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RESEARCH**

APPLICATION NUMBER:

204824Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Drug/Device Product Risk Management Review

Date: September 3, 2013; *Revised September 26, 2013*

Reviewer: Carolyn L. Yancey, M.D., Senior Medical Officer, Division of Risk Management (DRISK)

Team Leader: Kendra Worthy, Pharm. D., DRISK

Division Director: Claudia Manzo, Pharm. D., DRISK

Drug Name: OTREXUP (methotrexate) Injectable, Single-Use, Disposable Pre-filled Syringe Auto-Injector (Medi-Jet) Delivery Device

Therapeutic Class: Folate Analog Metabolic Inhibitor

Indication(s): For the treatment of adults with rheumatoid arthritis (RA), polyarticular juvenile rheumatoid arthritis (P-JRA) in pediatric patients 2 years of age and older, and severe, recalcitrant psoriasis not adequately responsive to other forms of therapy.

Dosage Forms and Route: Pre-Filled Syringe with 10 mg, 15 mg, 20 mg or 25 mg /0.4 mL methotrexate via subcutaneous (SC) administration with an auto-injector

Application Type/Number: NDA 204-824/Supplement 01/Sequence 01 and 012

Applicant: Antares Pharma, Inc.

PDUFA Goal Date: October 14, 2013; Action Date on October 11, 2013

OSE RCM #: 2013-284

TSI: Not Applicable

1 INTRODUCTION

This Division of Risk Management (DRISK) review evaluates the New Drug application for Otrexup (methotrexate, MTX) a novel injectable MTX product including a pre-filled syringe, auto-injector delivery device, and Antares Pharma's Risk Management Plan to assess the need for a Risk Evaluation and Mitigation Strategy (REMS). Otrexup is proposed for the treatment of adults with rheumatoid arthritis (RA), the treatment of pediatric patients with polyarticular juvenile rheumatoid arthritis (p-JRA) and the treatment of adults with severe psoriasis. This is a 505(b)(2) new drug application (NDA) 204-824 for MTX single-use, disposable, Medi-Jet PFS with an auto-injector device delivery system, intended for subcutaneous (SC) administration. Injection, a drug-device combination consisting of a Sentence was not complete No redactions were applied

This NDA was received by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) on December 14, 2012 and was administratively split to assign review of the proposed drug/device for RA and p-JRA indications to DPARP and to assign review of the proposed revision to the approved psoriasis indication (including the proposed drug/device) to DDDP.

2 BACKGROUND

Methotrexate is a folate analog metabolic inhibitor approved for the treatment of neoplastic diseases; severe, recalcitrant psoriasis, RA, and p-JRA. The proposed drug/device product is intended as a formulation for the convenience of self or caregiver use in non-clinical settings (e.g., at home). The applicant's proposed indications for Otrexup are limited to RA, p-JRA, and severe psoriasis and do not include the approved indications for the treatment of neoplastic diseases.

As noted by the applicant, "Antares ... originally... developed Otrexup (b) (4), a preservative-free MTX injection contained in a PFS system that is then assembled with a pressure assisted, auto-injection medical device for SC administration of a fixed-volume of 0.4 mL yielding the final delivered doses of MTX sodium equivalent to 10 mg, 15 mg, 20 mg or 25 mg MTX." The product is bioequivalent to parenteral MTX administered as intramuscular (IM) or SC routes. The recommended starting dose for the proposed indications is 10 mg (b) (4) given SC once weekly.

Higher doses of MTX are required for the treatment of neoplastic diseases than for the other approved indications. The route of administration of currently marketed MTX for neoplastic diseases is oral, IM, intravenous (IV), intrathecal (IT), and intra-arterial (IA). The proposed product, Otrexup, can only be administered SC and does not provide adequate MTX dosing for neoplastic diseases.

Approved Methotrexate Products

There are numerous approved generic MTX products on the current US market for both the oral and parenteral formulations. *See the website www.Drugs@FDA for a comprehensive listing of approved MTX products.* Currently, no approved MTX formulation on the US market has a REMS program or Medication Guide. Antares does not have other MTX products.

