

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205776Orig1s000

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA CHEMISTRY CONSULT

Application number: 205776
Supporting document/s: SD-1 (EDR)
Applicant's letter date: 9/10/13
CDER stamp date: 9/10/13
Product: Rasuvo (Methotrexate 50 mg/mL Pre-filled Pen,
injection)
Indication: Rheumatoid Arthritis, Juvenile Idiopathic
Arthritis, Psoriasis
Applicant: Medac Pharma, Inc
Review Division: Division of Pulmonary, Allergy, and
Rheumatology Products
Reviewer: Jane J. Sohn, PhD
Supervisor/Team Leader: Timothy Robison, PhD, DABT
Division Director: Badrul Chowdhury, MD, PhD
Project Manager: Sadaf Nabavian

Template Version: September 1, 2010

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Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205776 are owned by Medac Pharma, Inc. or are data for which Medac Pharma, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 205776 that Medac Pharma, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 205776.

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1 Executive Summary

1.1 Introduction

The sponsor Medac Pharma, Inc. (Medac) proposes a Methotrexate 50 mg/mL Pre-filled Pen (injection) for the treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), and psoriasis by the subcutaneous (SC) route. The sponsor submitted an assessment of leachables and extractables, which includes evaluation of

(b) (4)

A chemistry consult was requested via email on May 22, 2014 to evaluate the safety of the proposed exposures to five identified leachables. The formal consult request was entered on May 30, 2014, and is attached to this review. The internal deadline for primary reviews is June 5, 2014.

1.2 Brief Discussion of Nonclinical Findings

The sponsor submitted a study measuring the levels of five leachables from methotrexate in the proposed pre-filled pen. The review addresses the expected patient exposure levels for the following potential leachables:

(b) (4)

Based on the maximum expected patient exposure levels, and review of the available safety information for each of the potential leachables, Rasuvo is considered qualified from the nonclinical perspective.

2 Drug Information

2.1 Drug

CAS Registry Number: 59-05-2

Generic Name: methotrexate injection

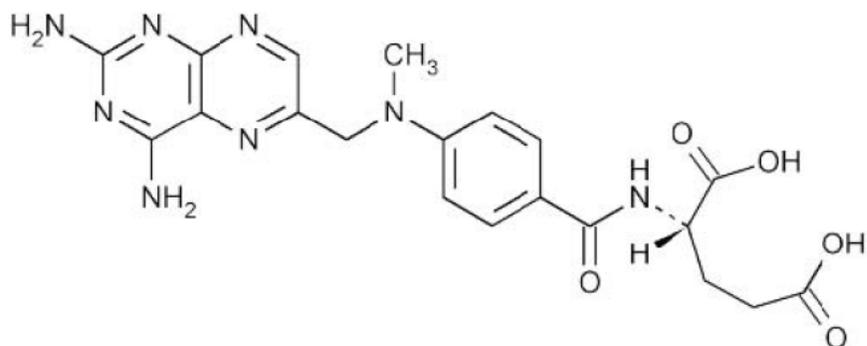
Proposed Trade Name: Rasuvo

Code Name: MTX, Metoject Pre-Filled Pen, (b) (4)

Chemical Name: L-Glutamic acid, N-[4[[[(2,4-diamino-6-pteridiny)] methyl]methyl-amino]benzoyl]-

Molecular Formula/Molecular Weight: C₂₀H₂₂N₈O₅, 454.44 g/mol

Structure or Biochemical Description:



Pharmacologic Class: Folate analog metabolic inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 109543, Division of Pulmonary, Allergy and Rheumatology Products (DPARP), treatment of rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA)
- IND 113735, Division of Dermatology and Dental Products (DDDP), treatment of psoriasis.



2.3 Drug Formulation

The drug product is a drug/device combination. The solution for injection contains the drug substance methotrexate (b) (4) in a sterile aqueous solution:

Table 1: Formulation

Ingredient	mg/mL	Function
Methotrexate	50	active
Sodium chloride	(b) (4)	(b) (4)
Sodium hydroxide	(b) (4)	pH adjusting agent
Hydrochloric acid (b) (4)	(b) (4)	pH adjusting agent
Water	(b) (4)	(b) (4)

The product includes ten different fill volumes, each having an identical composition of 50 mg/mL methotrexate. The different fill volumes allow for administration of methotrexate according to the proposed labeling for gradual dose increases:

- 0.15 ml pre-filled pen containing 7.5 mg methotrexate
- 0.20 ml pre-filled pen containing 10 mg methotrexate
- 0.25 ml pre-filled pen containing 12.5 mg methotrexate
- 0.30 ml pre-filled pen containing 15 mg methotrexate
- 0.35 ml pre-filled pen containing 17.5 mg methotrexate
- 0.40 ml pre-filled pen containing 20 mg methotrexate
- 0.45 ml pre-filled pen containing 22.5 mg methotrexate
- 0.50 ml pre-filled pen containing 25 mg methotrexate
- 0.55 ml pre-filled pen containing 27.5 mg methotrexate
- 0.60 ml pre-filled pen containing 30 mg methotrexate

2.4 Comments on Novel Excipients

There are no novel excipients.

2.5 Comments on Impurities/Degradants of Concern

This consult review evaluates the safety of leachables and extractables in Rasuvo. The sponsor's methods and results are outlined in the study report titled "Toxicological assessment for five leachables from Methotrexate prefilled syringes", listed under Studies Reviewed. The nonclinical safety evaluation of the study is included under the Integrated Summary and Safety Evaluation.

2.6 Proposed Clinical Population and Dosing Regimen

Rheumatoid Arthritis

Rasuvo is indicated for the management of patients with severe, active rheumatoid arthritis (RA), who are intolerant of or had an inadequate response to first-line therapy.

The recommended starting dose of Rasuvo is 7.5 mg given subcutaneously once weekly. (b) (4)

Juvenile Idiopathic Arthritis

Rasuvo is indicated for the management of patients with polyarticular juvenile idiopathic arthritis (pJIA), who are intolerant of or had an inadequate response to first-line therapy.

