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APPLICATION NUMBER:

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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/BLA REVIEW AND EVALUATION

Application number: NDA 204,824
Supporting document/s: EDR #1
Applicant's letter date: 12/14/2012
CDER stamp date: 12/14/2012
Product: OTREXUP (methotrexate)
Indication: Rheumatoid arthritis, juvenile rheumatoid
arthritis, psoriasis
Applicant: Antares Pharma, Inc.
Review Division: Division of Pulmonary, Allergy, and
Rheumatology Products (DPARP)
Reviewer: Andrew Goodwin, 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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1 Executive Summary

1.1 Introduction

Antares Pharma submitted 505(b)(2) NDA 204,824 on December 14, 2012 for the use of Otrexup (methotrexate) for the indications of rheumatoid arthritis (including juvenile rheumatoid arthritis (b)(4)) and moderate to severe psoriasis. The NDA was filed on February 26, 2013 as a standard review with a PDFUA goal date of October 14, 2013.

The safety profile of subcutaneously delivered methotrexate is established based on extensive clinical experience with the reference products under NDA 11-719 (methotrexate injection; Hospira), ANDA 40-632 (methotrexate preservative-free injection; Bedford), and NDA 08-085 (methotrexate tablets, Dava Pharmaceuticals). The only required nonclinical studies involved the toxicological evaluation of leachables and extractables from the Otrexup drug product. These studies were reviewed separately under a chemistry consult (see review filed by Dr. Andrew Goodwin on May 14, 2013). The Agency accepts reference to nonclinical information in the approved reference product labeling and the public literature to support NDA 204,824.

1.3 Recommendations

1.3.1 Approvability

NDA 204,824 is recommended for approval from the nonclinical perspective.

1.3.2 Additional Non Clinical Recommendations

See Section 1.3.3 below for recommended labeling changes to reflect current practices and Physicians Labeling Rule (PLR) guidelines as required by 21 CFR 201.56 and 201.57.

1.3.3 Labeling

The following labeling for nonclinical sections of the Prescribing Information is recommended based on the consensus of the NDA 204,824 review team. Insertions are noted in blue font and deletions in red-strikethrough font.

1. INDICATIONS AND USAGE

Otrexup is a folate analog metabolic inhibitor

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b)(4)
Pregnancy Category X. [see *Contraindications (4.1)*]

Methotrexate has been reported to cause (b)(4) embryotoxicity, fetal death, congenital anomalies, and abortion (b)(4) in humans and is contraindicated in pregnant

women.-

(b) (4)

8.6 Females and Males of Reproductive Potential

Otrexup is not recommended for females of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Females of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment [see *Use in Specific Populations (8.1)*].

Appropriate steps should be taken to avoid conception during Otrexup therapy. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients.

Methotrexate has been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

13. NONCLINICAL TOXICOLOGY

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)

Data are available regarding the risks for pregnancy and for fertility in human [see *Use in Specific Populations (8.1. And 8.6)*]

2 Drug Information

2.1 Drug

CAS Registry Number: 59-05-2

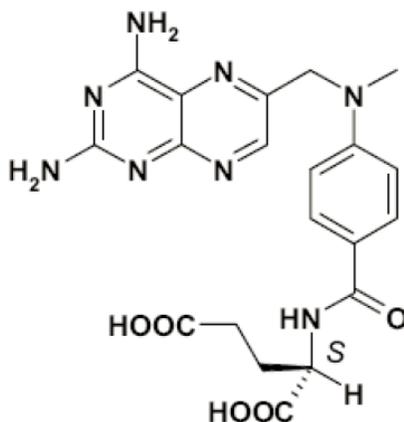
Generic Name: methotrexate

Proposed Trade Name: Otrexup

Chemical Name: [N-[4-[[[(2,4-diamino-6-pteridiny)methyl]methylamino]benzoyl]-L-(+)-glutamic acid

Molecular Formula/Molecular Weight: C₂₀H₂₂N₈O₅ (MW 454.54 g/mol)

Structure or Biochemical Description



Pharmacologic Class: Folate analog metabolic inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 103,738 (Antares Pharma; methotrexate)

2.3 Drug Formulation

The Sponsor seeks approval for a drug/device combination product that delivers a subcutaneous administration of methotrexate. The Medi-Jet autoinjector is a single-use device pre-filled with sterile, preservative-free methotrexate. A fixed volume of 0.4 mL is delivered via a 27-gauge, 1/2 inch needle containing doses of 10, 15, 20, or 25 mg. Details of the formulation are presented in the table below.

Table 1. OTREXUP formulation

Ingredient	Content in mg/mL				Content in mg/ unit dose (0.4 mL)			
	25	37.5	50	62.5	10	15	20	25
Methotrexate, USP.				(b) (4)				
Sodium Chloride, NF/Ph. Eur.					1.96	1.60	1.28	0.56
Sodium Hydroxide, NF, Ph. Eur.	X ²	X	X	X	X	X	X	X
Hydrochloric Acid, NF/Ph. Eur.	X	X	X	X	X	X	X	X
Water for Injection, USP/Ph. Eur.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

² X - As required to adjust pH
(b) (4)

Table generated by Sponsor

2.4 Comments on Novel Excipients

There are no novel excipients in OTREXUP.

2.5 Comments on Impurities/Degradants of Concern

Refer to nonclinical review filed by Dr. Andrew Goodwin on May 14, 2013.

2.6 Proposed Clinical Population and Dosing Regimen

The following clinical populations and dosing regimens are proposed by Medical Officer Dr. Peter Starke.

Rheumatoid Arthritis

Otrexup is indicated in the management of adults with severe, active rheumatoid arthritis (RA) (ACR criteria) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose non-steroidal anti-inflammatory agents (NSAIDs).

The recommended starting dose of Otrexup is 10 (b) (4) mg given subcutaneously once weekly. Dosages may be adjusted in 5 mg increments at (b) (4) week intervals to achieve optimal clinical response.

Juvenile Idiopathic Arthritis

Otrexup is indicated in the management of pediatric patients with active polyarticular-juvenile idiopathic arthritis (pJIA), who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose non-steroidal anti-inflammatory agents (NSAIDs).

The recommended dose of Otrexup is 10 mg/m² given subcutaneously once weekly. Use another formulation of methotrexate in patients requiring doses less than 10 mg per week. Dosages may be adjusted in 5 mg increments every (b) (4) weeks to achieve optimal clinical response.

Psoriasis

Methotrexate 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 Otrexup is 10 to 25 mg given subcutaneously once weekly. Dosages may be adjusted in 5 mg increments at (b) (4) week intervals to achieve optimal clinical response.

2.7 Regulatory Background

A pre-IND meeting for IND 103,738 was held between DPARP and Antares on February 5, 2009. At this meeting the Sponsor was informed that toxicological evaluation of leachables and extractables would be required to qualify the safety of the Otrexup methotrexate drug product via the parenteral route of administration. The Sponsor was also informed that adequate nonclinical data had not been provided to support the safety of the sub-cutaneous (SC) route of administration. DPARP indicated that, in the absence of meaningful pharmacokinetic differences between Otrexup (SC) and an approved parenteral route of administration such as intramuscular, a four-week local toxicity study with full histopathology in one species would be required.

The Sponsor submitted IND 103,738 on December 8, 2010. The only nonclinical data submitted with the IND was a non-GLP crossover PK study in minipigs comparing autoinjector vs. needle and syringe (12.5 mg/day SC).

On May 16, 2011, DPARP provided written responses to a Type C Meeting request regarding the design of a nonclinical study. DPARP indicated that the selection of the dog as a model species was appropriate and suggested protocol modifications for the 4-week local tolerance study (inclusion of higher dose to determine safety margins, histopathological assessment of injection site draining lymph nodes).

An End-of-Phase 2 (EOP2) meeting was held on September 13, 2011. In preliminary comments, DPARP agreed that the minipig would be an appropriate alternative model for evaluating local tolerance.

On February 10, 2012, DPARP provided written responses to a Type C Meeting request. DPARP indicated that the revised in vivo local tolerance study design was acceptable. In addition, the Sponsor was informed that upon further review it had been

determined that the available clinical data support the safety of SC methotrexate administration and that the nonclinical study was no longer considered necessary.

A pre-NDA meeting was held on November 2, 2012. The meeting minutes do not reflect discussion of any nonclinical matters.

3 Studies Submitted

3.1 Studies Reviewed

A Cross-over Pharmacokinetic Study of Methotrexate Injection USP Administered via Subcutaneous Infection to Minipigs. (b) (4)
(b) (4). Test facility (b) (4) and Sponsor reference #AP 09-006.

No toxicology studies were submitted or required for Otrexup. Studies to support the safety qualification of leachables and extractables from the Otrexup drug product were reviewed separately under a chemistry consult (see review filed by Dr. Andrew Goodwin on May 14, 2013).

