# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204824Orig1s000

# STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/ Serial Number:** 204824

**Drug Name:** Otrexup (methotrexate auto-injector)

**Indication(s):** Rheumatoid arthritis and polyarticular juvenile idiopathic arthritis

**Applicant:** Antares Pharma

**Date(s):** Received: 12-14-2012; PDUFA: 10-14-2013

**Review Priority:** S

**Biometrics Division:** Division of Biometrics 2

**Statistical Reviewer:** Joan Buenconsejo, PhD

**Medical Division:** Division of Pulmonary, Allergy and Rheumatology Products

**Clinical Team:** Peter Starke, MD

**Project Manager:** Sadaf Nabavian

**Keywords:** 505b2

# 1. EXECUTIVE SUMMARY

This is a 505(b)(2) new drug application submitted by Antares Pharma, Inc. for Methotrexate (MTX) Injection, a drug/device combination consisting of a single-use, prefilled auto-injector intended for subcutaneous (SC) administration. The application references three applications for methotrexate: NDA 11-719 for Methotrexate Injection EQ 50 mg base/2mL from Hospira, ANDA 40-632 for Methotrexate Preservative-Free Injection from Bedford, and NDA 08-085 for Methotrexate Tablets from Dava Pharmaceuticals. The proposed Trade Name for the product is Otrexup. The proposed product will be supplied in doses of 10 to 25 mg in 5 mg increments.

MTX is currently indicated for the treatment of neoplastic diseases, severe psoriasis, rheumatoid arthritis (RA), and polyarticularcourse juvenile rheumatoid arthritis (JRA), which is now called polyarticular juvenile idiopathic arthritis or pJIA. In this application, the applicant's proposed indications for this product are limited to RA, pJIA, and psoriasis, and do not include treatment of neoplastic diseases.

No clinical trials were performed to support this application. Support for approval of this application is based on:

1. The Agency's previous findings of the safety and effectiveness of methotrexate in patients with RA, JRA (pJIA), and psoriasis, including Agency's previous findings of the safety and effectiveness of SC administration in patients with JRA.
2. A BA study (and MTX-11-003) in adults that supports efficacy with SC administration in patients with RA and psoriasis because it showed equal or greater bioavailability of the proposed MTX auto-injector product administered SC when compared to systemic exposure with orally administered MTX tablets.
3. Literature reviews that support the safety and efficacy of SC administration of methotrexate for these conditions and for the age groups for which they are currently approved. The literature supports SC administration as an alternative to oral or IM administration of MTX, with higher systemic exposure and improvements in efficacy when administered SC or IM vs orally at similar doses, particularly when the doses are above 15 mg. The safety review of the literature and of the studies provided to this application did not reveal any new safety signals that would require additional labeling beyond those already labeled in the reference products.
4. A BE study (MTX-10-001) in adults that showed bioequivalence between this autoinjector product administered SC in either the abdomen or the thigh and the approved injectable product administered with a needle and syringe either by the SC or IM route.
5. An actual use labeling study and a labeling and human factors study.

Please refer to Dr. Sheetal Agarwals's review and Dr. Peter Starke's review regarding the adequacy of the program.

Because the current submission includes no trials assessing clinical efficacy, Biometrics has no comments.

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JOAN K BUENCONSEJO
09/12/2013

# STATISTICAL REVIEW AND EVALUATION

**Biometrics Division: VI**

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| **NDA NO.:** | 204-824 |
| **SERIAL NO.:** | S000 |
| **DATE RECEIVED BY THE CENTER:** | June 6, 2013 |
| **DRUG NAME:** | Otrexup™ (methotrexate) |
| **DOSAGE FORM:** | Injection |
| **INDICATION:** | For the treatment of rheumatoid arthritis including polyarticular-course juvenile rheumatoid arthritis, and moderate to severe psoriasis. |
| **SPONSOR:** | Antares Pharma, Inc. |
| **DOCUMENTS REVIEWED:** | June 6, 2013 |
| **NAME OF STATISTICAL REVIEWER:** | Meiyu Shen, Ph.D. (HFD-705) |
| **NAME OF CHEMISTRY REVIEWER:** | Arthur Shaw, Ph.D. |

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Meiyu Shen, PhD, Mathematical Statistician

Concur: _____

Yi Tsong, Ph.D.
Deputy Director, DBVI

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# 1 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

## 1.1 Introduction and Background

The sponsor revised the proposed shelf-life from (b) (4) months for all four strengths to (b) (4) months for the 10, 15, and 20 mg/0.4 mL doses and (b) (4) months for the 25 mg/0.4 mL dose using the available data in Table 1.

