CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204824Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2013
See OMB Statement on Page 3.

NDA NUMBER
204824

NAME OF APPLICANT/NDA HOLDER
Antares Pharma, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Otrexup

ACTIVE INGREDIENT(S)	STRENGTH(S)
Methotrexate	10 mg/0.4 ml, 15 mg/ 0.4 ml, 20 mg/0.4 ml and 25 mg/0.4 ml

DOSAGE FORM
Subcutaneous Injection

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
7,776,015	Aug. 17, 2010	08/10/2019

d. Name of Patent Owner
Antares Pharma, Inc.

Address *(of Patent Owner)*
100 Princeton South Corporate Center, Suite 300

City/State
Ewing, NJ

ZIP Code	FAX Number *(if available)*
08628	609 359 3015
Telephone Number	**E-Mail Address *(if available)***
609 359 3020	kdave@antarespharma.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Not applicable

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code	FAX Number *(if available)*
Telephone Number	**E-Mail Address *(if available)***

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☒ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
K Dave..	Nov 30, 2012

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Kaushik J. Dave R.Ph.,Ph.D.,MBA, Executive Vice President Product Development, Antares, Pharma, Inc.

Address	City/State
100 Princeton South Corporate Center, Suite 300	Ewing, NJ
ZIP Code	**Telephone Number**
08628	609-359-3017 (direct)
FAX Number *(if available)*	**E-Mail Address *(if available)***
609-359-3015	kdave@antarespharma.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

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NDA NUMBER
204824

NAME OF APPLICANT/NDA HOLDER
Antares Pharma, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Otrexup

ACTIVE INGREDIENT(S)	STRENGTH(S)
Methotrexate	10 mg/0.4 ml, 15 mg/ 0.4 ml, 20 mg/0.4 ml and 25 mg/0.4 ml

DOSAGE FORM
Subcutaneous Injection

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
8,021,335	Sep. 20, 2011	10/04/2026

d. Name of Patent Owner	Address *(of Patent Owner)*	
Antares Pharma, Inc.	100 Princeton South Corporate Center, Suite 300	
	City/State: Ewing, NJ	
	ZIP Code: 08628	FAX Number *(if available)*: 609 359 3015
	Telephone Number: 609 359 3020	E-Mail Address *(if available)*: kdave@antaresphama.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
Not applicable	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	Nov 30, 2012

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/ holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Kaushik J. Dave R.Ph.,Ph.D.,MBA, Executive Vice President Product Development, Antares, Pharma, Inc.	
Address 100 Princeton South Corporate Center, Suite 300	City/State Ewing, NJ
ZIP Code 08628	Telephone Number 609-359-3017 (direct)
FAX Number *(if available)* 609-359-3015	E-Mail Address *(if available)* kdave@antaresphama.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

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- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
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First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

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2. Drug Substance (Active Ingredient)

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2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

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ACTIVE INGREDIENT(S)	STRENGTH(S)
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FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,746,429	June 8, 2004	4/12/2020

d. Name of Patent Owner	Address *(of Patent Owner)*	
Antares Pharma, Inc.	100 Princeton South Corporate Center, Suite 300	
	City/State: Ewing, NJ	
	ZIP Code: 08628	FAX Number *(if available)*: 609-359-3015
	Telephone Number: 609-359-3020	E-Mail Address *(if available)*: kdave@antaresphama.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
Not applicable	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☐ Yes	☒ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	Nov 30, 2012

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Kaushik J. Dave R.Ph.,Ph.D.,MBA, Executive Vice President Product Development, Antares, Pharma, Inc.	
Address 100 Princeton South Corporate Center, Suite 300	City/State Ewing, NJ
ZIP Code 08628	Telephone Number 609-359-3017 (direct)
FAX Number *(if available)* 609-359-3015	E-Mail Address *(if available)* kdave@antarespharma.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2013
See OMB Statement on Page 3.

NDA NUMBER
204824

NAME OF APPLICANT/NDA HOLDER
Antares Pharma, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Otrexup

ACTIVE INGREDIENT(S)	STRENGTH(S)
Methotrexate	10 mg/0.4 ml, 15 mg/ 0.4 ml, 20 mg/0.4 ml and 25 mg/0.4 ml

DOSAGE FORM
Subcutaneous Injection

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
7,744,582	June 29, 2010	8/10/2019

d. Name of Patent Owner	Address *(of Patent Owner)*	
Antares Pharma, Inc.	100 Princeton South Corporate Center, Suite 300	
	City/State: Ewing, NJ	
	ZIP Code: 08628	FAX Number *(if available)*: 609-359-3015
	Telephone Number: 609-359-3020	E-Mail Address *(if available)*: kdave@antarespharma.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
Not applicable	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes	☐ No
4.2 Patent Claim Number(s) *(as listed in the patent)* 1, 22, 23	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*		

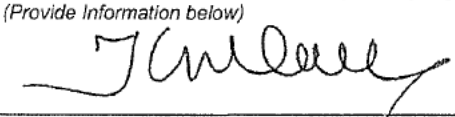
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	Nov 30, 2012

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Kaushik J. Dave R.Ph.,Ph.D.,MBA, Executive Vice President Product Development, Antares, Pharma, Inc.