The recommended dose of Rasuvo is 10 mg/m² given subcutaneously once weekly. Use another formulation of methotrexate in patients requiring doses less than 10 mg per week. (b) (4)

Psoriasis

Rasuvo is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation. It is important to ensure that a psoriasis “flare” is not due to an undiagnosed concomitant disease affecting immune responses.

The recommended starting dose of Rasuvo is 10 to 25 mg given subcutaneously once weekly. (b) (4)

3 Studies Submitted

3.1 Studies Reviewed

Toxicological assessment for five leachables from Methotrexate prefilled syringes (authored by (b) (4))

4 Integrated Summary and Safety Evaluation

The safety of the leachables and extractables in Rasuvo is based upon data submitted by Medac, and safety limits based on the threshold of toxicological concern, as outlined below. The highest dose for which Medac is seeking approval is 30 mg, given subcutaneously once weekly. The dose of 30 mg represents 0.6 mL of the drug product contained in the pre-filled syringe.

The sponsor submitted a toxicological evaluation for (b) (4) which are the five leachables assessed in this review. Leachables were measured by (b) (4) on behalf of the sponsor, from samples of methotrexate 50 mg/mL solution, contained in prefilled syringes. Three batches of the lowest and highest proposed doses of methotrexate (7.5 mg and 30 mg) were analyzed in duplicate. Study batches were stored for 6 months at 40°C/75%RH. The mean and range concentrations of the five leachables are shown in Table 2, highlighting the highest value measured. The sponsor used the highest concentration measured for their evaluation, and the same value is used for safety assessment in this review.

Table 2: Mean and range concentrations of leachables

Leach-able	Strength 7.5 mg			Strength 30 mg			Highest value* (µg/ml)
	Report	Report	Report	Report	Report	Report	
	B300220 /1	B300221 /1	B300222 /1	B300217 /1	B300218 /1	B300219 /1	
	Mean µg/mL (range)						

(b) (4)

*The right column indicates the highest single concentration reported in one of the analyses performed.

(Sponsor's table)

Based on the highest concentration measured for each leachable, and the maximum recommended human dose (MRHD) of 30 mg (0.6 mL), the maximum expected exposures were determined as follows:

Table 3: Maximum expected exposure for each leachable

Leachable	Maximum expected exposure (mcg)
(b) (4)	

For the purpose of this review, the exposure for each leachable will be analyzed based on total daily intake (TDI), without an adjustment for the proposed weekly administration. Additional safety margins are included by using this conservative

approach. A threshold of toxicological concern (TTC) was applied to all compounds, with a TTC of 1.5 mcg/day. A qualification threshold of 5 mcg/day was applied for compounds negative for genotoxic potential. Additional data are referenced to support the safety of the proposed exposures, as necessary.

The level of (b) (4) would result in an exposure above the TTC of 1.5 mcg/day, therefore the safety of the proposed daily exposure is evaluated below.

The level of (b) (4) would result in an exposure that is close to, but below the TTC. Despite the proposed level being lower than the TCC, the safety of (b) (4) is evaluated below.

The levels of (b) (4) were at or below (b) (4) which would not result in an exposure greater than the TTC. Based on exposure below the TTC, the levels of (b) (4) are judged to be reasonably safe and considered qualified. Additional information is provided below.

(b) (4)
The safety of (b) (4) was analyzed based on a TDI of (b) (4). The safety assessment was based on a study conducted by (b) (4) which is available in summary on TOXNET¹. The chronic toxicity and carcinogenicity of (b) (4) was evaluated in Fischer 344 rats. The NOEL for systemic toxicity of (b) (4) administered for 12 months was 1000 mg/kg/day. The NOEL for carcinogenicity of (b) (4) administered for 24 months was 1000 mg/kg/day.

In a 24-month carcinogenicity study, Fischer 344 rats were dosed with 0, 100, 300 and 1000 mg/kg/day of (b) (4) 10 cst fluid mixed into the feed. Animals were treated for 24 months (60 rates/sex/group), for 12 months followed by a 12 month recovery period (20 rats/sex/group), and for 12 months (10 rats/sex/group). There were no findings of systemic toxicity based on survival, body weight, food consumption, and clinical pathology parameters. Irritation was noted in the eye in all treatment groups at 24 months, and in the nasolacrimal duct (microscopically) at the HD in males at 24 months. The irritation in the eye and nasolacrimal duct was determined to be an effect of local toxicity, due to exposure of the eye and nasolacrimal duct to (b) (4) in the feed. There were no test article related neoplastic findings. Based on these results, the NOEL for systemic toxicity of (b) (4) administered for 12 and 24 months was determined to be 1000 mg/kg/day.

The oral NOEL for the 2 year carcinogenicity study with (b) (4) in rats was identified as 1000 mg/kg/day. The acceptable subcutaneous dose for (b) (4) is 10 mg/kg/day, based on safety factor of 10 for change of species from rat to human, and an uncertainty factor of 10 for the change of route. This provides a safety margin of (b) (4) for the proposed TDI of (b) (4) (for a 60 kg individual) for (b) (4).

(b) (4)

(b) (4)
The safety of (b) (4) was based on a TDI of (b) (4), which is below the TTC of 1.5 mcg/day. (b) (4)

(b) (4)

Using the lowest recommended allowance of (b) (4) provides a safety margin of (b) (4) based on a TDI of (b) (4) for (b) (4)

(b) (4)
The safety of (b) (4) is based on a TDI of < (b) (4) which is below the TTC of 1.5 mcg/day. (b) (4)

The carcinogenic risk from exposure to (b) (4) was evaluated (b) (4) which concluded that sufficient data were not available to evaluate the carcinogenicity of (b) (4). The following summary (b) (4) illustrates that the data were unclear³:

(b) (4)

(b) (4) was tested for carcinogenicity in mice and rats by oral administration in the diet. In one study in mice, there was no difference in tumour incidence among treated and controls groups. Another study in mice showed an increased incidence of pulmonary tumours in females at the lower but not at the higher dose level. In another study in mice using one dose level and a small number of animals, the number of mice with lung tumours was increased by feeding of (b) (4) this finding was not confirmed in a further study by the same investigator using a larger number of animals. In one study in rats, no increase in tumour incidence was seen. An increased incidence of pituitary adenomas was observed in female rats at the lower but not at the higher dose level in another study. In one further experiment in rats, liver tumours were observed; however, this study could not be evaluated because of differential survival among control and treated groups. (b) (4) was studied in mice and rats for its ability to modify the carcinogenicity of selected chemical agents. When administered with known carcinogens, (b) (4) either enhanced, inhibited or had no effect on carcinogenicity...