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

- Dr. Carol Rivera-Lopez, nonclinical review, IND 103,738, January 4, 2011
- Dr. Carol Rivera-Lopez, nonclinical review, IND 103,738, June 10, 2011
- Dr. Andrew Goodwin, chemistry consult review, NDA 204824, May 14, 2013

5 Pharmacokinetics/ADME/Toxicokinetics

Study Title: A Cross-over Pharmacokinetic Study of Methotrexate Injection USP Administered via Subcutaneous Infection to Minipigs.

Test facility: (b) (4)

Study Number: Test facility (b) (4) and Sponsor reference #AP 09-006.

GLP compliance: No

Date: Protocol signed 12/2/2009, experimental completion 3/15/2010, report signed 4/12/2010.

Test system: Gottingen minipigs, ~9 weeks of age, 7.0-8.0 kg

Test article: Commercially available Methotrexate Injection USP (25 mg/mL, Lot #W034457AA, 100% purity)

Control article: Sodium chloride for Injection USP

Dosing formulations: test article was stored at room temperature protected from light and was administered as received. Needle and syringe or autoinjectors were used to

administer the test and control articles. No analysis of dosing formulations was performed.

Study design:

In Phase 1, 3/sex received 12.5 mg methotrexate SC on Days 1 and 8. Males were administered methotrexate with the autoinjector on Day 1 followed by needle and syringe on Day 8. The order of administration modalities was reversed for females. An additional animal was injected with 0.5 mL India ink (two sites, autoinjector), 0.5 mL saline (four sites, autoinjector [2], 22-gauge needle, 27-gauge needle), or 0.5 mL methotrexate (25 mg/mL, two sites, autoinjector) and was examined for injection site reactions and depth of dye penetration.

Table 2. Grading Scale for Evaluating Skin Reactions

ERYTHEMA AND EDEMA OBSERVATIONS		
OBSERVATION	DEFINITION	CODE
Erythema - Grade 0	No erythema	0
Erythema - Grade 1	Very slight erythema (barely perceptible)	1
Erythema - Grade 2	Well-defined erythema	2
Erythema - Grade 3	Moderate to severe erythema	3
Erythema - Grade 4	Severe erythema (beet redness)	4
Maximized Grade 4	Notable dermal lesions (see below)	M - 4 (see below)
Edema - Grade 0	No edema	0
Edema - Grade 1	Very slight edema (barely perceptible)	1
Edema - Grade 2	Slight edema (edges of area well defined by definite raising)	2
Edema - Grade 3	Moderate edema (raised approximately 1 millimeter)	3
Edema - Grade 4	Severe edema (raised more than 1 millimeter and extends beyond the area of exposure)	4
NOTE: Each animal is assigned an erythema and edema score. The most severely affected area within the test site is graded. If eschar, blanching, ulceration and/or necrosis <u>greater than grade 1</u> is observed, then the "Maximized Grade 4" is assigned to the test site in place of the erythema score and the type of notable dermal lesion(s) (e.g., eschar - grade 2, blanching - grade 3, ulceration - grade 4, etc.) will be noted. The presence of any other dermal changes (e.g., desquamation, fissuring, eschar exfoliation, etc.) will also be recorded.		

Table generated by Sponsor

In Phase 2, the test site on each animal (4 males, 3 females) was clipped one day before dosing. The test and control articles were administered 30 minutes apart on Day 1 on one side of the animal as follows:

- Methotrexate by needle and syringe (penetration restricted to 5 mm)
- Methotrexate by autoinjector (4.5-5.5 mm needle exposure)

- Methotrexate by autoinjector (>8 mm needle exposure)
- Sodium chloride by autoinjector (4.5-5.5 mm needle exposure)

This series of injections were repeated on the second side after completion of the final dermal observation. Dermal observation was performed immediately after dosing and 1, 1.5, 24, 48, and 72 hours post-dose using the Macroscopic Dermal Grading System. The goal of Phase 2 was to assess whether erythema observed in Phase 1 was related to methotrexate or to the physical action of triggering the autoinjector.

Animal observations and procedures:

General health / mortality / moribundity checks were performed twice daily (morning and afternoon; Phases 1 and 2) and cage-side observations once daily on Days 1-8. Detailed clinical observations and body weights were recorded on Days -1, 1, and 8 (Phase 1) and prior to dosing on Day 1 (Phase 2). Following the completion of Phase 1 and 2, animals were euthanized by sodium pentobarbital injection followed by exsanguination and discarded without necropsy.

There was no mortality and no test article-related effects on body weights in the study.

In Phase 1, grade 1-2 erythema was observed following methotrexate autoinjector injections that resolved within 48 hours post-dose. No irritation was observed in animals receiving methotrexate SC by needle and syringe.

In Phase 2, very slight erythema was observed at most autoinjector sites immediately post-injection with diameter ranging from 4-15 mm. At the majority of sites, the irritation resolved within 0.5 hours.

Deviations:

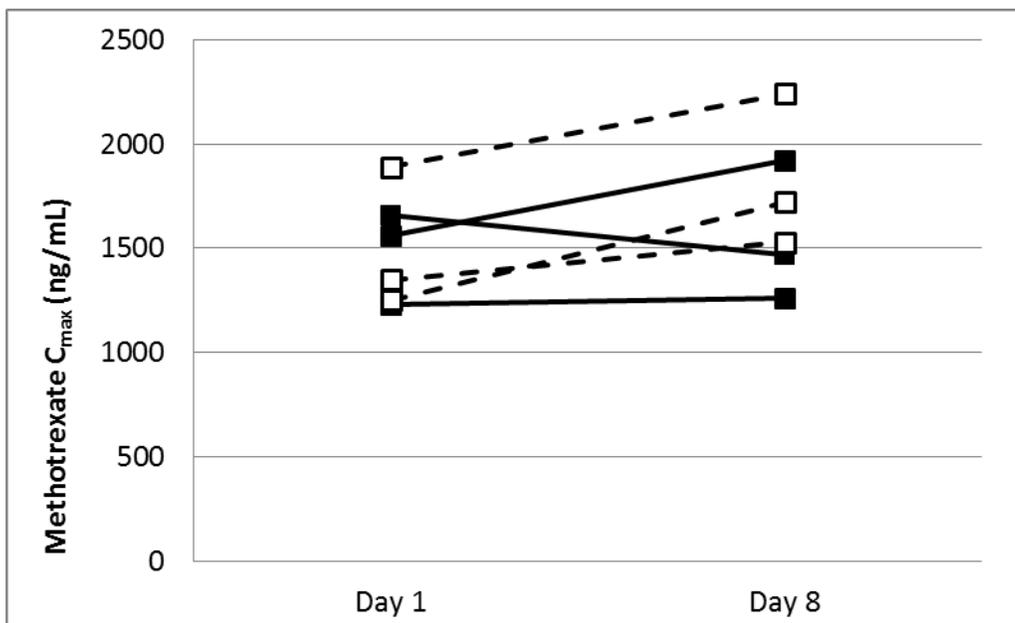
Deviations were noted that included delayed dosing at the second injection sites in most animals, extending up to 121 minutes after the initial dose instead of 30 minutes as specified in the protocol. Minor deviations from scheduled 1 and 1.5 hours post-dose dermal examination time points were also noted.

Pharmacokinetics:

Blood samples (1.0 mL) were collected with the anterior vena cava. Blood was collected into K₂EDTA tubes, chilled, centrifuged, and resulting plasma was stored at -70°C. Samples were collected prior to dosing (0 hour) and 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, and 24 hours post-dose on Days 1 and 8.

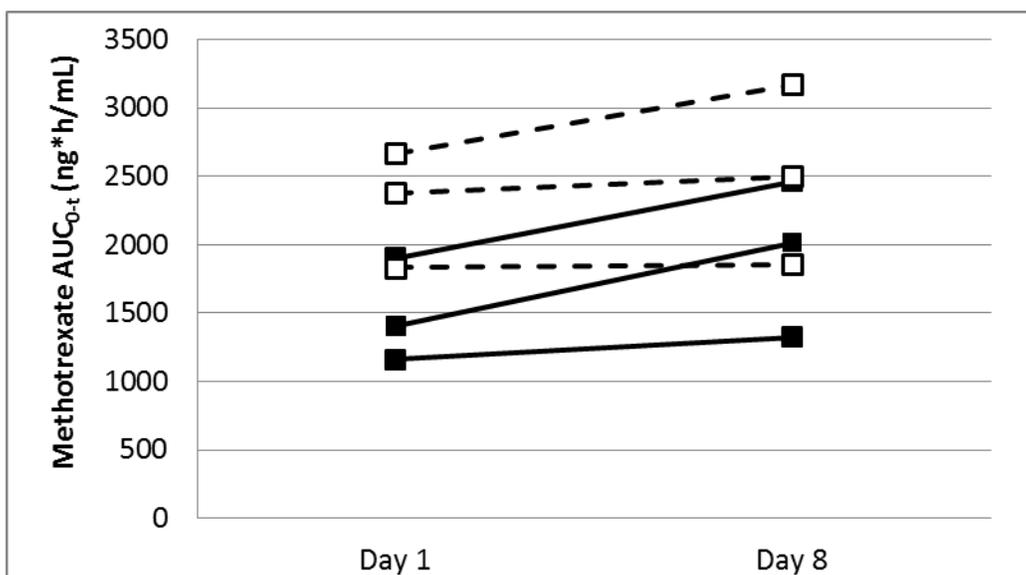
T_{max} after SC administration of methotrexate was 0.25 hours and terminal elimination half-life was in the range of 1.8-4.9 hours. While animal numbers were small, there were no clear differences between exposure in males vs. females or autoinjector vs. needle and syringe (see figures below).