Address	City/State
100 Princeton South Corporate Center, Suite 300	Ewing, NJ
ZIP Code 08628	Telephone Number 609-359-3017 (direct)
FAX Number *(if available)* 609-359-3015	E-Mail Address *(if available)* kdave@antarespharma.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
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- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
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- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 204824/Originals 1 & 2 SUPPL # HFD #

Trade Name: Otrexup

Generic Name: Methotrexate Injection

Applicant Name: Antares Pharma, Inc.

Approval Date, If Known: October 11, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The sponsor relied on published literature to support the safety and efficacy of the new route of administration for their proposed product, methotrexate (MTX) injection, to be administered subcutaneously (SC) (as auto-injector) for the indications of rheumatoid arthritis (RA), and psoriasis. The sponsor also relied on FDA's previous finding of safety and efficacy of MTX for those indications as well as the indication of polyarticular juvenile idiopathic arthritis (pJIA), which is already approved for treatment via the subcutaneous route of administration. In addition, the sponsor conducted a bioequivalence study demonstrating that MTX SC administered in the abdomen or thigh

by the auto-injector is bioequivalent to the approved parenteral MTX administered by needle and syringe by the SC or intramuscular (IM) route. Also, the sponsor conducted a relative bioavailability (BA) study demonstrating an equal or greater bioavailability of MTX SC administered by auto-injector compared to the exposure obtained with orally administered MTX tablets.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years of exclusivity requested by the sponsor

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 08085 Dava

NDA# 11719 Hospira

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Sadaf Nabavian, Pharm.D.
Title: Senior Regulatory Project Manager
Date: October 11, 2013

Name of Office/Division Director signing form: Badrul A. Chowdhury, M.D., Ph.D.
Title: Division Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Name of Division Director signing form: Tatiana Oussova, MD
Title: Deputy Director for Safety, Division of Dermatology and Dental Products (DDDP)

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

SADAF NABAVIAN
10/11/2013

SARAH K YIM
10/11/2013
Signing for Badrul Chowdhury, M.D., Ph.D.

TATIANA OUSSOVA
10/11/2013

Debarment Certification

Antares Pharma, Inc. (Device Division) hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Pursuant to Section 306(k) of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, Antares Pharma, Inc. Antares Pharma, Inc. (Device Division), hereby certifies that we did not and will not use, in any capacity, the services of any person debarred under subsection (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this New Drug Application (NDA).

Antares Pharma, Inc. (Device Division) certifies further that, during the previous five years, it has not sustained a conviction that is described in subsection (a) or (b) of the Generic Drug Enforcement Act of 1992. In addition, Antares Pharma, Inc. Antares Pharma, Inc. (Medical Device Division) certifies that no person affiliated with the company that was responsible for the development or submission of this application has been convicted of an offense described in subsections (a) or (b) of the Generic Drug enforcement Act of 1992.

Ronald Burke

Ronald Burke
Director of Quality and Regulatory Affairs
Antares Pharma Inc. (Device Division)

10/22/2012

Date

antares
pharma

Antares Pharma, Inc.
100 Princeton South, Suite 300
Ewing, NJ 08628
Tel. (609) 359-3020 • Fax (609) 359-3015

1.3.3 Debarment Certification

Antares Pharma, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Pursuant to Section 306(k) of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, Antares Pharma, Inc., hereby certifies that we did not and will not use, in any capacity, the services of any person debarred under subsection (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this New Drug Application (NDA).

Antares Pharma, Inc. certifies further that, during the previous five years, it has not sustained a conviction that is described in subsection (a) or (b) of the Generic Drug Enforcement Act of 1992. In addition, Antares Pharma, Inc. certifies that no person affiliated with the company that was responsible for the development or submission of this application has been convicted of an offense described in subsections (a) or (b) of the Generic Drug enforcement Act of 1992.

Kaushik J. Dave R.Ph., Ph.D., MBA
Executive Vice President Product Development
Antares Pharma Inc.