(b) (4) is listed as GRAS on the Database of Select Committee on GRAS Substances. The Select Committee reviewed the available information and determined that a possible "no-effect level" is equivalent to 50 mg/kg, but cautioned that (b) (4) increases the level of microsomal enzymes in the liver. Based on the available data, the Select Committee determined, "While no evidence in the available information on (b) (4) demonstrates a hazard to the public when it is used at levels that are now current and in the manner now practiced, uncertainties exist requiring that additional studies should be conducted."

The proposed levels are significantly lower than the possible "no-effect level" of 50 mg/kg proposed by the Select Committee on GRAS Substances, providing a safety margin of (b) (4) based on a TDI of < (b) (4) (for a 60 kg individual) for (b) (4). Based on this large safety margin, and the proposed level being lower than the TTC of 1.5 mcg/day, the proposed level of (b) (4) appears reasonably safe.

(b) (4)
The safety of (b) (4) is based on a TDI of < (b) (4) which is below the TTC of 1.5 mcg/day. (b) (4)

(b) (4) The carcinogenic risk from exposure to (b) (4) has been evaluated (b) (4) and (b) (4) was determined to be possibly carcinogenic to humans (Group 2B)⁴.

(b) (4)

The National Toxicology Program conducted chronic toxicology and carcinogenicity studies with (b) (4) in F334/N rats and B6C3F1 mice (inhalation studies)⁵. (b) (4) was vaporized, and administered as a vapor. The vapor concentration of the aerosol was monitored to confirm the doses.

In a 2 year carcinogenicity study in rats, animals were dosed with 0, 75, 250 or 750 ppm (b) (4) by inhalation, 6 hours per day, for 5 days per week. Test article related changes in survival, body weights, and clinical findings were noted at 750 ppm. Body weights were decreased at 250 and 750 ppm, compared to controls. Males exposed to 750 ppm developed renal tubule adenoma and adenoma or carcinoma (combined), as well as interstitial cell adenoma in the testes. The NOAEL appears to be 75 ppm, based on body weight loss.

In the 2 year carcinogenicity study in mice, animals were dosed with 0, 75, 250, or 750 ppm (b) (4) by inhalation, 6 hours per day, for 5 days per week. Males dosed with 750 ppm developed alveolar/ bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined). Females exposed to 750 ppm developed hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) at an incidence higher than controls, but the incidence was within the historical control ranges. Eosinophilic foci in 750 ppm females was significantly increased compared to that controls. Nonneoplastic liver changes were noted in male mice, including syncytial alteration of hepatocytes, hepatocellular hypertrophy, and hepatocyte necrosis. Hyperplasia of the pituitary gland pars distalis was noted in 250 and 750 ppm females. Thyroid gland follicular cell hyperplasia was noted in 750 ppm males and females. The NOAEL appears to be 250 ppm based on adenoma, and adenoma/carcinoma formation observed at 750 ppm.

The inhalation NOAELs for the 2 year carcinogenicity studies were identified as 75 ppm (75 mg/kg) in the rat and 250 ppm (250 mg/kg) in the mouse. The acceptable subcutaneous dose for (b) (4) is (b) (4) based on safety factor of 10 for change of species from rat to human, and an uncertainty factor of 10 for the change of route. A lung deposition factor of 10% was not applied, which is consistent with Agency practice for carcinogenicity studies supporting an NDA. The calculated acceptable subcutaneous dose provides a safety margin of (b) (4) based on a TDI of < (b) (4) (for a 60 kg individual). Based on the safety margin, and the proposed level being lower than the TTC of 1.5 mcg/day, the proposed level of (b) (4) appears reasonably safe.

(b) (4)
The safety of (b) (4) is based on a TDI of (b) (4) which is below the TTC of 1.5 mcg/day. (b) (4)

(b) (4)

(b) (4) The carcinogenic risk from exposure to (b) (4) has been evaluated in an IARC monograph, and it was determined that there is inadequate evidence in humans for the carcinogenicity of (b) (4) (b) (4) were not classifiable as to their carcinogenicity to humans (Group 3) .

Based on the lack of clear data, and the proposed level being lower than the TTC of 1.5 mcg/day, the proposed level of (b) (4) appears reasonably safe.

Conclusion

There are no concerns from the nonclinical perspective related to the safety qualification of leachables in Rasuvo.

(b) (4)

REQUEST FOR CONSULTATION

TO (Office/Division):
Marcie Wood
 Division Of Pulmonary, Allergy, And Rheumatology
 Products

FROM (Name, Office/Division, and Phone Number of Requestor):
Youbang Liu, ONDQA/Division III,
 301-796-1926

DATE 05/30/14	IND NO.	NDA NO. 205776	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT 09/10/13
NAME OF DRUG Methotrexate 50 mg/ml solution for injection in pre-filled pen		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE

NAME OF FIRM: **Medac Pharma Inc.**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END-OF-PHASE 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input checked="" type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|--|---|

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input checked="" type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|---|

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|---|
| <input type="checkbox"/> CLINICAL | <input checked="" type="checkbox"/> NONCLINICAL |
|-----------------------------------|---|

COMMENTS / SPECIAL INSTRUCTIONS:

Pharm/Tox consult for a tox evaluation of leachables in this NDA. The leachables report is located in P.7.1 and is titled "Leachables Study (Medac-001).

