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RESEARCH**

APPLICATION NUMBER:

205776Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sarah Yim, M.D. Supervisory Associate Director Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Subject	Division Summary Review
NDA/BLA #; Supplement #	NDA 205776 original
Applicant Name	Medac Pharma, Inc.
Date of Submission	September 10, 2013
PDUFA Goal Date	July 10, 2014
Proprietary Name / Established (USAN) Name	Rasuvo / methotrexate injection
Dosage Forms / Strength	Single-use prefilled autoinjectors (50 mg/mL) in the following strengths: 7.5mg/0.15mL, 10mg/0.20mL, 12.5mg/0.25mL, 15mg/0.30mL, 17.5mg/0.35mL, 20mg/0.40mL, 22.5mg/0.45mL, 25mg/0.50mL, 27.5mg/0.55mL, 30mg/0.6mL
Proposed Indication(s)	1. Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis 2. Severe Psoriasis
Action:	<i>Approval</i>

Material Reviewed/Consulted	
OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	DPARP: Peter Starke, MD; DDDP: Denise Cook MD
Pharmacology Toxicology Review	Jane Sohn, Ph.D.; Timothy Robison, Ph.D.
CMC Review	Arthur Shaw, Ph.D.; Craig Bertha, Ph.D.
CMC Microbiology Review	Robert Mello, Ph.D.
CDRH Human Factors (HF) Review	Quynh Nguyen; Ron Kaye
CDRH Device Review	Keith Marin
Clinical Pharmacology Review	DPARP: Sheetal Agarwal, Ph.D.; Satjit Brar, PharmD, Ph.D.; DDDP: Doanh Tran R.Ph., Ph.D.
DMEPA Labeling and HF Review	Teresa McMillan, PharmD; Lubna Merchant, PharmD, MS
DMPP/OPDP Patient Labeling Rev.	Sharon Williams BSN, RN; Roberta Szydlo RPh, MBA
OPDP Labeling Review	Roberta Szydlo; Puja Shah
OSI Review	Michael Skelly, Ph.D.
CDTL Review	Janet Maynard, MD, MHS

OND=Office of New Drugs

DDDP=Division of Dermatology and Dental Products

CDRH=Center for Devices and Radiological Health

DMPP=Division of Medical Policy Programs

OSI=Office of Scientific Investigation

DPARP=Division of Pulmonary, Allergy, and Rheumatology Products

CMC= Chemistry, Manufacturing, and Controls

DMEPA=Division of Medication Error Prevention and Analysis

OPDP=Office of Prescription Drug Promotion

CDTL=Cross-Discipline Team Leader

1. Introduction

This is a 505(b)(2) new drug application (NDA) submitted by Medac Pharma, Inc. for a drug/device combination product (tradename: Rasuvo) consisting of an injectable methotrexate (MTX) formulation in single-use, single-dose prefilled manually-triggered pen autoinjectors intended for subcutaneous administration only. Ten strengths are proposed: 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg, and 30 mg. Each strength utilizes the same MTX solution concentration (50 mg/mL) and the specified dose is achieved by varying the fill volume in the device.

Methotrexate tablets have been marketed since December of 1953 (NDA 08085, Dava Pharmaceuticals Inc.) when the product was approved for the treatment of acute leukemia in adults. In addition to tablets, MTX is approved as an injection (NDA 11719; approved 1959; Hospira) for intramuscular (IM), intravenous (IV), subcutaneous (SC), intra-arterial (IA), and intra-thecal (IT) administration. Methotrexate is currently available in 2.5 mg tablets (multiple companies), and 5, 7.5, 10, and 15 mg tablets (Barr). Injectable MTX is available from multiple companies in varying quantities of 25 mg/mL solution. At the time of submission of this NDA, approved indications and routes of administration for MTX included neoplastic diseases (oral, IM, IV, IA, and IT routes), rheumatoid arthritis (oral route), polyarticular course juvenile rheumatoid arthritis¹ (oral, IM, SC routes), and severe psoriasis (oral, IM, IV routes).