Figure 1. C_{max} After Methotrexate Administration in Minipigs



Filled squares with solid lines denote individual male minipigs which received 12.5 mg methotrexate SC by autoinjector on Day 1 and by needle and syringe on Day 8. Open squares with dashed lines denote individual female minipigs which received 12.5 mg methotrexate SC by needle and syringe on Day 1 and by autoinjector on Day 8.

Figure 2. AUC_{0-t} After Methotrexate Administration in Minipigs



Filled squares with solid lines denote individual male minipigs which received 12.5 mg methotrexate SC by autoinjector on Day 1 and by needle and syringe on Day 8. Open squares with dashed lines denote individual female minipigs which received 12.5 mg methotrexate SC by needle and syringe on Day 1 and by autoinjector on Day 8.

Conclusion:

In this small non-GLP study in minipigs, no clear pharmacokinetic differences were observed between methotrexate administered subcutaneously by needle and syringe vs. autoinjector. Minor injection site reactions that resolved quickly were noted with the autoinjector. These are attributed to the action of the device and were similar regardless of whether methotrexate or saline was delivered.

11 Integrated Summary and Safety Evaluation

Antares Pharma has submitted 505(b)(2) NDA 204,824 for Otrexup, a drug/device combination product consisting of a single-use, prefilled methotrexate autoinjector intended for sub-cutaneous (SC) administration. Methotrexate is a currently marketed product with three FDA-approved applications referenced by the Sponsor: NDA 11-719 (methotrexate injection; Hospira), ANDA 40-632 (methotrexate preservative-free injection; Bedford), and NDA 08-085 (methotrexate tablets, Dava Pharmaceuticals).

According to Medical Officer (MO) Dr. Peter Starke (see review filed August 20, 2013), methotrexate is currently labeled for the following indications and routes of administration:

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

The Otrexup product is intended to deliver weekly doses on 10, 15, 20 or 25 mg methotrexate SC. The proposed dose range covers the recommended dosing for psoriasis and RA, but does not adequately address the dosing for neoplastic diseases and pJIA which requires doses higher or lower than the 10-25 mg range, respectively. The oncologic indications are not being sought by the Sponsor and will not be included in the Otrexup label. Per the MO, issues with dosing raised by the limitations imposed by the product will necessitate Limitations of Use in the Dosing and Administration section of this product. On this basis, the nonclinical reviewer has assessed the safety of the Otrexup product in the context of a maximum patient exposure level of 25 mg methotrexate administered once weekly via a single autoinjector device.

As detailed in Section 2.7 above, the Sponsor and DPARP held discussions over the course of the Otrexup development program under IND 103,738 regarding the studies necessary to qualify the safety of the product from the nonclinical perspective. The conclusion was made that the clinical experience with SC administration of methotrexate was sufficient to qualify the safety of Otrexup and no in vivo local tolerance or general toxicology studies would be required. The only nonclinical study performed with Otrexup was the non-GLP minipig study reviewed above that evaluated PK and injection site reactions following methotrexate SC administration with either the autoinjector or needle and syringe.

The Chemistry review team requested a nonclinical consult review on January 28, 2013. The resulting consult review, filed by Dr. Andrew Goodwin on May 14, 2013, contains a detailed nonclinical safety evaluation of the findings of controlled extraction, leachables, and stability studies conducted on the syringe, needle shield, plunger stopper and aged methotrexate drug product and submitted in the NDA by the Sponsor. No concerns were identified that prevent recommendation for approval of the NDA from the nonclinical perspective.

Otrexup is the first methotrexate product to be approved and labeled under the Physicians Labeling Rule (PLR) format. Certain modifications to the labeling (including pregnancy and nonclinical toxicology sections as described above) have been recommended on this basis. Efforts were made to minimize the labeling differences between Otrexup and other methotrexate products, over which this product does not offer advantages other than convenience.

In summary the safety profile of methotrexate is well-established based on clinical experience by multiple routes of administration, including SC as applicable to Otrexup. No nonclinical safety studies were required and the NDA is recommended for approval from the nonclinical perspective.

12 Appendices/Attachments

Appendix 1: Dr. Carol Rivera-Lopez, nonclinical review, IND 103,738, January 4, 2011

Appendix 2: Dr. Carol Rivera-Lopez, nonclinical review, IND 103,738, June 10, 2011

Appendix 1: Dr. Carol Rivera-Lopez, nonclinical review, IND 103,738, January 4, 2011

**DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS (DPARP)
PRELIMINARY PHARMACOLOGY SAFETY REVIEW**

IND: 103,738

Sponsor: Antares Pharma Inc.

Drug: Methotrexate (Mini-needle Injection Device, Vibex™ MTX)

Drug Category: Antimetabolite

Indication: Rheumatoid Arthritis

Review Completion Date: 1/4/2010

Introduction

IND 103, 738 was submitted on 12/08/2010. The drug product, Methotrexate (MTX), is an antimetabolite that interferes with folate utilization and has been approved for use by the oral, intramuscular (IM), intravenous (IV), intra-arterial, or intrathecal routes of administration for the treatment of a number of diseases; including rheumatoid arthritis, severe psoriasis, and certain neoplastic diseases. It has been in use since 1959 and therefore, has a long history of clinical use. The pharmacology, pharmacokinetics, and toxicity of MTX are well known.

Antares Pharma proposes a subcutaneous (SC) route of administration using a pre-filled mini-needle injection device for self-administration of the drug in adult rheumatoid arthritis patients. They propose a three-way crossover bioequivalence study in adult subjects with rheumatoid arthritis to compare a currently approved MTX product (Bedford Laboratories) injected intramuscularly to MTX injection administered subcutaneously using a needle and syringe as well as using the Vibex™ MTX device.

No nonclinical data were submitted with this IND, except for a non-GLP cross-over PK study of MTX SC injection in minipigs. Information regarding potential toxicities was extracted from the label of an approved MTX product (Hospira's MTX label approved on 1/27/2004) and is based primarily on available clinical data. Major toxicities include bone marrow, liver, lung, and kidney toxicities. In addition, it has the potential to cause malignant lymphomas, embryotoxicity, abortion, and fetal defects in humans. Evaluation of local tissue tolerance in a sub-acute nonclinical study is planned by the sponsor in a single appropriate species for extrapolating human risk concerning local tissue tolerance. However, no timeframe was provided by the sponsor for submission of this study.

A pre-submission package was submitted on 1/6/2009 to the former Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP). A pre-IND meeting was held between DAARP and the sponsor on February 5, 2009. A nonclinical question by the sponsor and DAARP's response are provided below on page 2. Upon organizational changes within Office of New Drugs (OND) in March of 2010, the IND was reassigned to the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP).

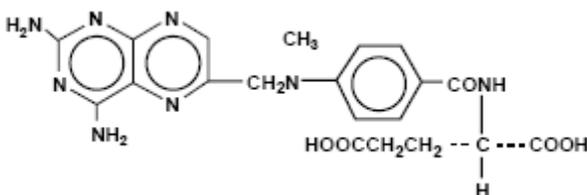
pIND nonclinical question

Question 4. Does the Agency concur that existing oral and parenteral methotrexate labeling and published data are sufficient to satisfy all nonclinical requirements for the registration of this novel dosage form of methotrexate?

FDA Response:

No. There is no information provided to indicate the quality of the drug product and, in particular, the possible presence of leachables and extractables. If found, provide a toxicological evaluation of those substances identified as leachables and extractables to determine the safe level of exposure via the parenteral route. The approach for toxicological evaluation of the safety of extractables should be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen.

