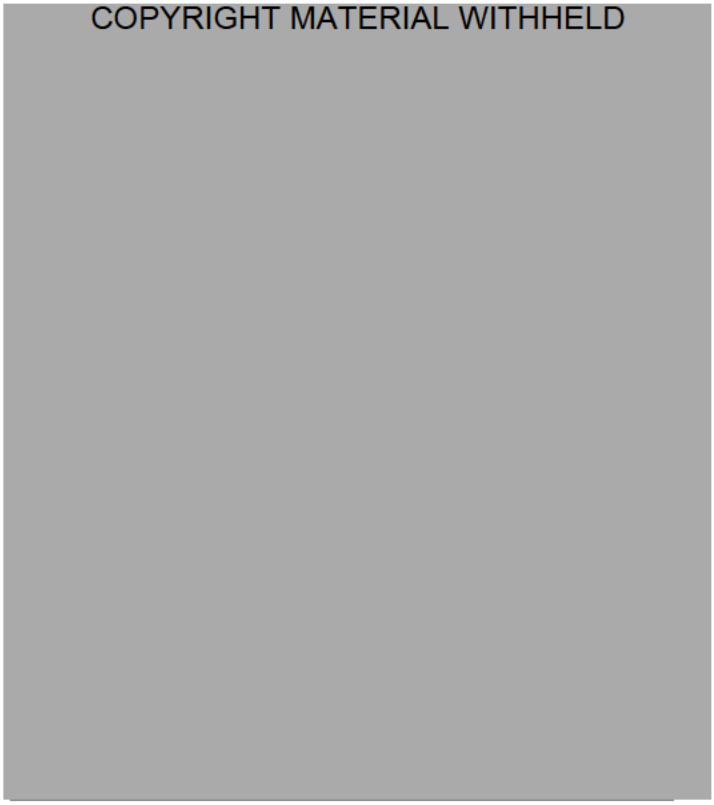


Figure 3–1. West Nomogram (for Estimation of BSA). The BSA is indicated where a straight line connecting the height and weight intersects the BSA column or, if the patient is roughly of normal proportion, from the weight alone (enclosed area). (Nomogram modified from data of E. Boyd by C. D. West; from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

Figure 11. Nomogram for estimation of body surface area (BSA)

Source: See notation within the figure.

Table 9. Corresponding weights for standardized 10 mg/m^2 doses in children

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

7 Review of Safety

Safety Summary

Two BA studies and one actual use study were submitted and reviewed for safety, and no unexpected findings were noted.

Review of the other studies submitted with the NDA revealed no unexpected local tolerability issues.

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

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

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

7.1 Methods

NA

7.2 Adequacy of Safety Assessments

NA

7.3 Major Safety Results

NA

7.4 Supportive Safety Results

NA

7.5 Other Safety Explorations

NA

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

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

7.6.2 Human Reproduction and Pregnancy Data

No new information is submitted with this NDA. Methotrexate is already labeled as Pregnancy Category X, with a contraindication for use in pregnancy in patients with psoriasis or rheumatoid arthritis and in breastfeeding mothers. Section 8.6, Males and Females of Reproductive Potential was added by the Agency as we converted the old labeling to PLR format to address issues in both males and females who are taking methotrexate.

7.6.3 Assessment of Effects on Growth

No new information is submitted with this NDA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

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

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

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

9 Appendices

9.1 Literature References

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9.2 Labeling Recommendations

During the course of the review, labeling consults were sent to the Division of Medication Error Prevention and Analysis (DMEPA), the Division of Medical Policy Programs (DMPP), and the Office of Prescription Drug Promotion (OPDP). DMEPA also provided comments regarding the container and carton labeling. Comments from all consulting teams were consolidated and forwarded to Medac as part of labeling negotiations. Labeling revisions are near complete but ongoing at the time of completion of this document. Therefore, this section provides a summary of the main issues found during the review, but is not intended as a complete review of the labeling.

9.2.1 Prescribing Information (PI)

As is appropriate, the proposed PI is in PLR format, whereas the reference products are not. This product will be the second instance of Prescribing Information (PI) in Physicians Labeling Rule (PLR) format for a MTX product. A similar methotrexate product for subcutaneous administration, Otrexup (NDA 204824), was approved on October 11, 2013, approximately one month after the submission of this application, for the same indications as requested in this application. Differences between this proposed product (Rasuvo) and Otrexup include (but are not limited to) that Otrexup is a true auto-injector that is available in four doses of 10, 15, 20 and 25 mg, whereas Rasuvo is a manually-triggered auto-injector that will be available in wider range of doses in 2.5 mg increments. The labeling for Otrexup was the first instance of PLR labeling for a MTX product.