Subsequent to the submission of this NDA, on October 14, 2013, a different methotrexate autoinjector product (NDA 204824, Antares Pharma, Inc.) was approved for subcutaneous administration for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis (PJIA)¹, and severe psoriasis. The Antares MTX autoinjector (tradename: Otrexup) differs from the Medac Pharma product in that it uses a fixed volume of differing concentrations to comprise its four available doses—10 mg/0.4 ml, 15 mg/0.4 ml, 20 mg/0.4 ml and 25 mg/0.4 ml. The Antares autoinjector device is also different and activates by pressure against the skin.

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

- The Agency's previous findings of safety and effectiveness of MTX in adults with RA (oral route) and psoriasis (oral, IM, and IV routes), and in children with JRA¹ (oral, SC, and IM routes)
- Information in the published literature supporting the safety and efficacy of subcutaneously administered MTX for RA, PJIA, and psoriasis

¹ "Polyarticular-course juvenile rheumatoid arthritis" is outdated terminology. Recent approvals use the term "Juvenile Idiopathic Arthritis" (JIA), along with a descriptor, such as polyarticular JIA (PJIA) or systemic JIA (SJIA).

- A relative bioavailability (BA) study (MC-MTX.14/PK) in healthy adults that showed equal or greater bioavailability of MTX SC administered via the Applicant's autoinjector compared to the exposure obtained with orally administered MTX tablets.

The primary data to support the approval of subcutaneous MTX for the RA indication are from the BA study comparing the proposed SC MTX product to oral MTX (MC-MTX.14/PK), because at the time of submission of this NDA, only oral dosing for RA was noted in the approved MTX labels for both oral and parenteral MTX products. The Applicant also performed a bioequivalence (BE) study (MC-MTX.12/PK) comparing the proposed product administered SC to the reference parenteral drug Hospira administered IM, from which results became available during the review cycle. However, because all three indications sought by the Applicant (RA, JIA, and Psoriasis) were approved for the oral route of administration, and MTX is titrated to desired effect within an approved dose range, a study demonstrating bioequivalence of the SC route of administration to the IM route of administration was not considered essential to support approval, as a relative bioavailability approach, similar to that used for RA, could be used to support the psoriasis and JIA indications as well.

2. Background

Methotrexate history

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

Although aminopterin was investigated as a treatment for RA as early as 1951, and MTX as early as 1962, use of MTX for RA languished until the 1970's and 1980's. The reason for this disinterest is not known, but is postulated by some to be due to a greater enthusiasm for corticosteroids during that time frame. Throughout the 1980's interest in MTX blossomed, prompting an increasing number of clinical studies and controlled trials of MTX, and culminating in the FDA approval of MTX for RA in 1988². Although the pivotal trials for the approval of MTX evaluated oral MTX, the gastrointestinal tolerability issues, relatively poor oral absorption of MTX at higher doses, and ready availability of parenteral MTX quickly led practitioners to use parenteral MTX as an alternative for patients who were not tolerating oral MTX³.

Presubmission regulatory history

The Agency had multiple pre-submission interactions with Medac between 2010 and 2013:

² Cury FF and Weinblatt ME, Clin Exp Rheumatol 2010;28(Suppl 61):S9-S12.

³ Visser et al, Ann Rheum Dis 2009 Jul;68(7)1086-93.