If adequate information is provided to ensure the quality of the drug product, data from human experience, along with nonclinical information which you will need to provide through appropriate reference to literature and/or the RLD, may be sufficient to allow initial clinical trials to commence. However, adequate nonclinical data has not been provided to support safety for registration of the drug product through the SC route. If early pharmacokinetic evaluation reveals significant differences in parameters from approved parenteral routes such as IM, additional evaluation of systemic and local toxicity with full histopathologic evaluation in a nonclinical model will be required. If meaningful differences in pharmacokinetic variables are not observed with the SC route compared to the IM route you, will need to provide an evaluation of local toxicity, including histopathologic evaluation. This study may be conducted in a single species if an adequate scientific justification can be provided which establishes the appropriateness of the model for extrapolating human risk. As clinical use allows for rotation of injection site, a sub-acute nonclinical study would be acceptable for registration (i.e. weekly for 1 month at the same location).

MTX Structure

Chemically: L-(+)-N-[p-[(2,4-diamino-6-pteridiny)methyl]methylamino]-benzoyl] glutamic acid

Drug Formulations

Unit composition for MTX 10 mg injection

Ingredients	Function of Components	Label Concentration	Content per syringe (0.4 mL fill)
Methotrexate, USP	Active Pharmaceutical Ingredient	(b) (4)	10 mg
Sodium Chloride, NF	(b) (4)	(b) (4)	1.96 mg
Sodium Hydroxide, NF	pH adjustor	(b) (4)	q.s.
Water for Injection, USP	(b) (4)	(b) (4)	q.s.

Unit composition for MTX 15 mg injection

Ingredients	Function of Components	Label Concentration	Content per syringe (0.4 mL fill)
Methotrexate, USP	Active Pharmaceutical Ingredient	(b) (4)	15 mg
Sodium Chloride, NF	(b) (4)	(b) (4)	1.6 mg
Sodium Hydroxide, NF	pH adjustor	q.s.	q.s.
Water for Injection, USP	(b) (4)	q.s.	q.s.

Unit composition for MTX 20 mg injection

Ingredients	Function of Components	Label Concentration	Content per syringe (0.4 mL fill)
Methotrexate, USP	Active Pharmaceutical Ingredient	(b) (4)	20mg
Sodium Chloride, NF	(b) (4)	(b) (4)	1.28 mg
Sodium Hydroxide, NF	pH adjustor	q.s.	q.s.
Water for Injection, USP	(b) (4)	q.s.	q.s.

Unit composition for MTX 25 mg injection

Ingredients	Function of Components	Label Concentration	Content per syringe (0.4 mL fill)
Methotrexate, USP	Active Pharmaceutical Ingredient	(b) (4)	25 mg
Sodium Chloride, NF	(b) (4)	(b) (4)	0.56 mg
Sodium Hydroxide, NF	pH adjustor	(b) (4)	q.s.
Water for Injection, USP	(b) (4)	(b) (4)	q.s.

The sponsor will provide reference IM and SC products as MTX sodium for injection for single use only. Investigational MTX product will be supplied in a single-dose vial. There are no novel excipients in the drug product. No new impurities or degradants of concern have been identified by the Quality reviewer as of the date of this review.

Clinical Protocol (MTX-10-001)

The proposed clinical study is a Phase 2, open-label, randomized, 3-way crossover study to compare the exposure, safety, and local tolerance of a SC injection of MTX using the Vibex™ MTX device with the SC injection (anterior abdomen wall) of MTX without the device and with the IM administration (outer leg) of MTX in adult (F/M >18 years old) subjects with rheumatoid arthritis currently receiving MTX doses of 10 mg to 25 mg per week. Women of child-bearing potential may be included only if highly effective contraception is in place and subjects are fully aware of the information relating to the potential for reproductive toxicity as detailed in the Informed Consent Form.

Four different dose groups will be studied: 10 mg, 15 mg, 20 mg, and 25 mg. Subjects will be allocated to one of the four dose groups as determined by the clinical investigator. Subjects will then receive one of the three treatments (MTX SC with Vibex™ device, MTX SC without Vibex™ device, or MTX IM) randomly during three treatment periods separated by a 1-week washout period. Blood samples will be collected for PK evaluation in each of the treatment periods. In addition, safety will be evaluated by physical examination, including examination of the injection site, vital signs assessments, routine clinical laboratory tests (e.g. blood chemistry, hematology, coagulation, and urinalysis), and adverse event assessments.

Previous Clinical Experience

MTX is widely used in the clinical setting for the treatment of rheumatoid arthritis (including Polyarticular-Course Juvenile Rheumatoid Arthritis), psoriasis, and neoplastic diseases. It is currently approved for use by the oral, intramuscular (IM), intravenous (IV), intra-arterial, or intrathecal routes of administration. The following dosing regimens were summarized from Hospira's 2004 label: for neoplastic diseases, MTX is administered via oral, IM, IV, or intrathecal (meningeal leukemia) routes at doses up to 30 mg/day or up to 50 mg/week. For RA, MTX is administered orally at weekly doses up to 10 mg/m². For psoriasis, MTX is administered via oral, IM, or IV routes at doses up to 25 mg/week.

Several clinical studies have been conducted using SC MTX (refer to table below reproduced from sponsor's submission). The MTX formulation used in the listed studies is not the sponsor's formulation.

Type	Objective(s)	Study Design	Test product, Dosage, Administration	N	Healthy vs. Patients	Duration	Status/ Report
BA	Comparison of SC vs IV, and SC vs p.o.	Cross over	7.5 mg/m ² twice/wk; 40 mg/m ² weekly	12	Children with acute lymphoblastic leukemia	1x/wk for 40 mg/m ² ; 2x/wk for 7.5 g/m ²	publication
BA	Comparison of IM vs SC	Randomized, cross over	12.5 – 25 mg	5	Severe RA patients	1x/wk	publication
BA	Comparison of oral solution vs oral tablet, and SC vs IM	Randomized, 3-period, cross over followed by a 4 th	7.5 – 17.5 mg	12	Stable RA patients	1x/wk	publication

		period(SC)					
BA	Comparison of oral tablet vs SC	Randomized, 3-period cross over	12.5 – 25 mg	10	Stable Crohn's disease patients	1x/wk	publication
BA	Comparison of oral tablet vs SC	Randomized, 2-period cross over	25 – 40 mg	15	Stable RA patients	1x/2 wk interval	publication
BA	PK following oral tablet and/or SC	Single or sequential administration	6.1 – 28.6 mg/m ²	17	Children with juvenile idiopathic arthritis	1x/wk	publication
BA	Compare MTX concentration after IM and SC	Sequential, repeat-dose	7.5 – 25 mg	8	Patients with rheumatic conditions	1x/wk for 13 weeks	publication

N = # of subjects; BA = bioavailability; SC = subcutaneous; IV = intravenous; p.o. = oral route; IM = intra-muscular

Pharmacology of Drug

MTX is an antimetabolite that 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, MTX interferes with DNA synthesis, repair, and cellular replication. Actively proliferating tissues (e.g. malignant cells, bone marrow, fetal cells) are in general more sensitive to MTX. However, the mechanism of action of MTX in rheumatoid arthritis remains unknown. It has been suggested that it may affect immune function (Hospira's approved label).

ADME: oral absorption appears to be dose-dependent. Peak serum levels are reached within 1-2 hours. At doses of ≤ 30 mg/m², MTX is generally well absorbed with a mean bioavailability of $\sim 60\%$. Absorption of doses > 80 mg/m² is significantly less, possibly due to saturation. Food has been shown to delay MTX absorption and reduce peak concentration. After IM administration, peak serum concentrations occur in 30 – 60 minutes.

After IV administration, the initial volume of distribution is ~ 0.18 L/kg (or 18% BW) and steady-state volume of distribution is ~ 0.4 - 0.8 L/kg (or 40-80% BW). MTX in serum is approximately 50% protein bound. It competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process.

MTX undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to MTX by hydrolase enzymes. Polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. MTX is partially metabolized by intestinal flora after oral administration.

Terminal half life of MTX is approximately 3 – 10 hours for patients receiving low-dose MTX (less than 30 mg/m²). For patients receiving high doses of MTX, terminal half life is 8 – 15 hours.

Renal excretion is the primary route of elimination of MTX and is dependent upon dosage and route of administration. It occurs by glomerular filtration and active tubular secretion. Clearance rates vary widely and are generally decreased at higher doses.

Summary of Nonclinical Information

The toxicological profile of MTX is well known and is described in the package insert of the reference product from Bedford Laboratories as well as in Hospira's approved label. MTX has the potential to cause fetal death and/or congenital anomalies, renal toxicity, hematologic toxicity (bone marrow suppression and aplastic anemia), hepatotoxicity (fibrosis and cirrhosis), lung disease (acute or chronic interstitial pneumonitis), GI toxicity (diarrhea and ulcerative stomatitis that may lead to hemorrhagic enteritis and death from intestinal perforation), malignant lymphomas, tumor lysis syndrome, skin toxicity (including fatal dermatologic reactions), immunologic toxicity (including infections), and neurologic toxicity.

MTX has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that MTX 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 MTX. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral MTX, which have regressed completely following withdrawal of MTX, without requiring anti-lymphoma treatment.

