

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204824Orig2s000

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 / Original 2 / 000
Drug Name: Methotrexate injection for subcutaneous use
Indication(s): Psoriasis
Applicant: Antares
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1 Executive Summary

One component of this 505(b)(2) application for Otrexup (methotrexate) injection for subcutaneous use is a proposal to expand the psoriasis indication from “the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy” (the indication approved for other methotrexate products, including the listed drug) to “moderate to severe psoriasis.” To support this proposed labeling change the applicant has submitted literature reports of studies in moderate to severe psoriasis subjects that included a methotrexate arm. The applicant has not conducted any clinical studies evaluating Otrexup in the treatment of moderate to severe psoriasis.

Although 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, a statistical review of efficacy and safety information relies on being able to access and independently analyze the underlying data. New efficacy claims (such as an expanded indication) that can be reflected in labeling need to be supported by studies prospectively designed to evaluate the desired claims and have appropriate corresponding statistical analysis plans. Brief descriptions of a study design and tables of results from literature are not adequate for assessing the efficacy and safety of a product. In particular, to support expanding the indication of methotrexate to subjects with moderate psoriasis, information on the efficacy and safety in subjects with moderate psoriasis is needed to assess whether the benefit outweighs the risk for these subjects. None of the literature reports submitted by the applicant contain the underlying data or sufficient information about the study design to adequately and independently assess the results in support of an efficacy claim.

However, even if the applicant were able to obtain the underlying data for the submitted literature reports, none of the studies have a design that would allow for an adequate assessment of whether subcutaneous injection of Otrexup is safe and effective in the expanded patient population of “moderate to severe psoriasis.” None of the studies used subcutaneous injection of methotrexate. Most studies used the oral formulation of methotrexate with various starting and maximum doses. None of the studies were designed to demonstrate the efficacy of methotrexate. The single study that included a placebo arm did not have a pre-specified analysis comparing methotrexate to placebo. All other randomized, double-blind, controlled studies with a methotrexate monotherapy arm either failed to find a statistically significant difference between treatment arms or found that the other evaluated therapy was superior to methotrexate. None of the studies provided information on efficacy or safety on moderate subjects in particular.

To expand the indication for Otrexup to moderate to severe psoriasis, the applicant will need to submit data from studies that adequately demonstrate that the benefit of Otrexup outweighs the risk in subjects with moderate to severe psoriasis.

2 Introduction

2.1 Overview

Otrexup (methotrexate) injection for subcutaneous use, supplied with an auto-injector, has been developed for the indications of adult rheumatoid arthritis, polyarticular-course juvenile rheumatoid arthritis, and psoriasis. Methotrexate is currently available as an oral tablet and as an injection for either intramuscular or subcutaneous use. Otrexup has been submitted as a 505(b)(2) application with Hospira's methotrexate sodium injection (NDA 011719) as the listed drug. Otrexup is delivered by way of an auto-injector and the proposed strengths are 10, 15, 20, and 25 mg/0.4 mL as sterile preservative-free solution. Hospira's methotrexate sodium injection is available as liquid in vial either with preservative as 50 mg/2 mL or without preservative as 20 mg/2 mL, 500 mg/20 mL, 1 g/40 mL, and 2.5 g/100 mL strengths. NDA 204824 has been administratively split into two units with the Division of Pulmonary, Allergy, and Rheumatology Products reviewing the information related to rheumatoid arthritis (RA), and the Division of Dermatology and Dental Products reviewing the information related to psoriasis.

The psoriasis indication and dosage and administration information for Hospira's methotrexate sodium injection (labeling dated 11/1/2011), which are also identical to the information for methotrexate sodium tablets for oral use, are as follows:

INDICATIONS AND USAGE

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.

DOSAGE AND ADMINISTRATION

Psoriasis: Recommended Starting Dose Schedule

1. Weekly single oral, IM or IV dosage schedule: 10 to 25 mg per week until adequate response is achieved.[†]
2. Divided oral dose schedule 2.5 mg at 12 hour intervals for three doses.[†]

[†] Methotrexate Sodium Tablets for oral administration are available.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded.

Once optimal clinical response has been achieved, each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

The applicant is proposing the following Indications and Usage and Dosage and Administration sections related to psoriasis for Otrexup:

The applicant has proposed modifying the psoriasis indication from “the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy” to “moderate to severe psoriasis.” To support this change the applicant has submitted a literature review of published studies and treatment guidelines involving methotrexate to support their case for expanding the labeled indication to moderate to severe patients. The applicant has not conducted any studies with Otrexup in psoriasis subjects. This review with briefly summarize the available literature information and evaluate its utility in supporting the expanded indication.