Administrative Split of NDA 204-824 for Otrexup (methotrexate) PFS, Auto-Injector

In the original submission of NDA 204-824 (dated December 14, 2012), the applicant proposed to revise the approved indication for psoriasis from “symptomatic control of severe recalcitrant, disabling psoriasis” to be “moderate to severe psoriasis.” This proposed revision to the approved psoriasis indication requires a risk benefit assessment and is not addressed in the risk benefit for the use of MTX by the SC administration using a PFS auto-injector in a home setting.

As stated in the Introduction of this review, the original NDA 204-824 was administratively split by the DPARP to assign review of the Otrexup (methotrexate) injectable, PFS auto-injector for SC administration in RA and p-JIA to the DPARP and to assign review of the proposed dermatologic revision to the approved psoriasis indication to the Division of Dermatology and Dental Products (DDDP).

Physician Labeling Rule and Methotrexate

Otrexup Injection, PFS Auto-Injector will be the first instance of labeling in the *Physicians Labeling Rule* (PLR) format for a MTX product. There will be differences between the labeling for Otrexup (methotrexate) Injection, PFS Auto-Injector from labeling of currently marketed originator and generic methotrexate products recognizing that there is not a specific advantage for use of proposed Otrexup (MTX) PFS auto-injector (Medi-Jet) delivery device over other products other than the convenience of a PFS auto-injector.¹

2.1 Regulatory History

The MTX oral tablet was first approved on December 7, 1953 for Dava Pharmaceuticals, Inc., NDA 08-085 for the treatment of acute leukemia in adults. In 1959, the Agency approved Hospira Pharmaceutical’s NDA 11-719 for MTX for the IM, IV, SC, IA, and IT routes of injection.

This 505(b)(2) NDA for Otrexup references two approved NDAs and one ANDA for MTX:

- Generic MTX Injection EQ 50 mg base/2 mL, approved under NDA 11-719, Hospira Pharmaceuticals, the referenced listed drug as the originator for generic MTX injectable products
- Bedford Pharmaceuticals. ANDA 40-632 approved on August 12, 2005, for MTX Sodium Preservative Free form
- Dava Pharmaceuticals Inc. NDA 08-085 for MTX Tablets approved December 7, 1953

• 2.2 Materials Reviewed

December 14, 2012: NDA 204-824/Suppl. 01 for MTX PFS/auto-injector proposed as a drug-device combination consisting of a single-use, PFS, auto-injector intended for SC administration for the treatment of RA, p-JRA, and severe psoriasis.

¹ Patient Labeling Review entitled, Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU) written by Sharon Williams, R.N., B.S. N., Division of Medical Policy Programs (DMPP)

June 7, 2013: Suppl. 01/Sequence 012, substantially complete proposed Otrexup labeling per the applicant.

July 23, 2013: Label, Labeling, Packaging, and Human Factors Study Review

September 5, 2013: Patient Labeling Review written by Sharon Williams, R.N., B.S.N., Division of Medical Policy Programs (DMPP)

3 Overview of Clinical Safety

Per the Clinical Review by Peter Starke, M. D. (dated August 19, 2013) ², this application does not include new clinical trial data in support of the proposed formulation and PFS auto-injector. This 505(b)(2) NDA for Otrexup is based on the following:

- The Agency’s previous findings of the safety and effectiveness of MTX in patients with RA, p-JRA, and severe psoriasis
- A bioavailability (BA) study (MTX -11-333) in adults that supported efficacy with SC administration in patients with RA and psoriasis that showed equal or greater bioavailability of the proposed MTX auto-injector product administered SC when compared to system exposure with orally administered MTX tablets.
- Literature reviews in support of the approved indications and populations for MTX. Safety review of the literature in this application did not demonstrate any new adverse events (AEs) or signals that require labeling changes beyond the current Warnings and Precautions in the labeling.
- A bioequivalent (BE) study (MTX-10-001) that demonstrated bioequivalence between this PFS auto-injector product, administered SC in either the abdomen or thigh, and the approved injectable product administered (with a needle and syringe) either SC or IM.