October 13, 2012
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 204824	NDA Supplement # NA BLA Supplement # NA	If NDA, Efficacy Supplement Type: NA
Proprietary Name: Otrexup Established/Proper Name: (methotrexate) 10 mg, 15 mg, 20 mg, 25 mg/0.4 mL Dosage Form: Injection		Applicant: Antares Pharma Inc. Agent for Applicant (if applicable): NA
RPM: Barbara Gould		Division: Dermatology and Dental Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

NDA 011719 (methotrexate sodium) Injection

NDA 008085 (methotrexate sodium) Tablets

ANDA 040632 (methotrexate sodium) Injection

Provide a brief explanation of how this product is different from the listed drug.

Route of administration

☐ This application does not reply upon a listed drug.
☒ This application relies on literature.
☐ This application relies on a final OTC monograph.
☒ This application relies on (explain) Bioequivalence data

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: 10/11/13

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions • Proposed action • User Fee Goal Date is October 14, 2013	☒ AP ☐ TA ☐ CR

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 3, New Dosage Form

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☒ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

Version: 07/17/2013

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	10/11/13
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☐ Included
Documentation of consent/non-consent by officers/employees	☐ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval 10/11/13
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	10/10/13
• Original applicant-proposed labeling	12/14/12
• Example of class labeling, if applicable	

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☒ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	10/10/13
• Original applicant-proposed labeling	12/14/12
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	6/7/13
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	Final Review 9/5/13 Granted Letter 3/13/13 Review 3/12/13
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 6/12/13; 2/25/13 ☒ DMEPA 7/26/13 ☒ DMPP/PLT (DRISK) 9/5/13 ☒ ODPD (DDMAC) 9/3/13 ☒ SEALD 10/8/13 ☐ CSS ☒ Other reviews Clinical 9/27/13
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	RPM Filing Review 2/25/13
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ 9/4/13
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ 10/11/13
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 6/5/13 If PeRC review not necessary, explain: ____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	Information Request 7/29/13 Information Request 7/1/13 Information Request 6/11/13 Information Request 6/7/13 Information Request 5/24/13 Information Request 5/17/13 Information Request 5/6/13 Information Request 4/30/13 Advice 3/21/13 Information Request 3/2/13 Filing Letter 2/26/13 Acknowledgement 12/27/12
❖ Internal memoranda, telecons, etc.	NA
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ 11/2/12
• EOP2 meeting *(indicate date of mtg)*	☒ 9/13/11
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ 10/10/13
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	Addendum 10/11/13 Review 9/20/13 PERC Review 5/30/13 Filing 2/8/13
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	p. 15 of Clinical Review 9/20/13

[6] Filing reviews should be filed with the discipline reviews.

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ CDRH Combination Product 9/10/13; CDRH Human Factors 7/18/13
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ Review 9/27/13
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☒ Review 8/1/13; Consult Review 6/26/13
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ Review 9/3/13; Filing 2/1/13
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ Review 8/30/13; 5/14/13; Filing 1/27/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☒ Review 9/11/13; Review 9/9/13 Filing 2/22/13 Filing Checklist 2/12/13
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Review 7/29/13; Filing 2/11/13 NA
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	p. 121 of CMC Review 9/9/13
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

/s/

STROTHER D DIXON
10/16/2013

From: Nabavian, Sadaf
To: "Susan Thornton"
Subject: RE: NDA 204824
Date: Friday, October 11, 2013 12:29:00 PM
Attachments: Otrexup FDA Final Revised PI 11Oct13.doc
Importance: High

Dear Sue,

There were many formatting issues that were addressed and corrected by our team, so to the attached you'll find our latest and final version of the proposed revised label. Please let me know if you agree and if so please go ahead and submit the final revised label to the NDA as soon as possible.

With Kind Regards,

Sadaf

From: Susan Thornton [mailto:Sthornton@antarespharma.com]
Sent: Friday, October 11, 2013 11:05 AM
To: Nabavian, Sadaf
Subject: RE: NDA 204824

Dear Sadaf,

I left you a voice message regarding this same matter. Would it be possible in the interest of time if you could convey the final comment verbally now? I am concerned that depending on the extent of the change, we would not be able to submit the formal submission to the NDA today due to the time required to make the publishing programming changes before 4:30 pm today so that the submission would be time stamped for today.
Regards,
Sue

From: Nabavian, Sadaf [mailto:Sadaf.Nabavian@fda.hhs.gov]
Sent: Friday, October 11, 2013 10:58 AM
To: Susan Thornton
Subject: NDA 204824

Dear Susan,
Please stand by for the final labeling comment which I plan to convey in the next hour, you can then submit the official submission to the NDA.
With Kind Regards,
Sadaf

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

/s/

SADAF NABAVIAN
10/15/2013

From: Nabavian, Sadaf
To: "Susan Thornton"
Subject: RE: NDA 204824
Date: Friday, October 11, 2013 7:43:00 AM

Dear Susan,

This is to acknowledge your email.