SIGNATURE OF REQUESTOR
Youbang Liu

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

YOUBANG LIU
05/30/2014

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/s/

JANE J SOHN
05/30/2014

TIMOTHY W ROBISON
05/30/2014
I concur

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 205776
Supporting document/s: SD-1, SD-5 (EDR)
Applicant's letter date: 9/10/13, 1/15/14
CDER stamp date: 9/10/13, 1/16/14
Product: Rasuvo (Methotrexate 50 mg/mL Pre-filled Pen,
injection)
Indication: Rheumatoid Arthritis, Juvenile Idiopathic
Arthritis, Psoriasis
Applicant: Medac Pharma, Inc.
Review Division: Division of Pulmonary, Allergy, and
Rheumatology Products
Reviewer: Jane J. Sohn, PhD
Supervisor/Team Leader: Timothy Robison, PhD, DABT
Division Director: Badrul Chowdhury, MD, PhD
Project Manager: Sadaf Nabavian

Template Version: September 1, 2010

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Table 1: Formulation 7

1 Executive Summary

1.1 Introduction

Medac Pharma, Inc. (Medac) submitted a 505 (b)(2) application for Methotrexate 50 mg/mL Pre-filled Pen (injection) for the treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), and psoriasis. The review is being conducted with a standard review clock of 10 months, with a PDUFA goal date of July 10, 2014.

The systemic safety of methotrexate is supported by reference to approved methotrexate products under NDA 011,719 (Methotrexate Injection; Hospira Worldwide Inc.) and NDA 008,085 (Methotrexate Tablets; Dava Pharmaceuticals Inc.). Local tolerance is supported by previous human experience, and a single dose GLP rabbit study reviewed here.

FDA accepts reference to approved listed product labeling and the public literature to support the labeling of the proposed product.

1.2 Brief Discussion of Nonclinical Findings

The pivotal single dose local tolerance study was conducted in male rabbits with methotrexate (50 mg/mL) administered subcutaneously. Animals received single doses of 25 mg methotrexate on the left side, and single doses of 0.9% aqueous NaCl solution on the right side. Animals were dosed by intravenous, intraarterial, intramuscular, paravenous and subcutaneous bolus injection. The SC route is the intended route of administration for humans; the additional routes reflect accidental injection sites. At 48 hours, 96 hours and 14 days after administration, 2 animals were sacrificed and the injection sites were examined macro- and microscopically. There were no test article related findings.

1.3 Recommendations

1.3.1 Approvability

NDA 205776 is recommended for approval from the nonclinical perspective.

1.3.2 Additional Non Clinical Recommendations

See Labeling Recommendations.

1.3.3 Labeling

Recommended line editing of the proposed text for the nonclinical sections of the Rasuvo label is provided below. Changes are presented as strikethroughs for deletions or in red font for additions. Indications and Usage and Sections 8.1, 8.3, 12.1, and 13.1 were reviewed and are shown below.

INDICATIONS AND USAGE

(b) (4)

8.1 Pregnancy

Pregnancy Category X [see Contraindications (4)]

Methotrexate has been reported to cause embryotoxicity, fetal death, congenital anomalies, and abortion in humans and is contraindicated in pregnant women.

(b) (4)

8.3 Nursing Mothers

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, (b) (4) methotrexate is contraindicated in nursing mothers (b) (4)

Therefore, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

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

12.1 Mechanism of Action

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

The mechanism of action in rheumatoid arthritis is unknown; it may affect immune function.

(b) (4)

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)
Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. (b) (4)

(b) (4)
Data are available regarding the risks for pregnancy and for fertility in humans [see Use in Specific Populations (8.1 and 8.6)].

2 Drug Information

2.1 Drug

CAS Registry Number: 59-05-2

Generic Name: methotrexate injection

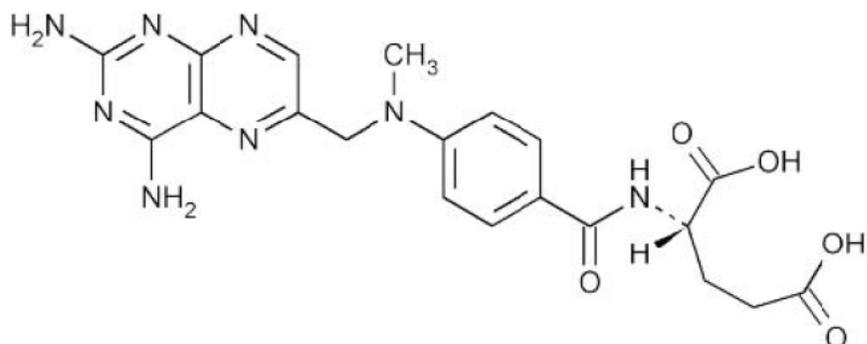
Proposed Trade Name: Rasuvo

Code Name: MTX, Metoject Pre-Filled Pen, (b) (4)

Chemical Name: L-Glutamic acid, N-[4[[[(2,4-diamino-6-pteridinyI) methyl]methyl-amino]benzoyl]-

Molecular Formula/Molecular Weight: C₂₀H₂₂N₈O₅, 454.44 g/mol

Structure or Biochemical Description:



Pharmacologic Class: Folate analog metabolic inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 109543, Division of Pulmonary, Allergy and Rheumatology Products (DPAAP), treatment of rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA)
- IND 113735, Division of Dermatology and Dental Products (DDDP), treatment of psoriasis.

• [Redacted] (b) (4)

• [Redacted]

• [Redacted]

• [Redacted]

• [Redacted]

2.3 Drug Formulation

The drug product is a drug/device combination. The solution for injection contains the drug substance methotrexate [Redacted] (b) (4) in a sterile aqueous solution:

Table 1: Formulation

Ingredient	mg/mL	Function
Methotrexate	50	active
Sodium chloride	[Redacted]	[Redacted] (b) (4)
Sodium hydroxide	[Redacted]	(b) (4) pH adjusting agent
Hydrochloric acid [Redacted] (b) (4)	[Redacted]	pH adjusting agent
Water	[Redacted]	[Redacted] (b) (4)

The product includes ten different fill volumes, each having an identical composition of 50 mg/mL methotrexate. The different fill volumes allow for administration of methotrexate according to the proposed labeling for gradual dose increases:

- 0.15 ml pre-filled pen containing 7.5 mg methotrexate
- 0.20 ml pre-filled pen containing 10 mg methotrexate
- 0.25 ml pre-filled pen containing 12.5 mg methotrexate
- 0.30 ml pre-filled pen containing 15 mg methotrexate
- 0.35 ml pre-filled pen containing 17.5 mg methotrexate
- 0.40 ml pre-filled pen containing 20 mg methotrexate
- 0.45 ml pre-filled pen containing 22.5 mg methotrexate
- 0.50 ml pre-filled pen containing 25 mg methotrexate
- 0.55 ml pre-filled pen containing 27.5 mg methotrexate
- 0.60 ml pre-filled pen containing 30 mg methotrexate

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

No impurities or degradants of concern were identified by the CMC reviewer. Leachables and extractables were reviewed under a separate Chemistry Consult.