Clinical Safety on the proposed Otrexup (MTX) Injectable, PFS Auto-Injector

No clinical trials were performed to support this 505(b)(2) application for Otrexup. Support for approval of this application is based on post market data, the well characterized safety and efficacy of MTX in adult patients with RA, pediatric patients with p-JRA and psoriasis, and the Agency’s findings on the safety and effectiveness of SC administration in P-JRA.

The safety review of the literature and of the studies provided in this application did not reveal any new safety signals that would require additional labeling beyond those risks in labeled reference products.

- Human Factor Study

In reference to the safety with the proposed Otrexup PFS auto-injector, the applicant submitted Study MTX -11-004 that claims to be a simulated-use, summative, usability testing for a Human Factor Study. This study was designed to “...evaluate whether the PFS auto-injector device could be used by representative users (e.g., patients, caregivers

² Clinical Review, NDA 204-824, MTX auto-Injector (Otrexup), Standard Review, written by Peter Starke, M. D., Senior Medical Officer, DPARP, (dated August 19, 2013)

and healthcare providers, such as nurses) under simulated conditions “without producing patterns of failures that could result in negative clinical impact to patients or injury to device users”¹

A Human Factor Study needs to test whether the proposed Otrexup Instructions for Use are adequate for non-coached patients to use this device in a non-clinical setting, e.g., at home. “However, in Study MTX-11-004, all the patients and caregivers received specific training in the use of the device, and the only participants who did not receive this training were the nurse practitioners. As a result, this study actually evaluated the entire training set and not specifically labeling comprehension of the instructions for use. That stated, with some reservations, the study appeared to show that the entire training set provides adequate instructions to allow appropriate use of the device.”¹

Division of Medication Error Prevention (DMEPA) Comments

The DMEPA review in regard to the safety concerns with self-administration of the proposed drug/device PFS auto-injector delivery device states that, “the Human Factor Study reports two (2) failures and 31 close-calls.”³ “The failures involve (1) the inability to deliver a complete injection as a result of the device being held at the injection site for less than one second and (2) the participant pointed the needle end of the device towards the hand. The applicant did not recommend any modifications to the IFU because the failures occurred due a test artifact and an uncooperative participant. However, we have concerns regarding these two failures for the following reasons and provide recommendations to the applicant to help mitigate these failures”³:

- “One participant was startled by the click at the start of the injection and removed the device prior to completion. The resettable demonstrator device used during training did not have an audible click. A commercial device which included an audible click was used for the remainder of the training to help mitigate this failure. Although there were no additional failures of this type reported as a result of using two different devices, one participant did not hold the device for the required 3 seconds per the IFU due to thinking the click meant to remove the device. The applicant did not consider this a failure because the dose is delivered within (b)(4) and the participant held for 1-2 seconds. The applicant also states the demonstrator device for market has a softer click than the commercial device. The training device and the commercial device should be the same in all aspects to help mitigate any confusion regarding the operation of the device.
- With respect to the second failure in which the needle end of the device was pointed towards the hand, the participant did not read the IFU and stated that her actions would not be equivalent to use in a “real world” scenario. The IFU contains a diagram which identifies the different parts of the device. However, there is no statement in the IFU which references this device and instructs the user that this is what the Otrexup device looks like.”³

³ Label, Labeling, Packing, and Human Factor Study Review (dated July 24, 2013) written by Teresa McMillan, Pharm. D., DMEP

Per the DMEPA reviewer, “The majority of the close calls observed with the critical tasks was consistent between all trained and untrained groups and consisted of the following:

- Held the device for 1 -2 seconds or less than 3 seconds (n = 11)
- Injected with inadequate force to fully retract the needle shield (n = 10)
- Confusion regarding the location and removal of the safety cap (n = 5)

As commented upon by the applicant in regards to close-call, the IFU includes instructions or diagrams for each close call noted and based on the participant’s responses the close calls may have occurred due to the user. Although no device misfires or incomplete injections were identified, we are particularly concerned with the number of close calls identified for the inadequate use of force and holding the device for 1-2 seconds.