Table 1 Available stability Data

| Strength (mg/0.4 mL) | Batch number | Data available (month) |
|---|---|---|
| 10 | 000123 | (b) (4) |
| | 000174 | |
| | 000175 | |
| 15 | 000132 | |
| 20 | 000124 | |
| 25 | 000133 | |
| | 000177 | |
| | 000179 | |

## 1.2 Data Analyzed and Sources

The sponsor submitted the data in electronic format on June 6, 2013. The data are located in the EDR.

## 1.3 Stability Study

The assay data of Assay (ASSAY), (b) (4), Total Impurity other than (b) (4) (TOTAL_I), and other characteristics were submitted under $25^0$C/60% RH condition in SAS xpt format.

## 1.4 The purpose of this statistical review

The office of new drug quality evaluation (ONDQA) requested the CMC statistical team to evaluate the following parameters for shelf-life estimation: Assay, (b) (4), and Total Imp other than (b) (4) (TOTAL_I).

## 1.5 Sponsor's Analysis, Results and Conclusions

The sponsor performed statistical analyses for Assay, (b) (4) and pH using ANCOVA model to estimate the shelf life with the following specifications in Table 2 and results from the sponsor's statistical analyses are listed in Table 3.

Table 2 The sponsor's proposed specification and actually used specification

| Parameter | Proposed specification limits | Actually used specification limits by the sponsor |
|---|---|---|
| Assay (b) (4) | (b) (4) | |
| pH | 7.0~9.5 | 7.0~9.55 |

Table 3 Sponsor's statistical analyses' results

| Parameter | Actually used Criteria Acceptance | Predicted Shelf-Life (months) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 10 mg/0.4 mL | | | 15 mg/0.4 mL | 20 mg/0.4 mL | 25 mg/0.4 mL | | |
| | | 000123 | 000174 | 000175 | 000132 | 000124 | 000133 | 000177 | 000179 |
| Assay (b) (4) | (b) (4) | | | | | | | | |
| pH | 7.0~9.55 | 65 (pooled) | | | 79 | 72 | 69 | 62 | 59 |
| Lowest | | | | | | | | | (b) (4) |

## 1.6 Reviewers' Analysis, Results and Conclusions

Referring to Table 2, we found that the sponsor used the upper limits which were actually larger than the proposed specification limits. Hence the sponsor over-estimated the shelf-life by using larger than the proposed specification limits.

This reviewer used the proposed specification and rerun the statistical analyses for Assay, (b) (4), and Total Imp other than (b) (4) (TOTAL_I). The reviwer's statistical analyses are listed in Table 4.

Table 4 Shelf-life estimation based on the proposed specification limits

| Parameter | Proposed Criteria Acceptance | Predicted Shelf-Life (months) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 10 mg/0.4 mL | | | 15 mg/0.4 mL | 20 mg/0.4 mL | 25 mg/0.4 mL | | |
| | | 000123 | 000174 | 000175 | 000132 | 000124 | 000133 | 000177 | 000179 |
| Assay (b) (4) | (b) (4) | | | | | | | | |
| Lowest | | | | | | | | | (b) (4) |

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## 1.7 Conclusions and Recommendation

Based on these analyses and evaluations of Assay, [redacted] and Total Imp other than [redacted] (TOTAL_I), the product of 10 mg/0.4 mL is expected to remain within specifications through [redacted] months, the product of 15 mg/0.4 mL is expected to remain within specifications through [redacted] months, the product of 20 mg/0.4 mL is expected to remain within specifications through [redacted] months, and the product of 25 mg/0.4 mL is expected to remain within specifications through [redacted] months (see Figures 1-4).

The sponsor's revised shelf-life [redacted] months for the 10, 15, and 20 mg/0.4 mL doses and [redacted] months for the 25 mg/0.4 mL dose are not acceptable because the sponsor used actual specification limits larger than the proposed specification limits.

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MEIYU SHEN
06/25/2013

YI TSONG
06/26/2013