- At the pre-IND meeting with DPARP (IND 109543) on October 14, 2010, the Applicant proposed a 505(b)(2) application using MTX solution as the reference listed drug. It was noted that, at the time, the approved MTX labels only contained information on parenteral routes of administration for psoriasis, PJIA, and oncology indications. The parenteral MTX labels referenced the oral dosing information for RA, but did not include efficacy, safety, or dosing information for a parenteral route of administration for RA. Thus, DPARP suggested that the Applicant consider the psoriasis indication as the parenteral route of administration was already approved for this indication. The Applicant was told that data would be needed to support SC dosing for an RA indication, although the data might be available in published literature.
- The Applicant submitted additional pre-IND questions to DPARP on October 31, 2011 and written responses were sent on December 27, 2011. At that time, the Applicant proposed a meta-analysis of all data regarding MTX in RA, an efficacy study evaluating the safety and efficacy of MTX administered SC, and a PK study of MTX administered SC with the proposed autoinjector compared to oral administration of the listed drug. DPARP noted that an efficacy study might not be necessary as evidence to support their planned 505(b)(2) application could come from published literature. The Applicant was told that to support approval of a MTX autoinjector for the indication of RA, the Applicant would need a bioavailability study comparing the proposed SC route of administration to the approved oral route of administration and an actual use study in RA patients where patients would employ the proposed autoinjector to self-administer MTX.
- At the pre-IND meeting with DDDP (IND 113735) on February 27, 2012, the division recommended a relative BA study comparing SC with IM MTX administered at the highest recommended dose of 30mg in psoriasis patients. However, at a joint pre-NDA meeting on June 17, 2013 with DDDP and DPARP, the Applicant was advised that it would be reasonable to perform a relative bioavailability study comparing oral MTX to SC MTX for all of the proposed indications.

3. CMC/Device

Drug substance

Methotrexate is a yellow to orange, crystalline powder, insoluble in water. The CMC information for MTX is covered in DMF (b) (4) which has been found acceptable.

Drug product

The drug product is formulated by (b) (4). No preservatives are added, since the drug product is intended for single use in a custom injector. The drug product solution is (b) (4) into glass syringes and closed with a plunger with a rubber stopper. Evaluation of leachables and sterility aspects have been reviewed and found to be acceptable.

The drug is formulated at one strength (50 mg/mL) to be delivered at 10 different volumes to achieve different strengths to be delivered to the patients (7.5 mg/0.15 mL, 10 mg/0.20 mL, 12.5 mg/0.25 mL, 15 mg/0.30 mL, 17.5 mg/0.35 mL, 20 mg/0.40 mL, 22.5 mg/0.45 mL, 25 mg/0.50 mL, 27.5 mg/0.55 mL, and 30 mg/0.60 mL). The drug product specifications are adequate to support release of the drug. An unidentified impurity at RRT=(b)(4) min increases steadily at (b)(4) reported in the application. The Agency's statistical analysis shows that the upper 95% confidence limit for this impurity exceeds the acceptance criteria of (b)(4) at 17 months. This will be the recommended expiration date.

The primary container closure for drug product is the (b)(4) 1mL long syringe made of Type I (b)(4) glass barrel, embedded with 27 gauge, ½ inch stainless steel needle, needle shield and (b)(4) rubber plunger stopper.

Device

The pre-filled syringes (PFS) are loaded manually into a custom device, covered by a device master file (MAF (b)(4)). The syringe inside the device is the to-be-marketed product, a drug-device combination. The device is designed to deliver a fixed volume with no measuring by the patient. The needle is completely covered when not in use both before and after activation of the device so that the chances of accidental injection or exposure to the needle are minimized. When the device is activated the force of delivery is controlled by a spring in the device, not the patient. The average injection delivery time for the 30 mg dosage strength is approximately 2.5 seconds. The needle is the correct length (exposed needle length 8mm±2mm) to ensure that the drug is administered subcutaneously. After the device is actuated there is no drug remaining in the syringe so that safe disposal is not an issue. The device performance was found acceptable by the CDRH Device reviewer.

An actual use study (Study MC-MTX.15/HF) was performed to evaluate the ability of patients to follow the instructions for use and use the device. This study is described in further detail in Section 8 below.

Facilities review/inspection status

The drug substance is manufactured at (b)(4) which has a satisfactory cGMP status as of 09/30/2013.

Microbiology testing and residual solvent testing is performed by (b)(4) which has acceptable status as of 11/22/2013.