Postmarketing experience with similar auto injectors has attributed inadequate force and not holding the device for the allotted time for administration as reasons for device misfires and incomplete injections. The testing device used in this study did not contain a needle or placebo solution.

Based on the above summarized information, the Human Factors Study confirmed that users may encounter difficulties while administering this product. Thus, DMEPA conclusions sent to the DPARP state, “that the proposed label and labeling can be improved to increase the prominence of important information on the label to promote the safe use of the product. We defer to the Center for Devices and Radiological Health to validate these aspects (delivery of the medication in (b)(4) and the amount of force needed to retract the needle shield) of the device design and they may have additional recommendations to help further optimize the device design.”

The DMEPA comments sent to the applicant follow: “Ensure that the training device and the commercial device operate the same in all aspects.” Per the Patient Labeling Review (dated September 5, 2013) ¹, the DMEPA and DMPP discussed the concerns with the Human Factor Study and DMEPA deferred to DMPP to provide IFU review comments. Comments from the DMPP on the PPI and the IFU that were communicated to the applicant follow:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information
- ensured that the PPI and IFU meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006) ¹

The DMPP concluded that “the PPI and the IFU are acceptable with our recommended changes.”

3.1 Clinical Safety

The serious AEs (SAEs) listed in the *Boxed Warning* and in the *Warnings and Precautions* section of the approved Methotrexate labeling are unchanged for this application. The contraindications for MTX include:

- Methotrexate has been reported to cause fetal death and/or congenital anomalies. There, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis or RA should not receive MTX. (See the Contraindications section of labeling).
- Alcoholic liver disease or other chronic liver disease patients should not receive MTX
- Patients with psoriasis or RA who have pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia, should not receive MTX
- Patients with known hypersensitivity to MTX should not receive MTX.

The well-characterized, potential SAEs risks associated with use of MTX follow:

5.1 Organ System Toxicity: Methotrexate has the potential for serious toxicity. Toxic effects may be related in frequency and severity to dose and frequency of administration but have been seen at all doses. Organ system toxicities have been observed with hematologic, hepatic, infection, vaccination and immunodeficiency, pulmonary, and skin. See the labeling sections *Box Warning*, *Warnings and Precautions*, and *Patient Counseling Information*.

5.2 Risk of Effects on Reproduction: Patients should be informed of the potential benefit and risk in the use of methotrexate. Fetal death and teratogenic effects are listed in the Box Warning for Methotrexate. Note that MTX is Pregnancy Category X product.

5.3 Laboratory Tests: Baseline assessment should include a complete blood count with differential and platelet count, hepatic enzymes, renal function tests and a chest X-ray.

5.4 Pneumonitis and Fibrotic Lung Disease: Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion, which may occur acutely or at any time during therapy and has been reported.

5.5 Intestinal Perforation: Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.

5.6 Opportunistic Infections: Potentially fatal opportunistic infections, especially Pneumocystis carinii pneumonia, may occur with methotrexate therapy.

3.2 Applicant's Proposed Risk Management Plan

The applicant submitted a position paper entitled, "REMS Requirement for Otrexup" that includes their rationale for why a REMS should not be required for Otrexup (b) (4) (dated September 7, 2012). This NDA 505(b)(2) submission does not include new clinical trials. See Section 3, subsection entitled, "*Clinical Safety with the proposed Otrexup (MTX) Injectable, PFS Auto-Injector*" for information obtained from the Human Factor Study for Otrexup.

Per the Medical Officer’s Clinical Review, the DPARP concluded that there are no recommendations for post market risk evaluation and mitigation strategies and no recommendations for post market requirements and commitments (see Sections 1.3 and 1.2, respectively, in the Clinical Review).¹

The SC route is not uncommon with other products, including therapeutic biologic products, indicated for the treatment of RA.