Local tissue tolerance of MTX SC administration has been evaluated in a limited number of nonclinical studies. Perrotez *et. al.*¹ evaluated tissue effects of MTX injected into the uterine horn of pregnant female rats. No significant findings were observed at the injection site. In addition, the sponsor submitted a non-GLP PK study of SC MTX in minipigs (study no. LNE00001). This study consisted of two phases; one to evaluate PK of 12.5 mg/day SC MTX injected using an autoinjector vs. needle/syringe. Phase two consisted of evaluation of the SC injection site (by dermal observations) with MTX vs. saline injected using the autoinjector. Erythema was observed at the injection site when using the autoinjector with either MTX or control (saline). PK parameters were comparable when injecting MTX subcutaneously using the autoinjector or the syringe. In addition, Balis, *et. al.*² conducted a PK study of SC MTX in Rhesus monkeys. They compared PK of SC, IV, and oral MTX administration. They found that MTX exposure (AUC) was higher in animals treated with SC MTX compared to oral MTX. However, exposure was comparable when MTX was injected IV vs. SC. They found no evidence of local toxicity at the injection site.

Although SC injection of MTX in animals has not been extensively studied, the toxicity profile of the drug is well established and available clinical data support the use of the SC route. No additional nonclinical pharmacology or pharmacokinetic studies are planned by the sponsor. However, evaluation of local tissue tolerance in a sub-acute (1-month repeat dose) nonclinical study is planned in a single appropriate species for extrapolating human risk concerning local tissue tolerance. No specific timeframe was provided by the sponsor for submission of this study. In addition, if in the proposed clinical trial clinical PK data following SC administration results in a clinically significant increased exposure to MTX compared to currently approved delivery routes, the sponsor proposes to conduct a full scale evaluation of systemic and local toxicity with full histopathologic evaluation in a nonclinical model of repeat SC administration.

¹ Perrotez C, Gébauer C, Ménard A, Guyard B, Michaud P, Madelenat P, and Feldmann G. *Tissue effects of methotrexate injected into the uterine horn of pregnant female rats*. Human Reproduction Vol. 6, No. 4, pp. 480-483, 1991.

² Balis FM, Mirro J, Reaman GH, Evans WE, McCully C, Doherty KM, Murphy RF, Jeffries S, and Poplack DG. *Pharmacokinetics of Subcutaneous Methotrexate*. Journal of Clinical Oncology, Vol. 6, No. 12, pp. 1882-1886, 1988.

Recommendation: Based on available published literature and clinical data, the proposed clinical protocol appears reasonably safe to proceed from a nonclinical perspective.

Nonhold nonclinical comments to be conveyed to the sponsor:

We have completed our preliminary nonclinical review of your IND 103,738 submitted on December 8, 2010 and have the following request for information:

In your submission you state that you will be conducting a nonclinical local tissue tolerance study to support your clinical studies using the subcutaneous route of administration. Please provide the time frame you plan to complete and submit this study to your IND.

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/s/

CAROL M RIVERA-LOPEZ
01/04/2011

MOLLY E TOPPER
01/04/2011

Appendix 2: Dr. Carol Rivera-Lopez, nonclinical review, IND 103,738, June 10, 2011

**DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS (DPARP)
PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION**

IND: 103,738

Sponsor: Antares Pharma Inc.

Drug: Methotrexate (Mini-needle Injection Device, Vibex™ MTX)

Drug Category: Antimetabolite

Indication: Rheumatoid Arthritis

Type C meeting

Antares Pharma submitted a Type C meeting package on 3/17/2011 to discuss design of their proposed in vivo subcutaneous (SC) local tolerance study (4-week toxicity study in dogs) for IND 103,738. The package included three nonclinical questions. Responses were provided to the sponsor in a communication dated 5/16/2011. Subsequently, Antares Pharma emailed Sadaf Nabavian, Project Manager, to request further clarification to our response to nonclinical question #2. The sponsor's request for clarification and a brief discussion follows:

Nonclinical Question #2

Does the Agency agree that the selected species and doses are appropriate for extrapolating human risk?

Agency Response: We agree that your selected species appears appropriate. However, we recommend that you include at least one higher dose group to allow for a safety factor to be determined for local tolerance. Additionally, we suggest that histopathological assessment of local injection site tissues in your proposed study include draining lymph nodes.

Sponsor's email:

"Reference is made to the Study Design and questions provided in the Type C Meeting Request Briefing Package provided as part of IND 103,738, SN0002 submitted March 17, 2011.

I am reaching out to you today seeking advice regarding the best approach to obtain additional clarification on one of the Division's responses. In particular, our team is seeking further clarification in relation to the response to Question #2. In this response, the Division indicates: *"However, we recommend that you include at least one higher dose group to allow for a safety factor to be determined for local tolerance."*

It is Antares' understanding that the proposed high dose of Methotrexate, 25 mg, to be used in the *In-vivo* Local Tolerance Study (4-week toxicity study in dogs) would satisfy the Division's recommendation. In particular, this 25 mg dose of Methotrexate results in a safety factor of more than 8-fold when comparing the human exposure on a weight basis since a dog's weight is approximately 8 kg and the average human weight is 70 kg. Hence, Antares believes the proposed high dose of 25 mg will result in an appropriate safety factor being achieved. Please provide your feedback and inform us if the Division agrees with Antares' aforementioned position.

Antares would appreciate the Division's feedback to gain the necessary clarification on this subject in order to permit finalization of the associated protocol or further evaluation of study design options."

Internal Comments: The reviewer considered the sponsor's argument for excluding a higher SC dose in their local tolerance study. In consideration of their argument, the reviewer considered the extensive previous human experience with methotrexate and its well characterized toxicity profile using various routes of administration. Additionally, the sponsor has proposed a thorough local toxicity assessment at a methotrexate dose that mimics what will be used clinically. Therefore, the previous recommendation to the sponsor to use an increased methotrexate SC dose is retracted.

Comments to the Sponsor:

We have considered your argument to exclude a higher methotrexate subcutaneous dose in your 4-week local tolerance dog study. We concur that no additional, higher methotrexate subcutaneous dose is necessary.

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/s/

CAROL M RIVERA-LOPEZ
06/10/2011

MOLLY E TOPPER
06/10/2011
I concur.

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

/s/

ANDREW C GOODWIN
08/30/2013

TIMOTHY W ROBISON
08/30/2013
I concur

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

PHARMACOLOGY/TOXICOLOGY NDA CHEMISTRY CONSULTATION

Application number: NDA 204,824
Supporting document/s: EDR #1
Sponsor's letter date: December 14, 2012
CDER stamp date: December 14, 2012
Product: OTREXUP (methotrexate)
Indication: Rheumatoid arthritis (including juvenile
rheumatoid arthritis (b)(4));
moderate to severe psoriasis
Sponsor: Antares Pharma Inc.
Review Division: Division of Pulmonary, Allergy, and
Rheumatology Products (DPARP)
Reviewer: Andrew Goodwin, PhD
Team Leader: Timothy Robison, PhD, DABT
Division Director: Badrul Chowdhury, MD, PhD
Project Manager: Sadaf Nabavian

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1 Executive Summary

1.1 Introduction

Antares Pharma submitted 505(b)(2) NDA 204,824 on December 14, 2012 for the use of OTREXUP (methotrexate) for the indications of rheumatoid arthritis (including juvenile rheumatoid arthritis (b)(4)) and moderate to severe psoriasis. The NDA was filed on February 26, 2013 as a standard review with a PDFUA goal date of October 14, 2013.

On January 28, 2013, a consult request was received by Dr. Timothy Robison (DPARP) from Dr. Youbang Liu (ONDQA/Division III) with a desired completion date of May 14, 2013. The consult request was as follows: "Please evaluate the tox report for leachables and extractables in Section P.2. in this NDA." Additional email communication during the review process occurred between the Reviewer and Dr. Arthur Shaw, Chemistry Reviewer for NDA 204824

OTREXUP is a single-use drug/device combination product consisting of a methotrexate pre-filled syringe (PFS) and an autoinjector device ("Medi-Jet") intended to achieve sub-cutaneous delivery of the drug. The Sponsor submitted controlled extraction studies of the syringe, needle shield, and plunger stopper. In addition, controlled extraction, leachables, and stability studies were performed with aged methotrexate and control drug product.

This consult report will provide our evaluation of the nonclinical safety profile of extractable and leachable compounds identified for OTREXUP. An overall assessment of impurities and degradants

1.2 Brief Discussion of Nonclinical Findings

Controlled extraction, leachables, and stability studies conducted using the autoinjector and methotrexate drug product components were evaluated to determine the identity of, and patient exposure levels to, potential leachables in OTREXUP. This review specifically addresses seven organic compounds and three metals:



Safety evaluation of two methotrexate-related degradation products ((b) (4)) identified in the long-term stability studies is also provided.