While Medac submitted proposed PLR labeling with this application, it is important to recognize that the Agency had already made a considerable effort to convert the PI for MTX to PLR format. The Agency had created a non-product-specific methotrexate PLR label based on the listed reference products and had provided that label to the previous applicant for use as a template for that application. After Medac submitted this application for Rasuvo, the Agency sent Medac the non-product-specific PLR PI template that the Agency had developed, requesting that Medac insert the Rasuvo product-specific information and re-submit the PI.

Changes to PLR format involve significant reorganization of sections of the labeling and revision of certain aspects of the labeling language. PLR conversion, of necessity, results in some differences between the PLR-formatted label and older labels in non-PLR format, such as those of currently marketed originator and generic methotrexate products. That said, the expectation is that this product would not differ substantially from the current reference products based on such a reorganization. Further, the Agency recognizes that there is no particular advantage for use of two new PLR-labeled products over the currently non-LPR labeled products other than perhaps convenience of the dosing form. Therefore, during the review of Otrexup, the Agency placed considerable effort to convert the labeling for methotrexate reference products to PLR format, creating a draft blank non-product-specific PLR label that the Agency provided to the previous applicant for their application to complete with their product-specific information. This entailed converting the currently marketed originator reference methotrexate product labels to PLR format while minimizing any differences between the labeling for a SC injectable MTX product from those of the reference and generic products, keeping intact all of the Boxed and other Warnings and Precautions, even if they did not specifically apply to the indications for an SC product, which does not contain the Indication for neoplastic diseases. During that process, the Agency took into consideration that the reference labels have some outdated language and incorrect scientific information, electing to retain the language until such time when the reference labels are updated. Because of the Agency's PLR conversion efforts, and since both applications referenced the same listed drugs, the PIs for both Otrexup and Rasuvo will appropriately bear striking similarities as well as retain much of the language that is in the reference labels, except with regard to any information that is product-specific. This is intentional on the Agency's part, as both products reference the same listed drugs and the Agency worked to create PLR conversions of these listed drugs.

In converting the referenced originator products to PLR-format, the Agency intentionally did not make an effort to update the scientific information in the labels because this beyond the scope of what was needed, and it would have required a far-ranging Agency-wide effort. In fact, a PLR labeling initiative is currently underway within the Agency to update the labeling for many older drug products to PLR format and in the process to bring the science and information in the labeling up to today's standards. However, it is unlikely that this initiative will be completed for the methotrexate products prior to the PDUFA date for this application. That said, once the PLR labeling initiative is completed for the reference products, the Agency will request PLR labeling supplements from the originators, followed by supplements from all of the generic and 505(b)(2) products, to update the labeling for their products accordingly. In so doing, all

methotrexate-containing products will receive new PLR labeling over the next several years.

The Agency's reasoning for leaving all of the Boxed and other Warnings and Precautions in the labels for the SC auto-injector products even if they did not specifically apply to the indications sought for these products was that the MTX SC auto-injectors are convenience products that have no particular advantage over the originators other than not needling to draw up MTX and administer with a needle and syringe. However, SC administration is not necessary for most patients with RA, pJIA, and severe psoriasis, since oral administration is the preferred route of administration. Therefore, the Agency did not want to give these products a marketing advantage by deleting any specific wording from the labels.

Because the product is an auto-injector intended only for SC administration and is available only in limited dosage strengths, the Indications and Dosage and Administration sections necessarily differ from the referenced originators, with Limitations of Use added for other routes of administration and for doses that cannot be achieved by the proposed product. For example, the available doses do not allow for use for treatment of neoplastic indications.

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

9.2.2 Patient Package Insert (PPI) and Instructions for Use (IFU)

The issues of making it clear where to give the injections, what to do if the injector is not held in place for at least 5 seconds, and the option for adults with RA who are not able to pinch, will be addressed as part of labeling negotiations.