Rationale to not require a REMS for Otrexup

The applicant’s rationale is based on addressing factors that the Agency considers in determining whether a REMS should be required for a product.⁴

- Expected benefit of Otrexup with respect to the populations of approved indications

Summary of the Applicant’s Rationale:

The approved MTX indications are RA, p-JRA, severe psoriasis, and oncology indication. Otrexup is proposed as a practical, convenient solution that will enable these patients to self-inject MTX in situations in which use of an injectable form of MTX is advised by a physician.

The applicant states that, “Although physicians have expressed interest in using the injectable form of MTX more frequently, they are hesitant to do so because of practical reasons. These concerns are related to assuming that patients and their caregivers draw an accurate dose from vials and correctly administer the product by SC injection. The difficulties may be particularly evident in the proposed RA population due to diminished manual dexterity sometimes observed in RA patients.”

The applicant explains that “the bioavailability of MTX administered SC with Otrexup is less variable than that of the orally administered MTX and is bioequivalent to that of IM administration. Because exposure with SC administration is likely to be better than that of oral, in most cases, certain patients may see an improvement in disease symptoms, especially, if the oral form produced dose-limiting gastrointestinal (GI) toxicity.” In regard to the dosage form, SC, the applicant states that, “studies have shown that patients prefer to inject a low volume product rather than a higher injection volume.”

The applicant concludes, “Therefore, Otrexup would be a new option for patients who could benefit by converting from oral to injectable MTX, but for whom their physicians feel the current product options are not practical for self-injection.”

- Safety of Methotrexate and the position to not recommend a REMS

Summary of Applicant’s Rationale

“MTX has been marketed in the US for five (5) decades and the risks of MTX are well characterized and understood. None of the currently marketed MTX products have a REMS. The issues regarding safety of MTX and its side-effect profile are well understood and recommendations for safe administration and monitoring are well described in professional practice guidelines for rheumatologists and dermatologists.”

⁴ See NDA 204-824, Section 1.16 risk Management Plan, written by OptumInsight as a Position Paper for Antares Pharma (dated November 12, 2012)

The applicant “advocates against an additional REMS requirement for the Antares Otrexup product. Otrexup will only be indicated for RA, p-JRA, and psoriasis. Therefore, dose-related risks associated with oncology do not apply to Otrexup. Like other MTX products, Otrexup will be used under the supervision of a physician. The currently established routine monitoring of blood tests and follow-up physician visits recommended to patients taking oral MTX will be the same for those patients prescribed Otrexup.”

“... It may be appropriate to remind them (patients) of the adverse events associated with the compound.” The applicant explains that the proposed *Patient Package Insert* is written to inform patients of the risks associated with the drug. These warnings would be in addition to providing detailed instructions to the patient regarding the use of Otrexup (MTX)/PFS.” Additionally, the applicant developed *Instructions for Use (IFU)*.”

- Expected duration of treatment with Otrexup

Summary of the Applicant’s Response

Treatment with the proposed MTX/PFS product in the proposed patient populations may require short-term (several months) to long-term therapy (years). Clinical management decisions for therapy vary based on the patient’s diagnosis, disease severity and clinical response to dosage, route and duration of treatment. As explained by the applicant

- Estimated size of the population likely to use Otrexup

Summary of the Applicant’s Response:

The applicant did not provide data on the projected use for Otrexup. However, the applicant acknowledges that the projected uptake for Otrexup will likely be those patients who did not tolerate or benefit from one of the approved MTX formulations and routes of administration. This reviewer adds that it is not uncommon in rheumatology to see different clinical responses to different routes of administration of MTX in the same patient.

The applicant states, “It probably is not feasible to predict the uptake of Otrexup by the patient population, but it will likely remain a small minority of patients who use parenteral MTX. Thus, the majority of patients at risk for side-effects from MTX will be unaffected by any REMS the applicant could create.”