Visual inspection of pre-filled syringes, testing of primary packaging materials, testing of excipients except physico-chemical testing of water for injection, and assembly, labeling, packing, storing, and release testing is performed at (b)(4) which has acceptable status as of July 8, 2014.

Manufacture of the 50mg/mL solution pre-filled syringes, (b) (4)
is performed at Oncotec Pharma
Produktion GmbH, Am Pharmapark 06861, Dessau-Roßlau, Germany, which was inspected
April 10-17, 2014, and was found to be acceptable (status date July 3, 2014).

Conclusions

I concur with the conclusions reached by the chemistry and device reviewers regarding the acceptability of the drug product and drug substance, as well as the device. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

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

5. Clinical Pharmacology/Biopharmaceutics

This NDA references two previously approved MTX products: NDA 11719 (Hospira's MTX injection, the reference listed drug for parenteral MTX products) and NDA 8085 (Dava's oral MTX tablets, the reference listed drug for oral MTX products).

Study MC-MTX.14/PK evaluated the PK of Medac's MTX autoinjector (trade name Rasuvo) compared to MTX oral tablets. The intent of this study was to allow for bridging to approved RA and psoriasis doses and inform SC dosing. Results indicated that MTX exposure ($AUC_{(0-\infty)}$) was higher with the Rasuvo MTX autoinjector compared to oral MTX at all dose levels tested (7.5, 15, 22.5, and 30mg). However, the quantitative difference in systemic exposure was not the same across the doses, and ranged between 33% higher (at the 7.5mg dose) to 66% higher (at the 30mg dose). This is consistent with the known properties of orally administered MTX; oral bioavailability decreases at high doses, likely due to a saturable intestinal active transport absorption mechanism with low capacity characteristics.⁴ The differences in bioavailability of MTX via Rasuvo autoinjector compared to oral MTX tablets will be included in the label. Overall, these results are consistent with the oral/SC relative bioavailability of MTX reported in the literature.^{5,6}

Study MC-MTX.15/HF was an actual-use study in RA patients that incorporated a small (n = 24 out of a total of 104 study patients) PK sub-study which evaluated the effect of body weight (60-100kg vs. less than 60kg and higher than 100kg) and the effect of injection site (abdomen vs. upper thigh) on systemic exposure of MTX when administered SC by the Rasuvo autoinjector. The PK data showed decreased exposure (~16% less in AUC and ~33% less in

⁴ Abolmaili et al., Cancer Chemother Pharmacol, 2013, 71:1115-1130.

⁵ Jundt JW et al., J Rheumatol 1993 Nov; 20(11):1845-9.

⁶ Hoekstra M et al., J Rheumatol 2004 Apr; 31(4):645-8.

C_{max}) in subjects weighing more than 100kg. There was also a suggestion of higher absorption of MTX through the abdomen in subjects weighing less than 100kg, but higher absorption of MTX through the thigh in subjects weighing more than 100kg; however the number of subjects in each of these categories was too small to draw definitive conclusions. Since MTX is generally titrated to a therapeutic dose, and the magnitude of the apparent differences was not large, the possible differences in absorption across subjects of different weights or through different injection sites was not considered clinically important and will not be included in the labeling.

Study MC-MTX.12/PK evaluated the PK of Medac's MTX autoinjector SC compared to MTX injection administered by needle and syringe IM in 34 adult psoriasis patients. This study was not required for submission or filing of this NDA, as a relative bioavailability approach to MTX oral tablets was considered adequate as the primary basis of approval of the subcutaneous route of administration of MTX for RA and psoriasis. However, results of this study became available during this NDA review and showed that the exposure of MTX (AUC values) when administered IM was comparable to Medac's MTX autoinjector when administered SC at the same dose. (b) (4)

Clinical (PK) study inspection

The Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and analytical portions of study MC-MTX.14/PK, which were determined to be acceptable.