9.3 Advisory Committee Meeting

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

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/s/

PETER R STARKE
06/02/2014

JANET W MAYNARD
06/02/2014

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 205-776 **Applicant:** medac Pharma **Stamp Date:** 9/10/13

Drug Name: Methotrexate injection (pen injector) **NDA Type:** 505(b)(2)

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

	Yes	No	N/A	Comment
FORMAT/ORGANIZATION/LEGIBILITY				
1. Identify the general format that has been used for this application, e.g. electronic CTD.	eCTD			
2. On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
3. Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4. For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5. Are all documents submitted in English, or are English translations provided when necessary?	X			
6. On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING				
7. Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57, current divisional and Center policies, and the design of the development package?	X			
SUMMARIES				
8. Has the applicant submitted all the required discipline summaries (*i.e*, Module 2 summaries)?	X			There are no clinical trials for this NDA for efficacy and safety. Only a BA study and Human Use Study
9. Has the applicant submitted the integrated summary of safety (ISS)?	X			ISS is in Module 5. Clinical overview is in Module 2.
10. Has the applicant submitted the integrated summary of efficacy (ISE)?	X			ISE is in Module 5. Clinical overview is in Module 2.
11. Has the applicant submitted a benefit-risk analysis for the product?	X			Risk-benefit submitted in the clinical overview
12. Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505(b)(2) referencing Methotrexate Injection (NDA 11-719) and Tablets (NDA 08-085)			
DOSE			X	Dose already

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

				established for the listed drug products
13. If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	No efficacy or safety studies were conducted. The application references approved drug products, with support for efficacy and safety based on the Agency's previous findings and on the literature.
EFFICACY				
14. On its face, do there appear to be the requisite number of adequate and well controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			X	
15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY				
18. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			As per filing review from DPARP.
19. Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (*e.g.*, QT interval studies, if needed?			X	
20. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?			X	No safety studies were performed. The application references approved drug products, with support for efficacy and safety based on the Agency's previous findings and on the literature.
OTHER STUDIES				
21. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	X			See DDDP biopharm filing review.
22. For an Rx-to-OTC switch application, are the necessary special			X	

OTC studies included (*e.g.*, labeling comprehension)?				
PEDIATRIC USE				
23. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The applicant has submitted a request for a waiver for all pediatric age groups because of safety concerns.
ABUSE LIABILITY				
24. If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES				
25. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS				
26. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			Datasets submitted for studies MC-MTX.14/PK and MC-MTX.15/HF
27. Has the applicant submitted datasets in the format agreed to previously by the Division?	X			As per filing review from DPARP.
28. Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	No efficacy studies
29. Are all datasets to support the critical safety analyses available and complete?	X			
30. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?			X	No efficacy studies
CASE REPORT FORMS				
31. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
32. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE				
33. Has the applicant submitted the required Financial Disclosure information for study investigators?	X			Financial certification was provided for study: MC-MTX.15/HF, but not for MTX.14/PK, which was a phase 1 PK study.[2]
GOOD CLINICAL PRACTICE				
34. Is there a statement of Good Clinical Practice; that all clinical	X			

[2] (e)*Covered clinical study* means any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase I tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols, and parallel track protocols. An applicant may consult with FDA as to which clinical studies constitute "covered clinical studies" for purposes of complying with **financial disclosure** requirements.

studies were conducted under the supervision of an IRB and with adequate informed consent procedures?				
CONCLUSION				
35. From a clinical perspective, is this application fileable? If "no", please state why it is not?	X			

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

There are none.

Reviewing Medical Officer

Clinical Team Leader

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

/s/

DENISE COOK
11/15/2013

GORDANA DIGLISIC
11/15/2013

CLINICAL FILING REVIEW / CHECKLIST

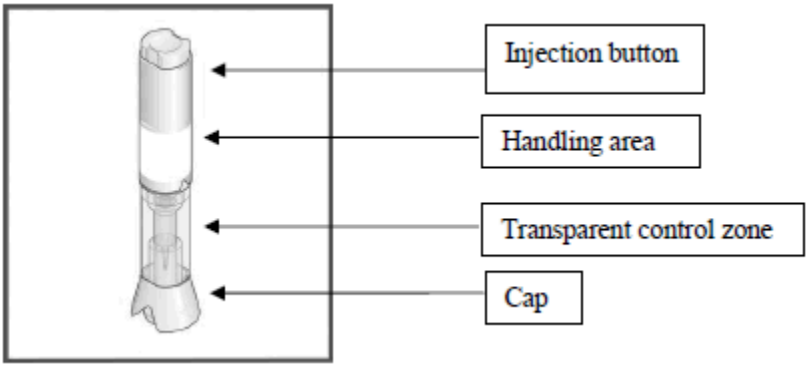
NDA:	**205-776**
Drug Name:	**Methotrexate injection (pen injector)**
Applicant:	**medac Pharma, a subsidiary of medac GmbH**
Type:	**505(b)(2)**
Stamp Date	**September 10, 2013**
PDUFA Date:	**July 10, 2014**
Reviewer:	**Peter Starke, MD**
Team Leader	**Janet Maynard, MD**
Review Date:	**November 5, 2013**

Background

This is a 505(b)(2) new drug application submitted by medac Pharma, for a drug/device combination of Methotrexate (MTX) Injection as a pen injector. The application references Methotrexate Tablets (NDA 08-085) and Methotrexate Injection (NDA 11-719), which are listed in the Orange Book as the reference drugs.