Based on the potential patient exposure levels and a review of available information the safety of each of these potential leachables, extractables, impurities, and degradants in OTREXUP is considered qualified from the nonclinical perspective.

2 Drug Information

2.1 Drug

CAS Registry Number: 59-05-2

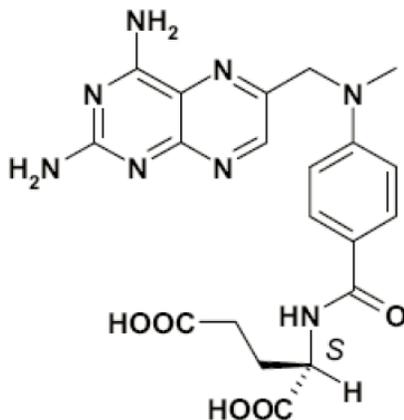
Generic Name: methotrexate

Proposed Trade Name: OTREXUP

Chemical Name: [N-[4-[(2,4-diamino-6-pteridiny)methyl]methylamino]benzoyl]-L-(+)-glutamic acid

Molecular Formula/Molecular Weight: C₂₀H₂₂N₈O₅ (MW 454. (b) (4) g/mol)

Structure or Biochemical Description



Pharmacologic Class: Folate analog metabolic inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 103,738 (Antares Pharma; methotrexate)

MF
MF
MF
MF

(b) (4)

2.3 Drug Formulation

Table 1. OTREXUP (methotrexate) formulation

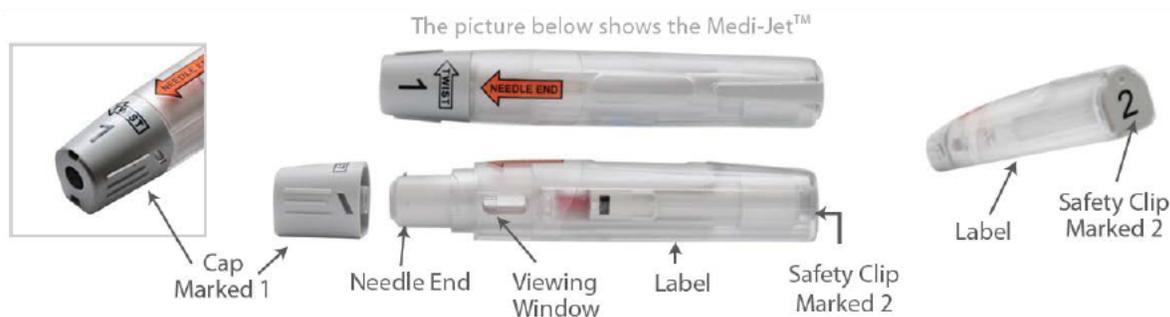
Ingredient	Content in mg/mL				Content in mg/ unit dose (0.4 mL)			
	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Methotrexate, USP.	(b) (4)	(b) (4)	(b) (4)	(b) (4)	10	15	20	25
Sodium Chloride, NF/Ph. Eur.	(b) (4)	(b) (4)	(b) (4)	(b) (4)	1.96	1.60	1.28	0.56
Sodium Hydroxide, NF, Ph. Eur.	X ²	X	X	X	X	X	X	X
Hydrochloric Acid, NF/Ph. Eur.	X	X	X	X	X	X	X	X
Water for Injection, USP/Ph. Eur.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

² X - As required to adjust pH

(b) (4)

The Sponsor seeks approval for a drug/device combination product that delivers a subcutaneous administration of methotrexate. The Medi-Jet autoinjector is a single-use device pre-filled with sterile, preservative-free methotrexate. A fixed volume of 0.4 mL is delivered via a 27-gauge, 1/2 inch needle containing doses of 10, 15, 20, or 25 mg.

Figure 1. Antares Pharma Medi-Jet Device



2.4 Comments on Novel Excipients

There are no novel excipients in OTREXUP.

2.5 Comments on Impurities/Degradants of Concern

This consult review evaluates the safety of leachables and extractables in OTREXUP MEDI-JET. The Sponsor's methods, assays, and conclusions as to potential leachables of concern are summarized in this section. The nonclinical safety evaluation of these

and select other compounds is evaluated below in the ***Integrated Summary and Safety Evaluation*** below.

Methods: Extractables and Leachables

The following samples were supplied to the testing laboratory by (b) (4) on behalf of the Sponsor:

- Syringes (broken apart for extraction studies): Lot #6101799615
- Needle Shield: Lot #6101799615
- Plunger Stopper: (b) (4)
- Methotrexate aged drug product (Lot #000123 manufactured July 2010).

The Sponsor submitted studies with the aim of identifying potential “worst-case” extractable compounds as well as actual leachables in aged methotrexate drug product via the following assays and experimental conditions:

- Device components (syringe, stopper, and needle shield) were extracted for 24 hours at room temperature in 1) pH 7.0 buffer; 2) pH 9.0 buffer; and 3) isopropanol, a strong organic solvent. Extracts were then analyzed for volatile and non-volatile extractables by direct injection GC/MS and LC/UV/MS.
- Device components were evaluated for water-soluble and water-insoluble volatile extractables following a 24-hour incubation at 80°C sealed in headspace vials followed by direct analysis by GC/MS.
- Device components were evaluated for metal extractables via a 24-hour, 80°C extraction with 0.1N nitric acid followed by analysis by ICP/MS.
- Device components were evaluated for (b) (4) via extraction with toluene followed by analysis by GFAA.
- Aged methotrexate drug product was evaluated by HS/GC/MS, GC/MS, LC/UV/MS, ICP/MS, and GFAA to determine leachables in the drug product.

All peaks and metal levels greater than (b) (4), as well as consistently noted peaks (b) (4) were reported. All aged drug product peaks (b) (4) signal: noise (and metal level (b) (4)) were reported. The predicted patient daily exposure (ug/day) was calculated in the report by summing the levels detected in each component (using the higher of the values for the two alternate stoppers for analysis).

Results: Leachables

True leachables were considered by the Sponsor to be peaks that were 1) detected in the methotrexate but not the control drug product; and 2) could be correlated to compounds identified in the extractables study. Validated methods for compounds of interest were developed in order to quantify compounds of interest in formal drug product stability studies. Target leachables identified in aged methotrexate drug product in (b) (4) study #040725-01-01 are summarized in the table below.

Table 2. Potential OTREXUP Target Leachables Identified by the Sponsor

Compound	CAS	Method	Amount (ug/syringe)
	(b) (4)	Headspace GC/MS	(b) (4)
		Direct injection GC/MS	
		Headspace GC/MS	
		Direct injection GC/MS	
		LC/UV/MS	
		Direct injection GC/MS	
		Direct injection GC/MS	
		Direct injection GC/MS	
		ICP/MS	
		ICP/MS	
		ICP/MS	

An additional peak was observed in the LC/UV/MS analysis but was not detected by the mass spectrometer and was therefore not structurally identified. Based on the observed level of 0.04 ug/syringe, there is no safety concern or need for further study of this unidentified compound. In addition, no leachable (b) (4) was detected by GFAA analysis in the aged drug product. The Sponsor determined to not further consider (b) (4) as target leachables due to the fact that they are "common ingredients in food and drug products and the level are low in the aged drug product."

Results: Extractables

As noted above, each of the target leachables listed above was also detected in the controlled extraction studies. The Sponsor also analyzed other identified extractables for inclusion as target leachables. (b) (4)

(b) (4) were added to the target leachables list by the Sponsor. The total daily intake (TDI) for each of the proposed target leachables in the controlled extraction studies are summarized in the table below.

Table 3. Levels of Potential Target Leachables in Controlled Extraction Study

Compound	CAS	Amount (ug/day)
(b) (4)		

Methods: Stability

The Sponsor proposes a (b) (4) month shelf-life for OTREXUP product. 18-month (lots 00174, 00175, 00177, and 00179) and 24-month (lots 00123, 00124, 00132, and 00133) stability data (25°C/60%RH) was provided for one lot at each proposed dose strength (10, 15, 20, 25 mg) as summarized in the table below.

Table 4. OTREXUP Stability Study Design

Sample Name	Lot Number	Dose/Strength	Manufacturer	Manufacture Date	Stability Start Date	Packaging Information
Vibex (Methotrexate) Pre-Filled Syringe	000123	0.4 mL (25 mg/mL)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	000124	0.4 mL (50 mg/mL)				1 mL long glass PFS w/ ½” 27g staked needle and (b) (4)
	000132	0.4 mL (37.5 mg/mL)				(b) (4)
	000133	0.4 mL (62.5 mg/mL)				(b) (4)
	000174	0.4 mL (25 mg/mL)				(b) (4)
	000175	0.4 mL (25 mg/mL)				(b) (4)
	000177	0.4 mL (62.5 mg/mL)				(b) (4)
	000179	0.4 mL (62.5 mg/mL)				(b) (4)

Levels of the target leachables listed above were measured in these aged drug product batches by GC/FID, except for (b) (4) which was measured by ICP/MS.