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

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

As discussed in Section 5, compared to oral methotrexate tablets, the exposure (AUC) of methotrexate given subcutaneously via the Medac methotrexate autoinjector was approximately 33 to 66% higher, depending on the dose. Therefore, the efficacy of SC methotrexate could be presumed based on exposures that are equal or greater than exposures via the approved oral route of administration.

In addition to this pharmacokinetic (PK) bridge, the Applicant summarized the clinical efficacy and safety data on SC MTX from the literature, as requested by the Agency. The Applicant also provided the full study report for the published randomized, controlled trial by Braun et. al, 2008, which showed a similar/somewhat higher proportion of patients experiencing American College of Rheumatology (ACR) 20%/50%/70% levels of response

with SC administration of MTX compared to the same dose of MTX given orally. The Applicant submitted many articles describing the efficacy of methotrexate in different groups of RA patients. These articles suggest the efficacy of methotrexate is similar, irrespective of the route of administration.

Supportive data in severe, disabling psoriasis

The Applicant also summarized the literature supporting subcutaneous methotrexate administration in severe, disabling psoriasis. There are no well-controlled trials evaluating SC MTX in psoriasis. The primary support was from two articles that described case series of psoriasis patients treated with methotrexate administered orally or SC.^{7,8} As described in these publications, the efficacy of SC MTX appeared to be roughly similar to oral MTX.

Supportive data in JIA

The Applicant also summarized the literature supporting subcutaneous methotrexate administration in children with juvenile idiopathic arthritis (JIA). However, as the approved methotrexate labels already note subcutaneous administration as an available route of administration for JIA, evidence to support the efficacy of this route of administration in JIA is not necessary.

Efficacy conclusions

Given that the SC route of administration results in 33 to 66% higher exposure compared to orally administered methotrexate, the efficacy of SC methotrexate may reasonably be extrapolated from the evidence supporting the efficacy of orally administered methotrexate for RA, JIA and severe, disabling psoriasis. This conclusion is supported by the published literature pertaining to SC methotrexate in these indications. The DPARP and DDDP clinical review teams are in agreement that the evidence to support the efficacy of the SC route of administration is adequate.

8. Safety

The experience with methotrexate over all the approved indications covers a much wider range of doses than those associated with RA, JIA, or psoriasis, which does not typically exceed 30 mg/week.^{9,10} The toxicity of MTX across its therapeutic range is well known, with the most common toxicities being gastrointestinal (worse with oral administration), and less common but serious toxicities including myelosuppression, pneumonitis, nephrotoxicity and possible long-term hepatotoxicity (primarily liver enzyme elevations). Doses of MTX used to treat neoplastic diseases are up to an order of magnitude higher (i.e. 20 to 30 grams for the treatment of osteosarcoma) than for RA or psoriasis, and approach the maximum tolerated

⁷ Inzinger M, et al 2013. JEADV 27, 861-866.

⁸ Yesudian et al, 2012. British J Derm 2012;167(Suppl. 1), 21-69.

⁹ Visser, et al. Ann Rheum Dis 2009; 68:1086-1093.

¹⁰ Kuijpers ALA, van de Kerhof. Am J Clin Dermatol 2000;1:27-39.

dose. Subcutaneous administration of methotrexate for RA, JIA, and psoriasis involves doses at the low end of the methotrexate therapeutic range, and a 33-66% higher exposure with the Rasuvo methotrexate autoinjector (study MC-MTX.14/PK) would not be expected to result in significant additional toxicities.

The safety experience specific to the Rasuvo methotrexate autoinjector product is limited to three single or 2-dose studies in 206 subjects—Study MC-MTX.14/PK (single-dose relative BA study in 65 healthy volunteers), Study MC-MTX.15/HF (2-dose actual use/PK study in 106 RA patients), and Study MC-MTX.12/PK (single-dose relative BA study in 35 psoriasis patients). Based on these limited data, no new safety signals were identified, but alone, these data would not be considered adequate evidence of safety for a new route of administration for a chronically administered drug. Nevertheless, there is adequate safety information to support the safety of subcutaneously administered MTX, because of the modest increase in exposure associated with the SC route of administration observed in relative bioavailability studies, in the context of the dosing of methotrexate in the proposed indications, which is in the lower end of the therapeutic range.