Thank you,

Regards,

Sadaf

From: Susan Thornton [mailto:Sthornton@antarespharma.com]
Sent: Thursday, October 10, 2013 5:28 PM
To: Nabavian, Sadaf
Subject: RE: NDA 204824

Dear Sadaf,

Here are all of the NDA 204824 Device labels revised to include the location of the lot and expiration date.
Regards,
Sue

From: Nabavian, Sadaf [mailto:Sadaf.Nabavian@fda.hhs.gov]
Sent: Thursday, October 10, 2013 5:26 PM
To: Susan Thornton
Subject: RE: NDA 204824

That's fine.
Thanks,
Sadaf

From: Susan Thornton [mailto:Sthornton@antarespharma.com]
Sent: Thursday, October 10, 2013 5:25 PM
To: Nabavian, Sadaf
Subject: RE: NDA 204824

Dear Sadaf,

I have all of the revised device labels and available now. Would you like me to email via a zip folder now?
Thanks,
Sue

From: Nabavian, Sadaf [mailto:Sadaf.Nabavian@fda.hhs.gov]
Sent: Thursday, October 10, 2013 5:24 PM
To: Susan Thornton
Subject: RE: NDA 204824

Dear Susan,

This is to acknowledge your email. I will let you know as soon as I hear back from the team and/or something new arises. I will be signing off at 5:30 p.m., so most probably I will have further feedback by tomorrow a.m.

Thanks again for your prompt attention and responses to all the emails throughout the day,

With Kind Regards,

Sadaf

From: Susan Thornton [mailto:Sthornton@antarespharma.com]
Sent: Thursday, October 10, 2013 4:55 PM
To: Nabavian, Sadaf
Subject: RE: NDA 204824

Dear Sadaf,

Antares accepts the changes to the Label and we have corrected the HL margin. I have attached the clean and redline versions.

Regarding the device labels, I have attached a revised device label which illustrate where the lot and expiration date is provided in the varnish free area. I have attached the 10 mg revised device label. I will include the revised device labels for all of the strengths and package configurations in the formal NDA submission for tomorrow.

Regards,
Sue

From: Nabavian, Sadaf [mailto:Sadaf.Nabavian@fda.hhs.gov]
Sent: Thursday, October 10, 2013 4:15 PM
To: Susan Thornton
Subject: RE: NDA 204824
Importance: High

Dear Susan,

Thank you for your email.

Please see the attached for the next round of our proposed labeling revisions and let me know if you have any questions. Also, regarding the device container label, can you provide clarification in where exactly the expiration date for the container label is located and what exactly is the purpose

of the Varnish Free space noted on the device labels for all 4 doses? I could not located the Exp. date in the submission dated October 2, 2013 (see attached) vs. in your previous submissions the expiration date was located [redacted] (b) (4), please clarify. In addition, please note that in your recent submission the two-column format did not contain ½ inch margin on all sides which needs to be done as a general format for the HL section, please make that correction.

It would be greatly appreciated to submit the revised label as soon as possible (at least via email for now) in order for our review team to take a final peak at it in case any additional comments need to be conveyed.

Please note that the Division plans to take action on your NDA tomorrow.

Again, let me know if you have any questions,

With Kind Regards,

Sadaf

From: Susan Thornton [mailto:Sthornton@antarespharma.com]
Sent: Thursday, October 10, 2013 3:26 PM
To: Nabavian, Sadaf
Subject: RE: NDA 204824

Dear Sadaf,

Thank you for the update. I will await your revisions.

Please note that we had just submitted the recent revisions to the NDA (SN0021).

Regards,
Sue

From: Nabavian, Sadaf [mailto:Sadaf.Nabavian@fda.hhs.gov]
Sent: Thursday, October 10, 2013 3:17 PM
To: Susan Thornton
Subject: NDA 204824
Importance: High

Dear Susan,

Please stand by as I have another round of proposed labeling revisions for NDA 204824 to communicate within the next hour. Hopefully this round will be our last one!

Thanks,

With Kind Regards,

~*Sadaf*

Sadaf Nabavian, Pharm.D.
CDR, U.S Public Health Service
Senior Regulatory Project Manager
FDA/CDERII/OND/DPARP

10903 New Hampshire Ave
Bldg. 22, Rm. 3306
Silver Spring, MD 20993-0002
Phone: (301)796-2777
Fax: (301)796-9718/9715
Email: sadaf.nabavian@fda.hhs.gov

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/s/

SADAF NABAVIAN
10/15/2013

From: Nabavian, Sadaf
To: "Susan Thornton"
Subject: RE: NDA 204824
Date: Friday, October 11, 2013 7:43:00 AM
Importance: High

Dear Susan,

Thanks again for sending the revised labeling, there's still a minor cosmetic issue with the margins for the Boxed Warning being offset to the right compared with the rest of the label, please address this issue before sending in the final version to the NDA. You can go ahead and email me the revised labeling (in pdf and word) and subsequently submit it officially to the NDA.