2.2 Data Sources

This reviewer evaluated the applicant’s “White Paper” for psoriasis studies, the literature references referred to in the White Paper, and proposed labeling. This submission was submitted in eCTD format and was entirely electronic. The applicant did not conduct any clinical studies in psoriasis and no datasets were submitted.

Literature References

El Eishi N, Hegazy R, Abou Zeid O, Shaker O. Peroxisome Proliferator Receptor (PPAR) β/δ in psoriatic patients before and after two conventional therapeutic modalities: methotrexate and PUVA. *Eur J Dermatol* 2011; 21(5): 691-5.

Flytström I, Stenberg B, Svensson A, Bergbrant IM. Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. *Br J Dermatol*. 2008 Jan; 158(1):116-21.

Gottlieb AB, Langley RG, Strober BE, Papp KA, Klekotka P, Creamer K, Thompson EH, Hooper M, Kricorian G. *Br J Dermatol*. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. 2012 Sep;167(3):649-57

Heydendael VM et al, Methotrexate versus cyclosporine in moderate to-severe chronic plaque psoriasis. *N Engl J Med* 2003;349:658-65.

Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, Gottlieb AB, Koo JYM, Lebwohl M, Lim HW, Van Voorhees AS, Beutner KR, Bhushan R. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. *J Am Acad Dermatol* 2009; 61(3): 451-485.

Reich K, Langley RG, Papp KA, Ortonne JP, Unnebrink K, Kaul M, Valdes JM. A 52 week trial comparing briakinumab with methotrexate in patients with psoriasis. *N Engl J Med*. 2011 Oct 27; 365(17):1586-96.

Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, Unnebrink K, Kaul M, Camez A; CHAMPION Study Investigators. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol*. 2008 Mar; 158(3):558-66.

Yan H, Tang M, You Y, Yu J-B, Zhang J-A, Li X-H, Sun J-F, Jiang Y-Q, Guo Z-P, Xiong L, He W, Li Z, Gu J, Gao C-F, Guo Z-L, Gao T-W, Wang G, Li X-P, Li J, Hao F, Guo Y-J. Treatment of psoriasis with recombinant human LFA3-antibody fusion protein: a multi-center, randomized, double-blind trial in a Chinese population. *Eur J Dermatol* 2011; 21(5): 737-43

3 Statistical Evaluation

3.1 Data and Analysis Quality

No datasets were submitted for the literature studies submitted in support of the psoriasis indication.

3.2 Evaluation of Efficacy

The applicant has not conducted any clinical studies evaluating Otrexup in the treatment of psoriasis. The adequacy of the applicant's bridge to the Agency's findings of safety and efficacy for Hospira's methotrexate sodium injection is beyond the purview of this review. This review will only evaluate whether the applicant has submitted adequate information from the literature to support the expansion of the indication to "moderate to severe psoriasis" from "severe, recalcitrant, disabling psoriasis that is not adequately

responsive to other forms of therapy.” Although 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, a statistical review of efficacy and safety information relies on being able to access and independently analyze the underlying data. New efficacy claims that can be reflected in labeling need to be supported by studies prospectively designed to evaluate the desired claims and have appropriate corresponding statistical analysis plans. Most literature reports of clinical trials do not contain all of the underlying data or sufficient information about the study design to adequately and independently assess the results in support of an efficacy claim. The summaries and tables typically contained in a literature report are not sufficient to support an efficacy claim.

The applicant has identified from the literature five randomized, double-blind, controlled trials in psoriasis subjects that included methotrexate monotherapy as one of the treatment arms. The applicant identified one additional study that was randomized and double-blind, but evaluated methotrexate only in combination with another treatment (etanercept + methotrexate vs. etanercept monotherapy). All of the studies used the oral formulation of methotrexate; none of them used injectable formulations. Only one study included a placebo arm.

The study that included a placebo arm (Saurat et al, 2008) had the objective of demonstrating that adalimumab was superior to placebo and non-inferior to (or superior to) methotrexate. No analysis was pre-specified comparing methotrexate to placebo. Subjects randomized to the oral methotrexate arm received a starting dose of 7.5 mg/week with possible dose escalation up to 25 mg/week. Methotrexate subjects received 7.5 mg in Weeks 0 and 1, 10 mg in in Weeks 2 and 3, and 15 mg in Weeks 4-7. Starting at Week 8, subjects not achieving PASI 50 increased their dosage to 20 mg. Any subjects escalated to 20 mg who had achieved PASI 50 at Week 12 were escalated to 25 mg. Doses could be withheld or reduced for safety reasons.