- Seriousness of the disease or condition that is to be treated by Otrexup

Summary of the Applicant’s Response:

- *Rheumatoid Arthritis*

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks flexible synovial joints. The pathology of the disease process often leads to the destruction of articular cartilage and ankylosis of the joints. Rheumatoid arthritis can also produce diffuse inflammation in the lungs, pericardium, pleura and sclera, and also nodular lesions, most common in subcutaneous tissue.” “About 1% of the world’s population is affected by RA, women three-time more often than men. The prevalence of RA is believed to range from 0.5 to 1.0% in the general population. In 2005, an estimated 1.5 million US adults aged ≥ 18 (0.6%) had

RA.⁵ It (RA) can be disabling and painful condition, which can lead to substantial loss of functioning and mobility if not adequately treated. Some people have mild short-term symptoms, but in most, the disease is progressive for life.

- *Juvenile Rheumatoid Arthritis*

“Juvenile rheumatoid arthritis (JRA)⁶ is the most common form of persistent arthritis in children. Juvenile Rheumatoid Arthritis (JRA) is a chronic disorder which if neglected can lead to serious complications. Children may become quite ill, presenting with flu-like symptoms that persist.

Polyarticular course JRA is defined as disease affecting five or more joints in the first 6 months of disease. This subtype usually affects symmetric joints, usually the smaller joint in the hands and feet although weight-bearing joints such as the hips, knees and ankles.” This reviewer adds that p-JRA may be severely disabling if not treated early and may evolve to be clinically similar to RA including erosions and disabling deformities.

- *Psoriasis*

The applicant explains that “Psoriasis is typically a lifelong condition. There is currently no cure but various treatments can help to control the symptoms. Individuals will often experience flares and remissions. Controlling the signs and symptoms typically requires life-long therapy.”

Use of Otrexup in These Diseases

The applicant explains, “For all patients with RA, treatment will be started on oral MTX, with the dose increasing until it reaches a level requiring parenteral therapy. At that point Otrexup may be introduced. Otrexup will not be the first line of treatment for RA patients. For patients with psoriasis, use of MTX will only occur in those whose disease cannot be managed in other less invasive ways.” The applicant concludes that, “these diseases are serious and Otrexup is used after other agents have not responded or are no longer responding to their current oral therapy.

Applicant’s Proposed Risk Mitigation for Otrexup

The applicant proposes to support risk mitigation for Otrexup by employing routine pharmacovigilance and risk minimization with systematic and regular review of aggregate safety data. This will include trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, pediatric and the elderly patients.

The applicant’s clinical safety database will contain information on AEs received from spontaneous sources, literature, regulatory agencies, and SAEs from post-marketing surveillance studies and clinical studies. Periodic safety issues will be identified from

⁵ Sacks JJ, Luo YH, Helmick CG. Prevalence of specific types of arthritis and other rheumatic conditions in the ambulatory health care system in the US, 2001-2005. *Arthritis Care Res (Hoboken)*. 2010 April 2 (4): 460-4.

⁶ Revised terminology is Juvenile Idiopathic Arthritis (JIA) and includes sub-type classification. Duffy CM, Colbert RA, Laxer RM, Schanberg LE, Boyer SL. Nomenclature and Classification in chronic Childhood Arthritis – Time for a Change?, 2005 *Arth & Rheum* , Vol 52:2, 382-385

individual case reviews, monthly summaries, signal detection with data mining activities, and Periodic Safety Update Reports (PSURs).

4 CONCLUSION

The DRISK and the DPARP are in agreement that Otrexup (methotrexate) injectable in a PFS does not require a REMS to ensure that the benefits outweigh the risks associated with use of this proposed drug. Methotrexate has a well characterized safety profile with over 50 years of post market experience. The DPARP and the DRISK do not recommend post market requirements or commitments. The DPARP should consult the DRISK if additional safety information is identified that warrants reevaluation of the current risk mitigation measures for methotrexate injectable, PFS.

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/s/

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09/27/2013

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concur