Thanks,

With Kind Regards,

Sadaf

From: Susan Thornton [mailto:Sthornton@antarespharma.com]
Sent: Thursday, October 10, 2013 4:55 PM
To: Nabavian, Sadaf
Subject: RE: NDA 204824

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It would be greatly appreciated to submit the revised label as soon as possible (at least via email for now) in order for our review team to take a final peak at it in case any additional comments need to be conveyed.

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To: Nabavian, Sadaf
Subject: RE: NDA 204824

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Sue

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Importance: High

Dear Susan,

Please stand by as I have another round of proposed labeling revisions for NDA 204824 to communicate within the next hour. Hopefully this round will be our last one!

Thanks,

With Kind Regards,

~*Sadaf*

Sadaf Nabavian, Pharm.D.
CDR, U.S Public Health Service
Senior Regulatory Project Manager
FDA/CDERII/OND/DPARP

10903 New Hampshire Ave
Bldg. 22, Rm. 3306
Silver Spring, MD 20993-0002
Phone: (301)796-2777
Fax: (301)796-9718/9715
Email: sadaf.nabavian@fda.hhs.gov

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/s/

SADAF NABAVIAN
10/15/2013

NDA 204824
Methotrexate injection
Antares Pharma, Inc.

Dear Ms. Thornton:

Your NDA submission dated, December 14, 2012, for methotrexate injection is currently under review. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are (underlined) and deletions are in (strike-out). Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

Submit revised labeling incorporating the changes shown in the attached marked up label via email to Sadaf.Nabavian@fda.hhs.gov by close of business today, Thursday, October 10, 2013, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/10.10.2013

Cleared by: LJafari/10.10.2013

Finalized by: SNabavian/10.10.2013

29 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SADAF NABAVIAN
10/10/2013

PeRC PREA Subcommittee Meeting Minutes
June 5, 2013

PeRC Members Attending:
Lynne Yao
Robert "Skip" Nelson
Hari Cheryl Sachs
Rosemary Addy
Patricia Dinndorf
Tom Smith
Julia Pinto
William J. Rodriguez
Peter Starke
Wiley Chambers
Lily Mulugeta
Daiva Shetty
Colleen LoCicero (Only present for [redacted] (b) (4), and Exelon)
Donna Katz (Only present for Oxrexup)
Barbara Buch
Gregory Reaman
Kevin Krudys

Guests Attending:
Dionna Green (OCP)
Courtney Suggs (PMHS)
Gil Burckart (OCP)
Nichella Simms (PMHS)
Jeremiah Momper (OCP)
Jessica Benjamin (DGIEP)
Justin Earp (OCP)
Mike DeMarco (DNP)
Nicole Tromm (OCP)
Carla Epps (DGIEP)
Lara Dimick-Santos (DGIEP)
Jian Wang (OCP)
Juliette Toure (DPP)
Arippa Ravindran (DPP)
Kohli-Chhabra, Kavneet-Ripi (DPP)
Ni Khin (DPP)
Thomas Birkner (OTS/OB)
Peiling Yang (OTS/OB)
Hao Zhu (OTS/OB)
Kofi Kumi (OTS/OB)
Theresa Michele (DPARP)
Janet Maynard (DPARP)
Tatiana Oussova (DDDP)
Snezana Trajkovic (DDDP)

Agenda

BLA	(b) (4)	(b) (4)
NDA	204-168	Levomilnacipran HCL (b) (4)
NDA	204-824	Otrexup (methotrexate) Full Waiver
NDA	22-106/	Doribax (doripenem) (b) (4)
BLA	125104	Tysabri (natalizumab) (b) (4)
NDA	(b) (4)	(b) (4)
NDA	(b) (4)	(b) (4)
NDA	22-083/19	Exelon (b) (4)
NDA	204-708	(b) (4)

(b) (4)

Levomilnacipran HCL (b) (4)

(b) (4)