2.6 Proposed Clinical Population and Dosing Regimen

Rheumatoid Arthritis

Rasuvo is indicated for the management of patients with severe, active rheumatoid arthritis (RA), who are intolerant of or had an inadequate response to first-line therapy.

The recommended starting dose of Rasuvo is 7.5 mg given subcutaneously once weekly. (b) (4)

Juvenile Idiopathic Arthritis

Rasuvo is indicated for the management of patients with polyarticular juvenile idiopathic arthritis (pJIA), who are intolerant of or had an inadequate response to first-line therapy.

The recommended dose of Rasuvo is 10 mg/m² given subcutaneously once weekly. Use another formulation of methotrexate in patients requiring doses less than 10 mg per week. (b) (4)

Psoriasis

Rasuvo is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation. It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune responses.

The recommended starting dose of Rasuvo is 10 to 25 mg given subcutaneously once weekly. (b) (4)

2.7 Regulatory Background

Methotrexate is approved for the treatment of adult rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), psoriasis and neoplastic diseases. Hospira Worldwide, Inc. (Hospira) produces a Methotrexate Injection (25 mg/mL), which is used by the subcutaneous route for the treatment of neoplastic diseases, psoriasis, adult RA, and pJIA under NDA 011719. Dava Pharmaceuticals, Inc. (Dava) produces a Methotrexate Tablet (2.5 mg per tablet), which is approved for the treatment of treatment of neoplastic diseases, psoriasis, adult RA, and pJIA under NDA 008085. Antares Pharma, Inc. produces OTREXUP, a methotrexate solution approved for subcutaneous injection for the treatment of adult RA, pJIA, and psoriasis under NDA 204824.

Rasuvo was developed under INDs 109543 and 113735 for methotrexate 50 mg/mL solution for injection in a pre-filled pen, submitted by medac Gesellschaft für klinische Spezialpräparate mbH, Germany (medac GmbH). Medac GmbH is the parent company of Medac Pharma, Inc (Medac). IND 109543 was submitted to the Division of Pulmonary, Allergy and Rheumatology Products on June 21, 2012 for the treatment of adult RA and pJIA. IND 113735 was submitted to the Division of Dermatology and Dental Products on February 15, 2013 for the treatment of psoriasis.

A pre-IND meeting was held with Medac on October 14, 2010 under IND 109543. The sponsor proposed the 505(b)(2) application pathway, using methotrexate solution as the reference listed drug. At the time, methotrexate solution was only approved for psoriasis and oncology indications. DPARP indicated that the Hospira methotrexate solution was the appropriate listed drug to reference; however, additional information would be needed to support the dosing, safety and efficacy of the parenteral routes of administration for indications which Medac plans to seek approval (i.e., RA and JIA). Evidence to support efficacy of parenteral MTX for RA and JIA may be available in the literature.

Additional pre-IND questions were submitted to FDA on October 31, 2011, and written responses were given on December 23, 2011 under IND 109543. The sponsor proposed a clinical development program to support the RA indication, including an efficacy and safety study in RA patients. FDA responded that the efficacy may not be necessary, and stated that the 505(b)(2) application could be supported by published literature. In addition, the FDA recommended that a 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.

In the opening IND submission (IND 109543), the sponsor proposed a bioavailability study comparing the proposed drug product (methotrexate 50mg/mL) administered subcutaneously by a disposable autoinjector with the marketed approved oral methotrexate tablets (Dava). The sponsor also proposed a human factors/usability study. Nonclinical and clinical data indicated possible teratogenicity, therefore the sponsor was asked to require that subjects use highly effective contraception. The sponsor addressed this issue, and the studies were determined safe to proceed.

3 Studies Submitted

3.1 Studies Reviewed

Local tolerance test of methotrexate 50 mg/mL in rabbits after a single intravenous, intramuscular, intraarterial, paravenous and subcutaneous administration (study #20070/06, GLP).

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

IND 109543, Division of Pulmonary Allergy and Rheumatology Products, Pharm/Tox Reviewer Dr. Mamata De, 7/19/2012 (single dose non-GLP local tolerance study in 2 rabbits).

4 Pharmacology

The pharmacology of methotrexate is well characterized. Methotrexate is a folic acid antagonist that causes competitive inhibition of the enzyme dihydrofolate reductase, leading to inhibition of DNA synthesis.

5 General Toxicology

5.1 Single-Dose Toxicity

Study title: Local tolerance test of methotrexate 50 mg/mL in rabbits after a single intravenous, intramuscular, intraarterial, paravenous and subcutaneous administration

Study no.:	20070/06
Study report location:	SD-1 (EDR)
Conducting laboratory and location:	 (b) (4)
Date of study initiation:	May 12, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Methotrexate, batch # M60410 AA, 97.9%

Key Study Findings

- Animals received single doses of 25 mg methotrexate on the left side, and single doses of 0.9% aqueous NaCl solution on the right side. The test article was administered by intravenous, intramuscular, intraarterial, paravenous, and subcutaneous administration.
- At 48 hours, 96 hours and 14 days after administration, 2 animals were sacrificed and the injection sites were examined.
- There were no mortalities.
- There were no test article related findings.

Methods

Doses: 0 (0.9% NaCl), 25 mg Methotrexate
 Frequency of dosing: Single dose
 Route of administration: Single intravenous, intraarterial, intramuscular, paravenous and subcutaneous bolus injection
 Dose volume: 0.5 mL
 Formulation/Vehicle: Not stated in study report.
 Species/Strain: Rabbit/Himalayan
 Number/Sex/Group: 2 males per time point (48 hrs, 96 hrs, 14 days after dosing)
 Age: 5.5 - 6 months
 Weight: 2.0 - 2.5 kg
 Satellite groups: None
 Unique study design: None
 Deviation from study protocol: The sponsor did not report any deviations.