The study enrolled adult subjects with moderate to severe psoriasis, defined as $\geq 10\%$ body surface area (BSA) involvement and PASI ≥ 10 . Subjects were to be candidates for systemic therapy or phototherapy and have active psoriasis despite topical treatment. The primary efficacy endpoint was PASI 75 at Week 16. The primary efficacy outcome results from the Saurat paper are presented in Table 1.

Table 1 – Primary Efficacy Results from Saurat, et al 2008

	Adalimumab N=108	Methotrexate N=110	Placebo N=53
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*Analysis not pre-specified

Saurat et al reported that methotrexate was superior to placebo, although they noted that the analysis was not pre-specified. The results of the Saurat paper were cited in an article entitled “Guidelines of care for the management of psoriasis and psoriatic arthritis:

Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents” (Menter, et al 2009) which summarized available evidence on the efficacy of methotrexate. In this article, the authors raised concerns about interpreting the methotrexate versus placebo comparison from the Saurat trial, noting “Furthermore, the placebo response rate of 19% is dramatically higher than is seen in a clinical trial of this type, raising doubt about the validity of the study.” Thus, members of a working group tasked with summarizing the available literature on the efficacy of methotrexate raised concerns about the utility of this study for supporting the efficacy of methotrexate in psoriasis.

Setting aside the concerns about the placebo response rate and the lack of pre-specification regarding the methotrexate versus placebo comparison, the literature report is not adequate for supporting the sponsor’s request to label Otrexup for moderate to severe psoriasis:

- The study used oral methotrexate rather than subcutaneous Otrexup, and it is not clear how the safety and efficacy observed in the study from the oral methotrexate dosing regimen would compare to the proposed regimen for Otrexup.
- The report did not provide information on the safety and efficacy among subjects with moderate psoriasis.
- The reports do not include any subject-level data for analysis.

Thus, although the Saurat study may provide some evidence that methotrexate might be superior to placebo, it does not provide evidence that the benefits for Otrexup in subjects with moderate psoriasis would outweigh the risks.

The remaining four randomized, double-blind, controlled studies identified by the applicant that included methotrexate as one of the treatment arms were all two-arm studies. All four studies enrolled subjects described by the authors as having moderate to severe psoriasis. None of the literature reports include subject-level data. Two studies compared methotrexate with cyclosporine (Heydendael et al, 2003 and Flytstrom et al, 2007), one compared methotrexate with briakinumab (Reich et al, 2011), and one compared methotrexate with rhLFA3-IgFP (Yan et al, 2011). The oral methotrexate dosing regimens and number of randomized methotrexate (MTX) subjects are as follows

- 15 – 22.5 mg/week [44 MTX subjects] (Heydendael)
- 7.5 – 15 mg/week [41 MTX subjects] (Flytstrom)
- 5 – 25 mg/week [163 MTX subjects] (Reich)
- 7.5 mg/week [105 MTX subjects] (Yan)

The final study identified by the applicant that was randomized and double-blind used methotrexate only in combination with etanercept [etanercept + methotrexate vs. etanercept alone] (Gottlieb et al 2012). The oral methotrexate dose used in the combination treatment arm in this study was 7.5 – 15 mg/week and 239 subjects were randomized to the etanercept + methotrexate arm.

The authors’ conclusions of these studies were:

- No significant differences in efficacy between methotrexate and cyclosporine (Heydendael)
- Cyclosporine was more effective than methotrexate in a short-term perspective (Flytstrom)
- Briakinumab showed higher efficacy than methotrexate (Reich)
- PASI 75 scores differed insignificantly between both groups (Yan)
- Combination therapy with etanercept plus methotrexate had acceptable tolerability and increased efficacy compared with etanercept monotherapy in patients with moderate to severe psoriasis (Gottlieb)

None of these two-arm studies was designed to establish the efficacy of methotrexate monotherapy, and none of the studies led to the conclusion that methotrexate monotherapy was efficacious in moderate to severe psoriasis (that is, demonstrate that methotrexate monotherapy was superior to a control group).