Otrexup Full Waivers

- NDA 204-824, Otrexup (methotrexate) injection, was studied for the treatment of:
  - *DPARP Indications* - juvenile rheumatoid arthritis (JRA) now called polyarticular juvenile idiopathic arthritis (PJIA) and rheumatoid arthritis (RA)
  - *DDDP Indications* - treatment of moderate psoriasis and the treatment of severe psoriasis
- The application was submitted December 14, 2012 and has a PDUFA date of October 14, 2013. It should be noted that methotrexate is available as a generic for oral tablets and for injection forms. The current NDA is for an auto-injector for SC administration. The addition of an auto-injector to methotrexate for injection makes it a drug/device combination but does not constitute a new dosage form (does not trigger PREA).
- PREA is triggered for the indications of RA (new route), severe psoriasis (new route), and moderate psoriasis (new indication) in this application. Note that for RA, methotrexate is only approved for oral use. For pJIA, methotrexate is approved for oral, IM, SC administration. Although pJIA is the pediatric form of adult RA and this is not a new route of administration for pJIA, the SC route is a new route of administration for RA in adults. The new route for RA triggers PREA, although pJIA is the indication required to be studied under PREA.
- For severe psoriasis, methotrexate is approved for oral, IM, and IV administration, but not for SC administration, so for this indication the SC route is a new route of administration that triggers PREA.
- Moderate psoriasis is a new indication.
- DPARP is requesting a partial waiver for the RA indication (new indication) in patients ages birth to 23 months because the disease/condition does not exist in children and a partial waiver in patients 2-16 years because the product does not represent a meaningful therapeutic benefit and is not likely to be used in a substantial number of pediatric patients.
- DDDP is requesting full waivers for each indication because the product would be ineffective or unsafe for use in the pediatric population.

- The PeRC agreed with the Division (DPARP) to grant a partial waiver in patients ages birth to 23 months with JIA because studies in this age group would be impossible or highly impractical. The PeRC agreed to a partial waiver in patients 2-16 years because the product does not represent a meaningful therapeutic benefit because a complete pediatric assessment was submitted by the reference product sponsor (innovator).
- The PeRC agreed with the Division (DDDP) to grant a full waiver for each dermatologic indication (moderate psoriasis and severe psoriasis) because the product would be unsafe for use in the pediatric population. Safety issues associated with this product include life-threatening neoplastic diseases and liver, bone-marrow, lung, and kidney toxicity. The Division noted that all immunomodulatory agents have been waived for the same reason for all pediatric age groups for psoriasis because the risks of the products do not outweigh the benefit for this non-fatal skin condition. The PeRC requests that safety information be incorporated into labeling in section 8.4, including a statement describing that the product should not be used in children with psoriasis because of safety concerns in this population as described above.

Doribax (b) (4)

(b) (4)

(b) (4)

Tysabri (b) (4)

(b) (4)

(b) (4)

Exelon (b) (4)

(b) (4)


(b) (4)

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/s/

JANE E INGLESE
10/10/2013

NDA 204824
Methotrexate injection
Antares Pharma, Inc.

Dear Ms. Thornton:

Your NDA submission dated, December 14, 2012, for methotrexate injection is currently under review. We are providing our labeling comments noted below for your consideration. Be advised that these labeling comments are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

Highlights (HL)

- Correct width of right, left and top of page margins to be 1/2 inch
- Product title: Insert a comma after "injection", i.e., "OXTREXUP (methotrexate) injection , for subcutaneous use".
- Boxed Warning (BW) heading: For consistency with the BW heading in the FPI, change "EMBYROFETAL" to "EMBYRO-FETAL" and insert a comma before "INCLUDING"; i.e., "WARNING: SEVERE TOXIC REACTIONS, INCLUDING EMBRYO-FETAL TOXICITY AND DEATH"
- In the last line of the HL Limitation Statement, remove extra white space before the drug name, "OTREXUP."

Table of Contents (TOC)

- In order to match the FPI, correct the following in the TOC: BW title, change "embryofetal" to "embryo-fetal" and remove hard return after "embryofetal" so that the title is presented as continuous wrapping text; subsection heading 1.3, change "Limitations" to "Limitation"; section 4, Contraindications, remove bulleted list of contraindications from the TOC (since these contraindications are not assigned subsection numbers, they should not be listed in the TOC); subsection heading 7.1, change "(NSAIDs)" to "Nonsteroidal Anti-Inflamatory Drugs"; and subsection heading 7.2, change "Proton Pump Inhibitor (PPI) Therapy" to "Proton Pump Inhibitors (PPIs)".
- BW title in TOC must match FPI. Correct BW title as stated above.

Full Prescribing Information (FPI)

- Attach Patient Information and Instructions for Use to the end of the PI.

Submit revised labeling incorporating the changes shown in the attached marked up label via email to Sadaf.Nabavian@fda.hhs.gov by the close of business on Wednesday October 9, 2013, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/10.08.2013

Cleared by: LJafari/10.08.2013

Finalized by: SNabavian/10.08.2013

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/s/

SADAF NABAVIAN
10/08/2013

NDA 204824
Methotrexate injection
Antares Pharma, Inc.