Study design:

Animals received single doses of methotrexate on the left side, and single doses of 0.9% aqueous NaCl solution on the right side. The test article was administered once in the following locations:

- intravenous (IV): into the marginal vein of the ear
- intramuscular (IM): into the gastrocnemius muscle (gluteus maximus)
- intraarterial (IA): into the central artery of the ear
- paravenous (PV): beside the vena saphena parva
- subcutaneous (SC.): under the dorsal skin

The SC route is the intended route of administration for humans. The additional routes reflect injections made in error. At 48 hours, 96 hours and 14 days after administration, 2 animals were sacrificed and the injection sites were examined macro- and microscopically.

Test item	Animal number/sex	Routes of administration	Time point of sacrifice
Methotrexat 50 mg/mL	1 m	Intravenous, intraarterial, intramuscular, paravenous and subcutaneous injection	After 48 hours
	2 m		
	3 m		After 96 hours
	4 m		
	5 m		
6 m	After 14 days		

'm' = male
(Sponsor's table)

Observations and Results**Mortality**

There were no mortalities.

Clinical Signs and Macroscopic Inspections

Clinical signs were checked and recorded daily. Local reactions were inspected macroscopically 2, 24, 48, 96 hours and 14 days after administration.

No clinical signs were noted by the sponsor.

Body Weights

Animals were weighed before dosing, and at weekly intervals. There were no notable test article related changes in body weight gain.

Gross pathology

Animals were sacrificed at 48 hours, 96 hours, and 14 days after dosing. Two animals were sacrificed at each time point by T61 injection into the contralateral ear vein, which had not been used for tattooing for animal identification.

There were no macroscopic findings.

Histopathology

Adequate Battery: Yes. Dosing sites were collected for evaluation.

Peer Review: No

Histological Findings:

There were no clear test article related findings for any of the routes of administration. For the IV route, there were no findings reported at the site of methotrexate injection. Histopathological findings were noted for the IM, IA, PV, and SC routes of administration, but they appeared to be nonspecific reactions.

Toxicokinetics

Not performed.

Dosing Solution Analysis

Not performed.

6 Integrated Summary and Safety Evaluation

Medac Pharma, Inc. (Medac) submitted a 505 (b)(2) application for Methotrexate 50 mg/mL Pre-filled Pen (injection) for the treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), and psoriasis. The sponsor is relying upon FDA finding of safety and effectiveness of marketed approved methotrexate tablets (USP, Dava Pharmaceuticals, Inc) under NDA 008085, and methotrexate injection (USP, Hospira Worldwide, Inc.) under NDA 011719. The proposed Methotrexate 50 mg/mL Pre-filled Pen (Rasuvo) differs from these products with regard to the route of administration for RA and psoriasis(subcutaneous), concentration (50 mg/mL), and the addition of a device.

Methotrexate is currently labeled for the following indications and routes of administration based on the labels for previously mentioned marketed approved products, methotrexate injection (Otrexup), and products approved under ANDA:

- Neoplastic diseases: oral, intramuscular (IM), intravenous (IV), intrathecal (IT), and intra-arterial (IA)
- Psoriasis: oral, IM, IV and SC
- Rheumatoid arthritis (RA): oral, IM, SC
- Polyarticular juvenile idiopathic arthritis (pJIA): oral, IM, and SC

Rasuvo is proposed for subcutaneous administration at weekly doses of 7.5, 10, 12.4, 15, 17.5, 20, 22.5, 25, 27.5, and 30 mg methotrexate. The drug product is proposed for the following pre-filled pen volumes:

- 0.15 ml pre-filled pen containing 7.5 mg methotrexate
- 0.20 ml pre-filled pen containing 10 mg methotrexate
- 0.25 ml pre-filled pen containing 12.5 mg methotrexate
- 0.30 ml pre-filled pen containing 15 mg methotrexate
- 0.35 ml pre-filled pen containing 17.5 mg methotrexate
- 0.40 ml pre-filled pen containing 20 mg methotrexate
- 0.45 ml pre-filled pen containing 22.5 mg methotrexate
- 0.50 ml pre-filled pen containing 25 mg methotrexate
- 0.55 ml pre-filled pen containing 27.5 mg methotrexate
- 0.60 ml pre-filled pen containing 30 mg methotrexate

The proposed dose range covers the recommended dosing for RA and psoriasis.

(b) (4)

For the purpose of this nonclinical review, the safety is evaluated for the maximum exposure of 30 mg methotrexate administered weekly in the proposed pre-filled syringe.

The systemic safety of methotrexate is supported by reference to approved methotrexate products under NDA 011,719 (methotrexate injection; Hospira Worldwide Inc.) and NDA 008,085 (oral methotrexate; Dava Pharmaceuticals Inc.) and bioavailability and human factors studies. No concern was identified for the level of impurities or degradants from the CMC perspective. Leachables and extractables were reviewed under a separate Chemistry Consult.

Local tolerance is supported by previous human experience, and a single dose GLP rabbit study reviewed here. A single dose local tolerance study was conducted in male rabbits with methotrexate (50 mg/mL) administered SC. Animals received single doses of 25 mg methotrexate on the left side, and single doses of 0.9% aqueous NaCl solution on the right side. Animals were dosed by intravenous, intraarterial, intramuscular, paravenous and subcutaneous bolus injection. The SC route is the intended route of administration for humans; the additional routes reflect injections made in error. At 48 hours, 96 hours and 14 days after administration, 2 animals were sacrificed and the injection sites were examined macro- and microscopically. There were no test article related findings. Under IND 109543, a non-GLP single dose, local tolerance study (study # 19015/05) was previously reviewed by Pharm/Tox Reviewer Dr. Mamata De

(July 19, 2012). Briefly, two concentrations of methotrexate were tested (50 mg/mL and 10 mg/mL). Animals (1 male, 1 female) received 0 (0.9% NaCl), 50 mg (50 mg/mL formulation), 100 mg (50 mg/mL formulation), and 10 mg (10 mg/mL formulation) methotrexate SC. Each animal received all 4 injections at separate administration sites, with methotrexate administered on the left side, and the control administered on the right side. There were no test article related macroscopic or microscopic findings.