The applicant has not identified any studies published in the literature that used subcutaneous injection of methotrexate. The applicant has identified one randomized (but not blinded) study in the literature that used intramuscular injection of methotrexate. This study (El Eishi et al, 2011) randomized 24 subjects (12 per arm) to methotrexate (2.5 mg/kg/week) or PUVA (3 times per week) for 10 weeks. The study was not blinded and enrolled subjects with extent of psoriasis with more than 30% body surface area (BSA). Because the study enrolled subjects with such a high BSA, it therefore does not appear to provide information about whether methotrexate is safe and efficacious in “moderate to severe psoriasis.”

The applicant has provided several other literature reports of studies involving methotrexate in psoriasis. None of these studies included both randomization and blinding (at least one of the two elements was not used) and all of the studies were considered by the applicant to be of lesser utility than the literature reports discussed above. None of the studies included placebo arms. These studies are not discussed further in this review.

3.3 Evaluation of Safety

The literature reports of studies involving methotrexate provide only brief summaries of observed adverse events; the complete database is not available for review. None of the literature studies used subcutaneous methotrexate, and the utility of the literature summaries from studies using relatively low doses of oral methotrexate to support the safety of subcutaneous methotrexate in moderate to severe psoriasis is limited.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, Age, and Geographic Region

Not applicable to this review.

4.2 Other Special/Subgroup Populations

Not applicable to this review.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The applicant has not conducted any clinical studies evaluating Otrexup in the treatment of psoriasis. Currently approved formulations of methotrexate have the indication: “the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy.” The applicant is seeking to expand the indication to “moderate to severe psoriasis,” by referring to literature reports of studies in moderate to severe psoriasis subjects that included a methotrexate arm.

Although 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, a statistical review of efficacy and safety information relies on being able to access and independently analyze the underlying data. New efficacy claims (such as an expanded indication) in labeling need to be supported by studies prospectively designed to evaluate the desired claims and have appropriate corresponding statistical analysis plans. Brief descriptions of a study design and tables of results from literature are not adequate for assessing the efficacy and safety of a product. None of the literature reports submitted by the applicant contain the underlying data or sufficient information about the study design to adequately and independently assess the results in support of an efficacy claim.

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.” In particular, even though several of the submitted literature reports defined their patient populations as subjects with moderate to severe psoriasis,

- None of the studies used subcutaneous injection of methotrexate. Most studies used the oral formulation of methotrexate with various starting and maximum doses. The benefit/risk of the proposed dose and regimen for Otrexup may differ from the various oral methotrexate regimens used in the submitted literature reports.
- None of the studies was designed to demonstrate the efficacy of methotrexate. The single study (Saurat et al, 2008) that included a placebo arm did not have a pre-specified analysis comparing methotrexate to placebo. Although oral methotrexate was nominally superior to placebo in a post-hoc analysis in that study, psoriasis experts have expressed concern (Menter et al, 2009) that the unusually high placebo response rate in that study “rais[es] doubt about the validity of the study.”
- All other randomized, double-blind, controlled studies with a methotrexate monotherapy arm either failed to find a statistically significant difference between treatment arms or found that the comparator therapy was superior to methotrexate. None of these studies were designed or able to support the claim that methotrexate is an efficacious therapy.

Thus, even if the applicant were able to get full access or right of reference to the underlying data from the studies reported in the literature, none of the studies is adequate to assess the benefit/risk of the proposed dose and regimen of Otrexup for subcutaneous injection in the treatment of moderate to severe psoriasis.

5.2 Conclusions and Recommendations

The literature reports of studies that included a methotrexate arm do not include the underlying data or sufficient information about the study design to adequately and independently assess the results in support of the proposed efficacy claim regarding expanding the indication for methotrexate to include moderate to severe psoriasis. Even if the applicant were able to get access to the underlying data, none of the studies was designed to establish the efficacy and safety of methotrexate in general, or Otrexup specifically, in moderate to severe psoriasis. To expand the indication for Otrexup to moderate to severe psoriasis, the applicant will need to submit data from studies that adequately demonstrate that the benefit of the proposed dosing regimen for Otrexup outweighs the risk in subjects with moderate to severe psoriasis.

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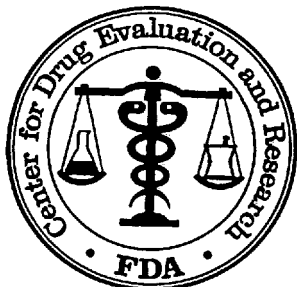
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STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

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)
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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°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

Statistical Review of NDA204824

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								
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 reviewer'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									

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1.7 Conclusions and Recommendation

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

The sponsor's revised shelf-life (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 are not acceptable because the sponsor used actual specification limits larger than the proposed specification limits.

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