Results: Stability

Detection and quantification results for the target leachables in aged drug product are summarized in the table below. The reporting limit for the test method was (b) (4) ug/syringe. The highest level detected for each compound is highlighted in **bold** font and this value will be used for safety evaluation. The Sponsor did not establish individual stability specifications for any of these compounds due to levels detected being below the TTC of 1.5 ug/day (per Chemist Dr. Arthur Shaw).

Table 5. Leachable Levels in Aged Methotrexate Drug Product Stability Study

Duration	18 months				24 months			
Lot	00123	00124	00132	00133	00174	00175	00177	00179
Compound	Amount (ug/syringe)							
(b) (4)								

<RL: Below reporting limit of (b) (4) ug/syringe
 ND: not detected

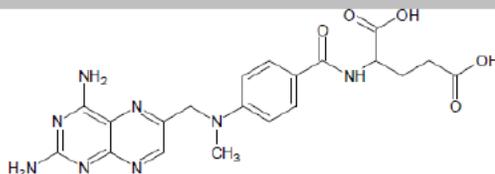
(b) (4) is the key degradant formed in methotrexate drug products, including OTREXUP. It differs in structure vs. methotrexate and folic acid by a single structural group (see figure).

Figure 2. Structural Similarity of (b) (4) Methotrexate, and Folic Acid

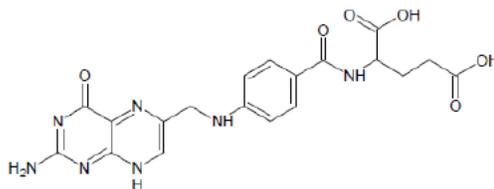
Chemical Structures of



b) Methotrexate
(CAS RN 59-05-2)



c) Folic acid
(CAS RN 59-30-3)



During OTREXUP stability studies, (b) (4) (also referred to as Impurity (b) (4)) levels in the drug product increased over time from (b) (4) % at initial testing to a high of (b) (4) % after 24 months at 25°C/65%RH or 12 months at 30°C/65%RH (see table below). The Sponsor proposes a release specification of (b) (4) % and a (b) (4) month shelf-life specification of (b) (4) %. A second drug product-related degradant, (b) (4) was found at (b) (4) % at initial testing and increased to no more than (b) (4) % after 24 month on stability testing.

Table 6. Formation of (b) (4) Degradant in OTREXUP Drug Product

Storage Condition	Time/ Months	(b) (4) Impurity (b) (4)							
		Proposed Shelf-Life Acceptance Criteria: (b) (4) %							
		000123 ¹ 10mg/0.4mL	000174 ² 10mg/0.4mL	000175 ² 10 mg/0.4mL	000132 ¹ 15mg/0.4mL	000124 ¹ 20mg/0.4mL	000133 ¹ 25mg/0.4mL	000177 ² 25mg/0.4mL	000179 ² 25mg/0.4mL
Initial	0	(b) (4)							
25°C/60%RH	1								
	3								
	6								
	9								
	12								
	18								
24									
30°C/65%RH	1								
	3								
	6								
	9								
	12								

¹ Stability data for combination product (PFS assembled with the auto-sampler)

² Stability data for PFS

Finally it is noted that the maximum stability specification limit for unknown impurities (including theoretical leachables not included among the target compounds), was (b) (4) %. A single unknown degradation product (b) (4) with a level greater than (b) (4) % was detected. Levels of this unknown impurity increased from (b) (4) % at initial testing to a maximum of (b) (4) % after 24 months at 25°C/65%RH and (b) (4) % after 12 months at 30°C/65%RH (see table below).

Table 7. Levels of Unknown Impurity (b) (4) in OTREXUP Stability Studies

Storage Condition	Time/ Months	Unknown Impurity (b) (4)																																																																																															
		Proposed Shelf-Life Acceptance Criteria: (b) (4)%																																																																																															
		000123 ¹ 10 mg/0.4 mL	000174 ² 10 mg/0.4 mL	000175 ² 10 mg/0.4 mL	000132 ¹ 15 mg/0.4 mL	000124 ¹ 20 mg/0.4 mL	000133 ¹ 25 mg/0.4 mL	000177 ² 25 mg/0.4 mL	000179 ² 25 mg/0.4 mL																																																																																								
Initial	0	(b) (4)																																																																																															
25°C/60%RH	1									(b) (4)																																																																																							
	3																	(b) (4)																																																																															
	6																									(b) (4)																																																																							
	9																																	(b) (4)																																																															
	12																																									(b) (4)																																																							
	18																																																	(b) (4)																																															
24	(b) (4)																																																																																																
30°C/65%RH																																																										1	(b) (4)																																						
																																																										3									(b) (4)																														
																																																										6																	(b) (4)																						
																																																										9																									(b) (4)														
																																																										12																																	(b) (4)						

3 Studies Submitted

3.1 Studies Reviewed

- Non-Clinical Toxicology Review of the Methotrexate Degradation Product (b) (4) on behalf of Sponsor. Report date 28 June, 2011.
- Report for the Controlled Extraction Study of Pre-filled Syringe Components and Leachables Evaluation of Methotrexate Aged Drug Product. Project #040725-01-01. (b) (4)
- Determination of Target Leachables Compounds for Leachables Method Development and Validation. Project #040725-01-01, Report Date 28 September 2012. (b) (4)
- Cumulative Stability Test Results for Vibex (Methotrexate) Pre-filled Syringes. Project #044338-01-01, Amended Report Date 8 November, 2012. (b) (4)
- Toxicological Evaluation of Extractables of Pre-filled Syringe Components for Methotrexate Drug Product. (b) (4). Report Date 1 October 2012.

3.3 Previous Reviews Referenced

IND 103,738 Pre-IND Meeting (Face-to-face meeting February 5, 2009; minutes filed to DARRTS 3/5/2009)

The Nonclinical response (Dr. Adam Wasserman, Pharmacology/Toxicology Supervisor, Division of Anesthesia, Analgesia, and Rheumatology products) contained the following comment related to the subject of this consult review: *“There is no information provided to indicate the quality of the drug product and, in particular, the possible presence of leachables and extractables. If found, provide a toxicological*

evaluation of those substances identified as leachables and extractables to determine the safe level of exposure via the parenteral route. The approach for toxicological evaluation of the safety of extractables should be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen.” No further discussion occurred at the meeting with the Sponsor.

11 Integrated Summary and Safety Evaluation

This review evaluates the safety of leachables and extractables in OTREXUP based on data submitted by the Sponsor and other available information. The Sponsor is seeking approval for once weekly administration of the product at doses of 10, 15, 20, or 25 mg methotrexate delivered sub-cutaneously via the autoinjector device in a 0.4 mL volume. All discussion of safety qualification of leachables levels (generally ug/day of potential patient exposure) in this review will not adjust for the fact that these dose levels are only expected to be administered one day per week. This conservative approach provides a margin of safety above and beyond the calculations presented below.

In general, any compound with expected patient exposure of less than 1.5 ug/day (the safety concern threshold, SCT) was considered qualified for safety regardless of the available nonclinical data. A qualification threshold of $(b) (4)$ ug was applied for compounds lacking genotoxic potential. Further discussion of qualification and/or additional threshold levels for selected leachables is presented below.

Organic Leachables

As shown in Table 5 above, the Sponsor identified seven target organic leachables compounds for evaluation in OTREXUP drug product. Four of these $(b) (4)$ were never detected at a level greater than $(b) (4)$ /syringe. As exposure to these compounds is less than the 1.5 ug/day SCT, there is no safety concern.

$(b) (4)$ has been assigned an oral reference dose (RfD) of $(b) (4)$ /day by the U.S. Environmental Protection Agency (EPA), indicating that adverse health risks are unlikely below that level. The RfD was based on body weight loss in a chronic rat study $(b) (4)$ with a NOAEL of $(b) (4)$ day. No conclusion about the carcinogenicity of the compound has been made. In 18-24 month stability studies, $(b) (4)$ was detected at a maximum level of $(b) (4)$ /syringe. This exposure level is $(b) (4)$ -fold lower than the oral RfD (based on 60 kg body weight) and is also below the 1.5 ug/day SCT. The safety of $(b) (4)$ is considered qualified.