FDA accepts reference to approved listed product labeling and the public literature to support the labeling of the proposed product. Recommendations to the nonclinical portions of the label are shown in Section 1.3.3 of this review, and are consistent with approved methotrexate products.

Based on the well-established safety of methotrexate and the lack of findings in the nonclinical local tolerance study, there are no safety issues from the nonclinical perspective. The NDA is recommended for approval from the nonclinical perspective.

7 Appendix/Attachments

Appendix 1: Pharm/Tox Review by Dr. Mamata De, IND 109543, July 19, 2012.

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/s/

JANE J SOHN
05/28/2014

TIMOTHY W ROBISON
05/28/2014
I concur

Division of Pulmonary, Allergy, and Rheumatology Products Preliminary Pharmacology/Toxicology Safety Review

IND: 109,543

Sponsor: medac Gesellschaft für klinische Spezialpräparate mbH (medac GmbH)

Agent for sponsor: Antoinette Azevedo

Drug Product: Metoject® Pre-Filled Pen (Methotrexate 50 mg/mL solution for injection in prefilled syringe)

Indication: Treatment of rheumatoid arthritis, psoriasis, and JIA

Overview: The proposed clinical trial, MC-MTX.15/HF, is safety to proceed from nonclinical perspective. The sponsor did not submit any pivotal nonclinical data, but such data may not be needed because there is sufficient clinical data to evaluate the safety of the proposed use.

Background: Methotrexate (MTX) is a folic acid antagonist; it inhibits dihydrofolate reductase and thus inhibits DNA synthesis. MTX oral tablets have been approved for use in RA patients for a long period of time. While the injectable formulation of MTX is not approved for RA, the label references the RA indication. In addition, there is extensive clinical experience and publications regarding the safety and efficacy of injectable MTX in RA.

The Sponsor plans to seek approval for a subcutaneous injectable formulation of methotrexate in an autoinjector, via a 505(b) (2) application with oral methotrexate as the reference listed drug.

Clinical Protocol: For the marketing of MTX by subcutaneous injection in USA, the Sponsor proposed a clinical protocol, MC-MTX.15/HF, entitled 'Evaluation of Rheumatoid Arthritis Patient Performance Using the Metoject® Prefilled Pen (Methotrexate 50 mg/mL, prefilled pen) for Subcutaneous Injection and Subsequent Pharmacokinetic Assessment of Drug Delivery. This clinical protocol is a human factors/usability study in adults to assess the usability, safety, and pharmacokinetics of methotrexate injection, (50 mg/mL solution) delivered in a prefilled syringe that is sealed in a disposable prefilled pen (Metoject®) for patients with RA. Under this protocol, the patients will inject Methotrexate (50 mg/ml) 15 mg (0.3 ml) SC weekly for 2 doses. It will be injected by an autoinjector. Male and female RA patients (age 21 years of age and older) will be included in the study. Women of childbearing potential will be included in this study. In an IR dated June 21, 2012, the Sponsor was asked to include appropriate contraceptive methods as MTX is a known teratogen.

Previous Human Experience:

Sponsor' Previous Clinical Experience: The Sponsor conducted 6 clinical trials in Europe to support marketing of the 50 mg/mL MTX injectable solution as follows.

Study ID	Study title	Primary objectives
Pharmacokinetic studies		
MC-MTX.7/PH	Clinical study to evaluate the pharmacokinetic characteristics and the rate of absorption of 16.5 mg methotrexate disodium salt as an aqueous solution corresponding to 15.0 mg methotrexate when given subcutaneously as compared to an equal dose after intramuscular administration as reference in 16 healthy male volunteers.	To evaluate the pharmacokinetic characteristics and the rate and extent of absorption of 15.0 mg methotrexate based on the parent compound methotrexate when given subcutaneously (SC) as compared to an equal dose after intramuscular (IM) administration as reference in 16 healthy male subjects.
MC-MTX.9/PH	Study on the relative bioavailability of MC-PK 0406 (methotrexate disodium salt aqueous solution, 50 mg methotrexate/ml) compared to a market standard (methotrexate disodium salt aqueous solution, 10 mg methotrexate/ml) as reference, when administered as a single subcutaneous or intramuscular dose of 15 mg methotrexate in healthy male subjects.	To assess the relative bioavailability of 15 mg methotrexate (50 mg/ml) based on the parent compound methotrexate when given subcutaneously (SC) / intramuscularly (IM) as compared to an equal dose with a concentration of 10 mg/ml, in 12 healthy male subjects.
Efficacy studies		
MC-MTX.6/RH	Double-blind, multicentre, randomised clinical trial phase IV to evaluate efficacy of subcutaneous administered methotrexate (Metex [®]) in comparison with oral treatment in patients with active rheumatoid arthritis	To compare the efficacy of subcutaneous methotrexate and oral methotrexate in patients with rheumatoid arthritis, as measured by standard clinical and laboratory parameters, and to compare the frequency and severity of adverse events in the two treatments groups.
Safety studies		
MC-MTX.5/RH	Clinical study to assess the local tolerability of repeated subcutaneous injections of methotrexate and the suitability of the administration system in patients with rheumatoid arthritis	To assess the local tolerability of repeated subcutaneous injections of methotrexate in patients with rheumatoid arthritis in an exploratory sense. The local tolerance symptom score was recorded as well as the dermal score.
MC-MTX.10/RH	An open, comparative, within patient controlled multicentre study of repeated subcutaneous injections of methotrexate 50 mg/ml and 10 mg/ml to compare patient satisfaction and local tolerability in patients with active rheumatoid arthritis	To quantify the patient's decision for future MTX treatment (50 mg/ml syringe vs 10 mg/ml syringe) following repeated subcutaneous injections of 10 mg/ml and 50 mg/ml syringes.