Dear Ms. Thornton:

Your NDA submission dated, December 14, 2012, for methotrexate injection is currently under review. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are (underlined) and deletions are in (strike-out). Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

Submit revised labeling incorporating the changes shown in the attached marked up label via email to Sadaf.Nabavian@fda.hhs.gov by the close of business on Monday October 7, 2013, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/10.04.2013

Cleared by: LJafari/10.04.2013

Finalized by: SNabavian/10.04.2013

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/s/

SADAF NABAVIAN
10/04/2013

NDA 204824
Methotrexate injection
Antares Pharma, Inc.

Dear Ms. Thornton:

Your NDA submission dated, December 14, 2012, for methotrexate injection is currently under review. We are providing additional preliminary labeling comments. Please note that we may have additional labeling comments as we continue the review of your application.

1. We have made significant changes to the proposed Prescribing Information (PI). Otrexup relies on listed drug labeling and studies have not been conducted to justify having a PI with significant differences compared to the listed drug labeling. After our review of your proposed labeling, we chose to carry over the labeling of the listed drugs to PLR format, to keep much of the language the same as the reference listed drugs, and added information specific to and appropriate for your product.

   Note that the PI contains comments that may clarify our reasoning for the proposed revisions. Additionally, the document contains an embedded, highlighted comment in Section 2.4, Administration and Handling, that you will need to address. In the other highlighted area, update the contact information, phone number, and the revision date.

   We also have the following comments:

   a) PLR labeling necessitates moving information from one section to another within which the information is appropriately presented. Many sections, paragraphs, and sentences, are rearranged in order to keep the language the same as that of the listed drugs as much as possible.
   b) In certain instances, we deleted information that pertains to an indication (i.e., treatment of malignancies), dose (high-dose regimens and leucovorin rescue regimens), or route of administration (i.e., intrathecal administration) which is not appropriate for your product.
   c) The Dosage and Administration section was adjusted to address that other formulations may need to be used for alternative doses and routes of administration, that the starting doses of methotrexate for RA and pJIA in the listed products differ from those available with Otrexup, and that patients are likely to be transferred to Otrexup after starting with other formulations.
   d) When a Boxed Warning appears in a labeling, the Warnings and Precautions section must contain the same information. We therefore made substantial changes to this section to include this information.

e) The Clinical Studies section now contains studies from other parts of the labeling of the listed drugs, and does not include any of the information you proposed from the literature.

2. Although you do not plan to co-package the active and "trainer" devices, we note that the proposed devices look very similar. This is a potential safety issue, in that the active and the trainer devices may easily be confused with each other. To minimize confusion between the two devices, use the color gray only for the demonstration "trainer" devices that contain no active drug. The active drug product will not contain any visible components with a gray color. Revise the active and trainer products as follows.

    f) Revise the labeling on the trainer device to distinguish the trainer device from the active product:

        i) Replace the word [redacted] (b) (4) with the word "TRAINER", and add the words "Contains NO needle and NO medicine." This information should be prominently displayed, such that the font for the word "TRAINER" is larger than that of "Otrexup".

        ii) Change the [redacted] (b) (4) background color to gray.

        iii) Provide an additional instruction showing how to reset the trainer device.

    g) Revise the color scheme for the active product :

        i) Choose a different color for the plastic twist-off cap (currently gray in color and marked as 1). This may be done as a post-marketing commitment (PMC) if you are unable to make these changes quickly.

        ii) Choose a different color for the safety clip (currently gray in color and marked as 2). This may be done as a PMC if you are unable to make these changes quickly.

        iii) Change the cover on the needle guard (currently white in color and unmarked) to distinguish the end containing the needle. For example, you may wish to consider changing it to orange to match the body color of the arrow pointing to the needle end.

3. We refer you to the labeling requirements outlined in 21 CFR 201.10(g)(2), 21 CFR 201.15(a)(5), and 21 CFR 201.15(a)(6) for all instances of appearance of the proprietary name and established name on the container, carton, Package Insert (PI), and Instructions for Use (IFU) of your drug product. We have the following requests:

    (a) For all instances of the established name, change the font size to be at least half the font size of the proprietary name. The font should be easily readable and not in *italics*.

(b) Remove the "(b) (4)" from above the proprietary name in the carton and container labeling, as it distracts from the proprietary name.

(c) Increase the font size of “injection xx mg.0.4 mL” on all carton and container labels.

(d) Increase the font size of “for subcutaneous use only” on all carton and container labels.

Submit revised labeling incorporating the changes shown in the attached marked up label via email to Sadaf.Nabavian@fda.hhs.gov by the close of business on Thursday, September 26, 2013. The email should be followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Regulatory Management Officer at 301-796-2777.