MTX is a folate analog metabolic inhibitor currently indicated for the treatment of various malignancies, severe, recalcitrant, disabling psoriasis, and severe, active rheumatoid arthritis (RA) including polyarticular-course juvenile rheumatoid arthritis (JRA) [now called polyarticular juvenile idiopathic arthritis (pJIA)]. The proposed indications for this product include the RA, JRA, and psoriasis indications, but not the malignancy indication.

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 methotrexate solution at a concentration of 50 mg/mL, (b) (4) The injection is manually triggered by a button at the opposite end from the needle; hence the similarity to a pen-like device. The applicant has requested a proposed Trade Name of (b) (4)™.



The clinical program was discussed over several interactions with the Agency. No clinical trials were performed to support the therapeutic effect, i.e., safety or efficacy, of methotrexate using the proposed drug-device combination. Rather, this was an abbreviated clinical program that primarily relies on the Agency's previous findings of efficacy and safety of the referenced listed

methotrexate products, along with a clinical pharmacology study linking the proposed product to the reference oral product and literature data supporting the SC route of administration as safe and effective route of administration for the proposed indications. The clinical pharmacology study was a single, open-label, randomized, 2-way crossover bioavailability study (MC-MTX.14/PK) that compared the systemic exposure of 7.5, 15, 22.5 and 30 mg of methotrexate dosed orally vs a similar dose administered SC using the to-be-marketed pre-filled pen injector in healthy subjects. The higher systemic exposure with this product administered by the SC route when compared with that of the approved oral product provides support for efficacy of the proposed product, which is supported by the labeled safety with much higher doses as evidenced in the current labeling of the listed products.

The applicant also conducted an actual use study that evaluated two doses of MTX administered via the pre-filled pen injector in RA patients, for which the applicant states that they included evaluations of label comprehension, human factors, usability, device durability, and PK in a subset across a range of body weights (MC-MTX.15/HF). Datasets are submitted for these two studies. The applicant only submitted financial certification/disclosure information for investigators participating in one of these two studies, study MC-MTX.15/HF. The applicant omitted financial certification/disclosure information for study MC-MTX.14/PK, stating that the study was a single-center, Phase 1 PK study, and therefore this information is not required to be submitted.

The application includes a literature review summarizing the efficacy and safety of SC administration because SC administration is not currently in the label of either of the listed products, with the exception that an option for SC dosing is included in the D&A section for pJIA.

Of incidental note, a different single-dose methotrexate product intended for SC administration, Otrexup (NDA 204824) was approved on October 11, 2013, after submission of this application. While Otrexup is now approved for the same route and indications requested by this applicant, the two products differ in that Otrexup is an auto-injector whereas this product is a manually triggered device. Additionally, Otrexup is only available in doses of 10 to 25 mg in 5 mg increments.

The applicant states that they have conducted a number of other patient preference, efficacy and safety, or PK that they consider to be supportive of the application. This includes a 6-month efficacy and safety study that compared methotrexate administered SC with a needle and syringe to oral dosing in RA patients. The study report for this study was submitted without the datasets, which is appropriate since the to-be-marketed device was not evaluated in the study. It will therefore be considered as part of the literature supports for the application. The other studies submitted used either a different formulation and/or device, or were marketing studies that compared the to-be-marketed product with a pre-filled 50 mg/mL MTX syringe that is already approved in Germany and several other EU countries. Additionally, for several studies, only the protocol was submitted, and in all cases no datasets were submitted.

The full listing of study reports [and/or protocols] submitted to the application is shown in Table 1 below, broken down by pivotal studies for which datasets are provided, and non-pivotal studies for which no datasets are provided.