Regarding the safety of the device itself, one use and handling study was performed to evaluate the ability of patients to follow the instruction set and use the device (MC-MTX.15/HF). This study is intended to support the conclusion that the device can be used safely if approved, but is not informative to prescribers and will not be described in labeling. In this study, all devices appeared to have functioned appropriately. A total of 210 injections were documented over the course of the study. Upon inspection, all pens (210/210) were found to be intact after use. 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. Six injections were not adequately completed due to human factors (nervousness and lifting the injector out too early). No significant safety concerns were observed.

While incomplete injections occurred in the study due to human factors, this is not overly concerning, as the context of use is chronic administration, where increasing familiarity with the device and injection process should mitigate these types of errors. Additionally, because methotrexate is not an emergency medication, and is not a narrow therapeutic index product, lack of, or partial, administration would not be expected to result in clinically significant concerns. Reviewers from the Division of Medication Error Prevention and Analysis (DMEPA), CDRH, DDDP and DPARP were in agreement that the study appeared to support the adequacy of the device, and I concur.

9. Advisory Committee Meeting

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

10. Pediatrics

The application triggers the Pediatric Research Equity Act (PREA, 21 U.S.C. 355c) for the indications of RA and severe psoriasis, for which this is a new route of administration. Approvals in RA have triggered pediatric study requirements in PJIA under PREA. The Applicant has asked for a waiver for children ≤ 2 years because the necessary studies are impossible or highly impractical as the number of patients with JIA is not substantial. This is acceptable and consistent with what the Division has done for other applications with these indications. For children greater than 2 years of age, the PREA requirements are satisfied by the Agency's previous findings of safety and effectiveness of methotrexate for JIA.

With regard to the psoriasis indications, the Applicant has asked for a waiver in children 0 to 17 years because of safety concerns with the use of MTX for psoriasis in this population. 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 applications.

Both Divisions discussed their recommendations with the Pediatric Review Committee (PeRC) on April 2, 2014, and PeRC concurred with the recommendations stated above.

11. Other Relevant Regulatory Issues

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

(b) (4)



12. Labeling

- *Proprietary name*

The proposed proprietary name Rasuvo was determined to be acceptable.

- *Physician labeling*

The Rasuvo autoinjector is essentially a parenteral MTX formulation, like the currently approved parenteral MTX formulations (e.g., listed drug NDA 11719, Hospira), only packaged for subcutaneous injection. The parenteral MTX formulations are also labeled for subcutaneous use (albeit only directly mentioned for the polyarticular course juvenile idiopathic arthritis indication). The labeling for the Rasuvo autoinjector is the second instance of Prescribing Information (PI) in Physicians Labeling Rule (PLR) format for a MTX product. A different methotrexate autoinjector, Otrexup (NDA 204824) was approved on October 11, 2013, approximately one month after submission of this application. (b) (4)

However, unless a given toxicity was clearly only applicable to the neoplastic disease setting, safety information remained in the label, even if likely derived from cancer studies. Product-specific data was included in Section 12.3 Pharmacokinetics and in Section 2 Dosage and Administration.

This same approach is applicable for the Rasuvo autoinjector. Since Otrexup and Rasuvo referenced the same listed drugs, the PIs for both labels will be similar and retain much of the language that is in the reference labels, except with regard to any information that is product-specific, i.e. in Section 12.3 Pharmacokinetics and in Section 2 Dosage and Administration.

- *Carton and immediate container labels*

No outstanding or unresolved issues.

- *Patient labeling/Medication guide*

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

13. Decision/Action/Risk Benefit Assessment

- ***Regulatory Action***

The action on this NDA will be approval.

- ***Risk Benefit Assessment***

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

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

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

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

No postmarketing requirements or commitments are warranted.

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/s/

SARAH K YIM
07/10/2014