CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204824Orig2s000

SUMMARY REVIEW

Summary Review for Regulatory Action
Division of Dermatology and Dental Products

Date	(electronic stamp)
From	Tatiana Oussova, Deputy Division Director for Safety Division of Dermatology and Dental Products (DDDP)
Subject	Summary Review
NDA/BLA # **Supplement #**	20-4824 Original 2
Applicant Name	Antares Pharma Inc.
Date of Submission	December 14, 2012
PDUFA Goal Date	October 14, 2013
Proprietary Name / **Established (USAN) Name**	Otrexup (methotrexate) injection
Dosage Forms / Strength	10 mg/0.4 mL autoinjector, 15 mg/0.4 mL autoinjector, 20 mg/0.4 mL autoinjector, and 25 mg/0.4 mL autoinjector
Proposed Indication(s)	1. Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis 2. Moderate to Severe Psoriasis
Action/Recommended Action for NME:	*Approval without revision to psoriasis indication*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Snezana Trajkovic, M.D. (DDDP) Peter Starke, M.D. (DPARP)
Statistical Review	Kathleen Fritsch, Ph.D.
Pharmacology Toxicology Review	Andrew C. Goodwin, Ph.D.
CMC Review/OBP Review	Arthur B. Shaw, Ph.D.
Microbiology Review	n/a
Clinical Pharmacology Review	Sheetal Agarwal, Ph.D
DDMAC	n/a
DSI	n/a
CDTL Review	Sarah Yim, M.D. (DPARP)
OSE/DMEPA	n/a
OSE/DDRE	n/a
OSE/DRISK	n/a
Other	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

This is a new drug application (NDA) for a drug/device combination product Otrexup (methotrexate) injection seeking an approval under Section 505 (b)(2) of the Federal Food, Drug and Cosmetic Act for the subcutaneous route of administration. This drug-device combination product consists of an injectable methotrexate (MTX) formulation in a single use prefilled autoinjector intended for subcutaneous administration only. The applicant proposed four strengths: 10 mg, 15 mg, 20 mg, and 25 mg, each in a fixed volume of 0.4 mL. No MTX autoinjectors have been approved in the US.

In addition, the applicant proposed to expand the currently approved indication of severe psoriasis to include treatment of patients with moderate to severe psoriasis. Expanding this indication means to include patients with less severe form of disease.

This NDA was submitted to the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) and then administratively split to: "Original 1" to be reviewed by DPARP and "Original 2" to be reviewed by Division of Dermatology and Dental Products (DDDP). This review focuses on the proposed extension to psoriasis indication.

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2. Background

Methotrexate is currently approved in different dosage forms, including tablets and injections for intramuscular (IM), intravenous (IV), subcutaneous (SC), intra-arterial (IA), and intrathecal (IT) administration. Currently approved indications and routes of administration include neoplastic diseases (oral, intramuscular, intravenous, intra-articular, and intra-thecal routes), rheumatoid arthritis (oral route), polyarticular course juvenile rheumatoid arthritis (oral, intramuscular, subcutaneous routes), and severe psoriasis (oral, intramuscular, intravenous routes). In this NDA, the applicant is seeking approval of the product for the subcutaneous (SC) route of administration for the rheumatoid arthritis (RA) and psoriasis indications, as well as the polyarticular juvenile arthritis indication which is already approved for subcutaneous administration in other parenteral MTX labels. Since this is a 505(b)(2) application, the applicant conducted two bioavailability/ bioequivalence (BA/BE) studies establishing a clinical bridge to previously approved products. The applicant has shown that Otrexup, when administered subcutaneously, is bioequivalent to the Listed Drugs (LD) administered subcutaneously or intramuscularly. It has equal or higher bioavailability compared to orally administered product.

Currently marketed methotrexate products were approved for the following psoriasis indication: "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."

In support of an extension to the currently approved indication to include treatment of patients with moderate to severe psoriasis, the applicant submitted published reports of studies in patients with moderate to severe psoriasis. These data has been determined during review cycle to be inadequate to justify the extension of psoriasis indication to include patients with less severe form of disease.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

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

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

No new clinical studies have been submitted in support of an extended psoriasis indication. The 505(b)(2) pathway allows an applicant to rely on published literature for specific information to which the applicant does not have a right of reference. The applicant submitted published reports of studies conducted in a population of patients with moderate to severe psoriasis. The adequacy of those published studies was assessed in clinical and statistical reviews by Drs. S. Trajkovic and K. Fritsch. Of note, none of the studies evaluated the efficacy or safety of subcutaneously administered methotrexate. I agree with both reviewers conclusion that the published studies did not provide adequate evidence of methotrexate efficacy in patients with moderate to severe psoriasis. However, despite the lack of adequate and well controlled studies evaluating the efficacy of methotrexate in patients with moderate to severe psoriasis, it would be reasonable to assume that the efficacy of MTX in this patient population would not be much different from its efficacy in patient with more severe forms of psoriasis. The major concern here is not MTX efficaciousness but whether or not its benefits outweigh its risks in a population of patients with moderate to severe psoriasis, as will be discussed in the next section.

8. Safety

To support safety of Otrexup in the treatment of patients with moderate to severe psoriasis the applicant submitted published literature. None of the literature reports submitted by the applicant contain the underlying data that would allow to adequately and independently assess MTX safety.
However, even if the applicant were able to obtain the underlying data for the submitted literature reports, none of the studies appear to have a design that would allow for assessment of whether subcutaneous injection of Otrexup is safe and effective in the expanded patient population of moderate to severe psoriasis.
I concur with the conclusion made by clinical and statistical reviewers that determination whether the benefit of Otrexup therapy outweighs the risks in subjects with moderate to severe psoriasis cannot be made.
There are multiple efficacious therapies available on the market today for the population of patients with moderate to severe psoriasis. Given considerable risks associated with treatment with methotrexate as reflected in its currently approved label, including potential life-threatening adverse events, the clinical benefit for patients with moderate to severe psoriasis do not outweigh its risks and expanding the indication to patients with moderate to severe psoriasis as proposed by the applicant cannot be justified.

9. Advisory Committee Meeting

Current application does not present novel issues which would warrant advisory committee input.

10. Pediatrics

The applicant has asked for a waiver of studies in children 0 to 17 years because the product does not present a meaningful therapeutic benefit over the available already marketed products. The waiver request was discussed with PeRC and given potential safety concerns associated with the use of methotrexate (as reflected in approved labels for currently marketed MTX products) the risks outweigh benefits and therefore the full waiver of studies in pediatric population with psoriasis will be granted.
The label will state that safety and efficacy has not been established in children with psoriasis.

11. Other Relevant Regulatory Issues

There are no unresolved relevant regulatory issues

12. Labeling

There are no unresolved labeling issues.
There are no substantial changes in the labeling relevant to psoriasis indication.

13. Decision/Action/Risk Benefit Assessment

- I recommended an Approval action without changes to psoriasis indication.

- Risk Benefit Assessment

The risk benefit assessment is found to be similar to the approved products. No additional safety concerns have been identified.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

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/s/

TATIANA OUSSOVA
10/10/2013