Table 1. Studies Submitted to the Application

Study	Type	Design	Products	Doses (mg)	N	Comments
Studies With Data (datasets submitted)						
MC-MTX.14/PK	BA	R, single-center, OL, 2-way, SD crossover in healthy adults	MTX Tabs [Dava] orally MTX pre-filled pen SC in abdominal wall	4 dosing levels: 7.5 mg 15 mg 22.5 mg 30 mg	65 (62): 16 19 16 14	
MC-MTX.15/HF	Human Factors (HF) and Actual Use (AU)	8-10 day, OL, single-arm 2-dose study in patients ≥16y with RA. Included, label comp exam, device robustness, "human factors" observation at day 8-10, and PK in a subset of patients ≥21y.	MTX pre-filled pen SC in abd or upper thigh weekly 2x	15 mg	106 (104) PK: 24	
Other Studies (studies without datasets)						
MC-MTX.10/RH	Patient preference and local tolerability	OL, single-arm MD crossover study in patients with RA, 18-75y	MTX pre-filled syringe, 10 mg/mL MTX pre-filled syringe, 50 mg/mL	20 mg x3 (injections 1-3) 20 mg x3 (injections 4-6)	132 (131)	Marketing study
MC-MTX.13/PK	BE	R, single-center, OL, 2-way, SD crossover in healthy males	MTX pre-filled pen MTX pre-filled syringe	15 mg SC	14 (14)	Marketing study
MC-MTX.9/PH	BA	R, single-center, OL, 2-group, 2-treatment, SD crossover in healthy males	Group 1: MTX pre-filled syringe 50 mg/mL MTX pre-filled syringe 10 mg/mL Group 2: MTX pre-filled syringe 50 mg/mL MTX pre-filled syringe 10 mg/mL	Group 1 (n=12): 15 mg SC 15 mg SC Group 2 (n=12): 15 mg IM 15 mg IM	25 (24)	Used a different device and formulation
MC-MTX.12/PK	BA	OL, 2-way, SD crossover in healthy adults	MTX pre-filled pen SC MTX inj [Hospira] IM		--	Protocol only
MC-MTX.11/RA	Patient preference and local tolerability	OL, 2-way, SD crossover in healthy adults	MTX pre-filled pen MTX pre-filled syringe		--	Protocol only
MC-MTX.6/RH	Efficacy and Safety	6-month, R, DB, DD, MC, AC in adults (18-75y) with RA	MTX pre-filled syringe 10 mg/mL Oral MTX	15 mg SC 15 mg orally	381 (375)	Used a different device and formulation. No datasets
AU = Actual use; HF = Human factors; BA = Bioavailability, BE = Bioequivalence; S&E = Safety and efficacy						

This new drug-device combination will trigger PREA because of the new SC route of administration and also the new dosing regimen. For RA/pJIA, the applicant has requested a

waiver in children less than 2 years of age because the necessary studies are impossible or highly impractical, i.e., because the product would not likely to be used in a substantial number of patients in this age group. For severe, disabling psoriasis, the applicant has submitted an Initial Pediatric Study Plan requesting a waiver of pediatric studies in all ages due to safety reasons. Both of these requests are appropriate and match what was done for Otrexup. The waiver requests will be discussed with the Pediatric Review Committee (PeRC) during the review.

The application is all-electronic in eCTD format. The application is complete and fileable from a clinical perspective.

Table 2. Clinical Filing Checklist

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic in eCTD format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			ISS is in Module 5. Clinical overview is in Module 2.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			ISE is in Module 5. Clinical overview is in Module 2.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Risk-benefit submitted in the clinical overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2) referencing Methotrexate Injection (NDA 11-719) and Tablets (NDA 08-085)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	Dose already established for the listed drug products
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			X	No efficacy or safety studies were conducted. The application references approved drug products, with support for efficacy and safety based on the Agency's previous findings and on

	Content Parameter	Yes	No	NA	Comment
					the literature.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	No safety studies were performed. The application references approved drug products, with support for efficacy and safety based on the Agency's previous findings and on the literature.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA 8.1
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

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

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

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			RA/pJIA: The applicant has submitted a request for a waiver for patients less than 2 years of age because the product is not likely to be used in a substantial number of patients in this age group. Psoriasis: The applicant has submitted a request for a waiver for all pediatric age groups because of safety concerns.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			Datasets submitted for studies MC-MTX.14/PK and MC-MTX.15/HF (see Table 1)
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	No efficacy studies
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	No efficacy studies
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			Financial certification was provided for study:

	Content Parameter	Yes	No	NA	Comment
					MC-MTX.15/HF, but not for study MC-MTX.14/PK, which was a Phase 1 PK study.[3] Financial certification was not provided for the non-pivotal studies.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

Filing Recommendations

The application is fileable from a clinical perspective. I recommend a standard review timeline for this application.

Potential Review Issues and Clinical 74-Day Comments

None

[3] (e)*Covered clinical study* means any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase l tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols, and parallel track protocols. An applicant may consult with FDA as to which clinical studies constitute "covered clinical studies" for purposes of complying with **financial disclosure** requirements.

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/s/

PETER R STARKE
11/05/2013

JANET W MAYNARD
11/06/2013