The results from the pharmacokinetics studies showed that exposures from SC and IM administration were comparable. The exposure from SC MTX solution is similar to the exposure from the IV parenteral solution which is an approved product for neoplastic lesions. The bioavailability from oral MTX tablets is 50%. On the methotrexate injectable label, the data from oral methotrexate in RA is referenced. MTX IV (16 mg) is approved as per MTX injectable label for parenteral injection. No new safety concerns were identified after SC administration (15 mg) in human (Medical reviewer, Dr Janet Maynard agreed with the assessment email dated July 12, 2012).

Drug Formulation: The drug/device combination product to be used in this study is the Metoject[®] prefilled pen. The drug product contains methotrexate (b) (4)

(b) (4) in an aqueous sterile solution for injection. There are no novel excipients in the drug product.

Regulatory History: A Pre-IND meeting was held on October 14, 2010. In the PIND meeting minutes (dated 11-08-2010) the Sponsor was recommended to monitor impurities and degradation products of all active and inactive ingredients.

Note: Based on the summary of study reports submitted with the IND, no new impurities, which need to be qualified in the IND stage were identified from the drug product or drug device combination product (CMC reviewer Dr Arthur Shaw agreed with the assessment, email dated 7-11-2012).

In the PIND meeting minutes (dated 11-08-2010), the Sponsor was also recommended to provide a summary of non-clinical information for the referenced product in support of the 505 (b)(2) application. In addition, you will need to provide safety data for IV, IM and SC route following once a week injection for one month when the treatment is repeatedly given at the same site of injection. However, the need for non-clinical data may be waived if you provide sufficient clinical safety data when methotrexate is injected repeatedly at the same site in humans.

Note: The Sponsor provided local toxicity study reports in New Zealand white rabbits (reviewed below); clinical data for local tolerability is also available. No further local toxicity evaluation in non clinical species will be required.

Local Toxicity: In support of this IND, the Sponsor submitted two local toxicity study reports. In the study report # LPT20070/06 (GLP study), 50 mg/mL of MTX solution was administered as a single injection in rabbits (n=6 males) by the intravenous, intraarterial, intramuscular, paravenous and subcutaneous routes in a dose volume of 0.5 ml (single injection) for any route. Saline was use as control. The animals were observed for local toxicity macroscopically 2, 24, 48, 96 hours and 14 days. The animals were sacrificed at 48 hr, 96 hr, and 14 days postdose (2 animals/time point) for histological examination. There were no macroscopic, microscopic, and morphological changes that can be attributed to the test article. No morphological differences between test article and control injections were observed. This study showed that MTX SC administration was well tolerated by the rabbits.

In the study report # 19015/05 (non-GLP) single injections of 10 mg/ml (1.0 ml/animal) and 50 mg/ml (1.0 and 2.0 ml/animal) MTX were administered in rabbits (n=2, 1 male, 1 female) by the subcutaneous route. The test article related local reactions were inspected macroscopically at 2, 24, 48 and 96 hours after administration; 96 hours after administration, both animals were sacrificed for microscopic evaluation. In this study, no macroscopic observation was noted. However, microscopic evaluation noted minimal focal epithelial hyperplasia and subcutaneous mixed cell infiltration in the skin treated with 2 mL test solution/animal (50 mg/mL) in the male rabbit. This was a non GLP study. The

findings were noted in one male animal. The number of rabbits per group was small for an adequate investigation. Therefore, the findings are questionable.

Also, the local tolerability of the drug product in humans appears to be acceptable based on clinical studies (study # MC-MTX.5/RH, reviewed by Dr. Janet Maynard, Medical Reviewer).

Safety Evaluation: There was no well designed single or repeat dose oral, IV, or SC toxicity study in animals. However, MTX has been marketed for more than 60 years. There is extensive clinical experience with MTX and the safety issues for MTX are well known. There is extensive clinical experience and publications regarding the safety and efficacy of injectable MTX in RA.

MTX was genotoxic in chromosomal aberration assay. In the product label, the carcinogenicity section provides the following information.

'No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Non-Hodgkin's lymphoma and other tumors have been reported in patients receiving low-dose oral methotrexate. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral methotrexate, which have regressed completely following withdrawal of methotrexate, without requiring active anti-lymphoma treatment. Benefits should be weighed against the potential risk before using methotrexate alone or in combination with other drugs, especially in pediatric patients or young adults'.

MTX is labeled as pregnancy category X. The BOX warning section of the product label provides the following information.

'Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis or rheumatoid arthritis should not receive methotrexate'

Based on the above discussion no new toxicity studies are recommended for the subcutaneous administration of MTX for RA, psoriasis, and JIA (age 2.5-16 years).

Recommendation: Oral MTX was approved for the treatment of rheumatoid arthritis (RA) and there is extensive clinical experience with MTX use. While the injectable formulation of MTX is not approved for subcutaneous administration to RA patients, the label references the RA indication. In addition, there is

extensive clinical experience and publications regarding the safety and efficacy of injectable MTX in RA. Two non-GLP studies with rabbits did not identify any local toxicity associated with SC administration.

From the nonclinical perspective, the proposed clinical trials appear reasonably safe and should be allowed to proceed.

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/s/

MAMATA DE
07/19/2012

TIMOTHY W ROBISON
07/19/2012
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205776 Applicant: Medac Pharma, Inc. Stamp Date: 9/10/13

Drug Name: Methotrexate 50 mg/mL Pre-filled Pen NDA/BLA Type: 505 (b)(2)

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		One GLP-compliant local tolerance test conducted in rabbits is included in the NDA submission. (See comments under Question 8 and 9).
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	x		Excipients are covered by approved products.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	x		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	x		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x		At the preNDA meeting, conducted under IND 109453, the Agency stated that no further non-clinical studies are required and requested reference to scientific literature

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
				and to the label for the reference drug (NDA 08085). It appears that the sponsor has provided the recommended references.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		Human dose multiples are not required because clinical data are used to support the safety of the drug.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X (see note)		Impurities will be reviewed under a CMC consult.
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _Yes_____

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

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

None.

Jane J. Sohn

10/21/2013

Reviewing Pharmacologist

Date

Team Leader/Supervisor

Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

JANE J SOHN
10/22/2013

TIMOTHY W ROBISON
10/22/2013
I concur