$(b) (4)$ has been assigned an oral RfD of $(b) (4)$ day by the EPA based on stomach and kidney lesions in a sub-chronic rat toxicology study $(b) (4)$ with a NOEL of $(b) (4)$ /day. $(b) (4)$ is negative in bacterial reverse mutation assays but positive in chromosomal aberration

and mouse lymphoma genotoxicity assays. NTP two-year carcinogenicity studies detected increased forestomach hyperplasia and squamous cell papillomas in mice but not rats at (b) (4)/day. (b) (4) was detected as a leachable at a maximum of (b) (4)/syringe in stability studies with aged drug product. This exposure level is (b) (4) lower than the oral RfD (based on 60 kg body weight) and is also below the 1.5 ug/day SCT. The safety of (b) (4) is considered qualified.

(b) (4) does not have an assigned RfD or any other governmental exposure level recommendation. According to the (b) (4) published by (b) (4), animal toxicology data has been reported including acute inhalation in rat (LD₅₀ (b) (4) after 4 hours), acute dermal toxicity in rat (LD₅₀ > (b) (4)), and repeat-dose oral toxicity in rat (NOAEL (b) (4); duration of study not reported). (b) (4) is negative for mutagenicity in a bacterial reverse mutation assay. In stability studies with aged drug product, the Sponsor reported a maximum exposure of (b) (4) syringe. This exposure level is (b) (4) lower than the rat oral NOAEL and is also below the 1.5 ug/day SCT. The safety of (b) (4) is considered qualified.

Metals Leachables

A variety of nonclinical data and human exposure recommendations are available for (b) (4), though the focus has often been on the inhalation route of exposure and many studies did not utilize the metallic form of (b) (4). Occupational guidelines have been established by NIOSH (recommended exposure limit of 5 mg/m³) and OSHA (permissible exposure limit of 1-5 mg/m³). Using the most conservative (b) (4) limit and adjusting for air intake ((b) (4)) and worker body weight (70 kg) yields a level of (b) (4)/day. An adjustment factor of (b) (4)-fold was then applied to account for differences in exposure frequency and health status of workers vs. patients, along with calculation based on the standard 60 kg representative patient body weight yields an applicable limit for (b) (4) of (b) (4)/day (inhalation route). While (b) (4) is not specifically discussed in the European "Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents," application of a conservative Class 1C designation for (b) (4) as a "metal of significant safety concern" yields a similar (b) (4) day threshold for parenteral administration. (b) (4) was identified as a target leachable by the Sponsor and results of the stability studies indicate a potential patient exposure of up to (b) (4) syringe. This level is (b) (4) lower than the parenteral guideline and (b) (4) lower than the inhalation guideline referenced above. In terms of nonclinical studies in rats, the (b) (4)/day exposure level provides a margin of well over (b) (4) (b) (4) or intraperitoneal (b) (4) administration of metallic (b) (4); and an (b) (4) margin over a carcinogenic dose ((b) (4) intramuscular dose of (b) (4)). The safety of (b) (4) as a leachable in the drug product is considered qualified.

Two other metals, (b) (4), were observed at levels of (b) (4)/syringe in controlled extraction studies but were not selected as target leachables by the Sponsor. According to the Institute of Medicine, the daily adequate intake of (b) (4) is (b) (4) grams, the average dietary intake in the U.S. population is (b) (4) grams, and

clinical studies involving dietary supplementation have utilized up to (b) (4) grams per day without resulting in plasma concentrations outside of the normal range of (b) (4). A tolerable upper limit was not established because excess (and the bulk of typical dietary intake) (b) (4) is generally excreted in the urine. While data based on the parenteral route of administration is lacking, the safety of (b) (4) is considered qualified on the basis of (b) (4) safety margins compared to known, safe oral human consumption levels.

According to the Agency for Toxic Substances and Disease Registry (ATSDR, U.S. Department of Health and Human Services, Public Health Service), daily dietary intake of (b) (4) is in the range of 6-7 mg per day in U.S. adults but consumption of up to 40 mg occurs with the use of antacids and similar drugs. Animal toxicology studies have identified the nervous system as the most sensitive target of (b) (4) toxicity and a minimum risk level of 1 mg/kg/day for chronic oral exposure was established. While data based on the parenteral route of administration is lacking, the safety of (b) (4) is considered qualified based on safety margins of 30 to 200-fold vs. human oral consumption and 300-fold vs. the oral minimum risk level as determined by ATSDR.

Methotrexate-related Degradants

As summarized above, two degradation products of methotrexate were identified in the OTREXUP stability studies. (b) (4) was detected as levels no greater than (b) (4) % (corresponding to (b) (4) /day at the 25 mg dose). The (b) (4) levels are below the ICH Q3A and Q3B qualification thresholds for impurities/degradants and therefore no further safety qualification is required.

(b) (4) is a well-established degradation product in methotrexate injection formulations. The Sponsor proposes a (b) (4) % stability specification, equivalent to a maximum exposure of (b) (4) /day at the 25 mg dose, which is above the ICH qualification threshold of 1.0%. While there is little formal nonclinical safety evaluation of (b) (4), the following factors were considered to evaluate support for patient exposure to (b) (4) per injection:

- (b) (4) is structurally very similar to methotrexate and shares (b) (4) pharmacological activity. Current methotrexate product labels contain a boxed warning regarding the risk of multiple potential serious adverse effects that is only justified in patients with severe disease.
- The (b) (4) % specification level for (b) (4) has been deemed acceptable in an FDA-approved product (ANDA 40632, methotrexate lyophilized powder for injection solution, Bedford Laboratories) according to Chemistry review Dr. Arthur Shaw.
- Several studies found that marketed methotrexate preparations contained an average of about (b) (4) % (b) (4), with individual values as high as (b) (4) %.
- Parenteral acute toxicity studies in the mouse suggest that (b) (4) (lowest reported lethal dose of (b) (4) /kg) may be less toxic than either methotrexate (b) (4) unspecified parenteral route) or (b) (4). The potential patient exposure of (b) (4)

(b) (4)/day (b) (4) represents a (b) (4)-fold safety margin to the LD₁₀ reported above.

- Methotrexate is administered at significantly higher doses in cancer indications, and (b) (4) itself has been described as a cancer therapy administered daily via the parenteral route at a dose of 2 mg. These factors were raised in the NDA by the Sponsor, but are not considered relevant to the safety assessment for the proposed OTREXUP patient populations.

Using a weight of evidence approach and considering the factors described above, there does not appear to be nonclinical safety concern for the potential (b) (4)/day exposure to (b) (4) in patients receiving methotrexate via the OTREXUP autoinjector product. The (b) (4)% stability specification for (b) (4) is considered qualified.

Unknown Leachables

A single unknown impurity (b) (4) was detected at a level of up to (b) (4)% in aged methotrexate drug product. This could potentially represent an unknown leachable, including the various compounds identified in the controlled extraction studies. Based on the highest proposed dose of 25 mg, the potential exposure to unknown (b) (4) would be (b) (4) syringe. This level is about the (b) (4) day threshold, but is below the ICH Q3B(R2) identification threshold of 0.2% (50 ug for a 25 mg dose) and therefore no further structural determination or safety evaluation is necessary. All other unknown impurities were detected at levels no higher than (b) (4)%, which is below the Q3A and Q3B identification thresholds. Taken together, there is no nonclinical safety concern for as-yet unidentified leachables in the OTREXUP drug product based on the available 18-24 month stability study results.

Conclusion

In conclusion, there are no nonclinical concerns related to the safety qualification of impurities, leachables and extractables in OTREXUP.

12 References

(b) (4)

“Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products.” Product Quality Research Institute. August 2006.

“Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents.” Committee for Medicinal Products for Human Use, European Medicines Agency, February 2008.

“Draft Guidance for Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches.” December 2008.

“Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.” International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH]. Step 2 version, February 2013.

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/s/

ANDREW C GOODWIN
05/14/2013

TIMOTHY W ROBISON
05/14/2013
I concur

PHARMACOLOGY/TOXICOLOGY NDA FILING CHECKLIST

NDA/BLA Number: 204824 Applicant: Antares Pharma Stamp Date: 12/14/2012

Drug Name: OTREXUP NDA 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		The applicant is relying upon approved, reference listed drugs (methotrexate for injection and methotrexate tablets) as well as published scientific literature for the PharmTox. The PharmTox information is summarized in Module 2 as written and tabulated summaries. Module 4 only contains the reference publications. No new studies were conducted.
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		No nonclinical studies were required or submitted. Literature references were submitted.
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).			Not applicable. See Comment in #1.
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?			Not applicable. See Comment in #1.
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?			Not applicable. See Comment in #1.

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

PHARMACOLOGY/TOXICOLOGY NDA FILING CHECKLIST

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable, no studies were requested.
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		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		The PharmTox Reviewer will consult with the CMC Reviewer regarding impurity issues.
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.

Andrew C. Goodwin, PhD
 Reviewing Pharmacologist

25 January 2013
 Date

Timothy W. Robison, PhD, DABT
 Team Leader/Supervisor

25 January 2013
 Date

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

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/s/

ANDREW C GOODWIN
01/25/2013

TIMOTHY W ROBISON
01/27/2013
I concur