Drafted by: SNabavian/09.13.2013

Cleared byChill/9.16.2013
JMaynard/09.16.2013

Finalized by: SNabavian/09.16.2013

25 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SADAF NABAVIAN
09/16/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204824 **INFORMATION REQUEST**

Antares Pharma, Inc.
Attention: Kaushik J. Dave, RPh., Ph.D, MBA
Executive Vice President, Product Development
100 Princeton South Corporate Center, Suite 300
Ewing, NJ 08628

Dear Dr. Dave:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Otrexup™ (methotrexate) injection.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response (preferably by August 9, 2013) in order to continue our evaluation of your NDA.

A. Submit the revised batch record to include the revised direction at Step (b) (4), per your commitment in your response (July 22, 2013) to Question A.3. in our July 1, 2013 Information Request letter.

B. Regarding the Stability

1. Please clarify which stability protocol will be used for post-approval stability studies. In Section 3.2.P.8.3 you state: "The drug product lots in the Primary Stability studies were filled into the same PFS primary container closure system and assembled with the same auto-injector as proposed for the commercial drug device combination product. The Primary Stability studies have been conducted using storage conditions and sampling intervals that meet ICH Q1A (R2) requirements. The stability testing for the proposed commercial combination product is described in Section 3.2.8.1…" However Table 5 in Section 3.2.P.8.1 contains two different protocols.

Strength (mg/0.4 mL)	Batch Number	PFS Not Assembled in Autoinjector	PFS Assembled in Autoinjector
10	000123	Sterility	All other tests
	000174	All other tests + Description	Description, Volume in Container, Uniformity of Dosage Unit, & Functionality
	000175		
15	000132	Sterility	All other tests
20	000124		
25	000133		
	000177	All other tests + Description	Description, Volume in Container, Uniformity of Dosage Unit, & Functionality
	000179		

Using the information in that table results in the identification of two different protocols

Protocol	PFS Not Assembled in Autoinjector	PFS Assembled in Autoinjector	Batch Numbers used in Primary Stability Studies
A	All other tests + Description	Description, Volume in Container, Uniformity of Dosage Unit, & Functionality	000174 000175 000177 000179
B	Sterility	All other tests	000123 000132 000124 000133

Specify which protocol will be used for post-approval studies. If Protocol A will be used provide information to ensure that the Pre-Filled Syringes are protected from light during storage.

Note that there was no discussion in the Type 2B EOP2 meeting on September 13, 2011 for IND 103738 (Minutes Communicated October 13, 2011) regarding the use of two different protocols.

2. Provide a revision to all sections in P.8. to reflect the updated stability data, including the tables in P.8.1.2.7 and the commitments for post-approval reporting in P.8.3 to reflect the updated data submitted on June 6, 2013.

3. Revise the acceptance criterion on stability for Impurity (b) (4) to NMT (b) (4) %. This value will be used by FDA to determine the expiration date.

If you have any questions, contact Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
07/29/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204824 **INFORMATION REQUEST**

Antares Pharma, Inc.
Attention: Kaushik J. Dave, RPh., Ph.D, MBA
Executive Vice President, Product Development
100 Princeton South Corporate Center, Suite 300
Ewing, NJ 08628

Dear Dr. Dave

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Otrexup™ (methotrexate) injection.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response (preferably by July 21, 2013) in order to continue our evaluation of your NDA.

A. Regarding the manufacturing

1. Explain which testing functions are performed at (b) (4) facilities, which are identified as facilities used for the shipping studies in section P.2.2. We note that the (b) (4) facility was not listed on the 356h form.
2. Explain why the Master Batch Record does not contain directions to discard the first (b) (4) of the (b) (4), as specified on Page 10 of Section 3.2.P.2.3.
3. Amend the Master Batch Records to include directions to take samples for checking fill weight at intervals to ensure adequate control of the fill weight during processing.

B. Regarding the Specifications

1. Explain why the Pre-Filled Syringes are not tested for "Volume in Container," before assembling the autoinjector, since this could result in defective syringes being assembled.
2. Amend the directions for the HPLC assay for the drug product to include phrase (b) (4) "
3. Explain how the length of the exposed needle is measured following the directions: "5.5.4 Check exposed needle length. If the needle is flush or extends beyond the end of the fixture it passes." If the measurement is based on the thickness of the holder specify how the thickness of the holder is confirmed. Describe how the actual needle length was measured for batches 123, 124, 132 and 133.

4. Explain why the test parameter "Uniformity of Dosage Units" is not reported in the COAs for the pre-filled syringes, even though it is part of the drug product. specification. Conversely, the Volume in Container and Osmolarity are reported in the COA, even though they are not in the PFS specifications.
5. Explain the following discrepancies between the Specifications in P.5.1 and the matrix for testing in Section P.5.6. The following tests are performed on stability for the PFS in P.5.1 but are not reported according to P.5.6.

   Bacterial Endotoxins
   Description
   Methotrexate assay
   Particulate Contamination sub- visible
   pH
   Related Substances
   Uniformity of Dosage Units (Weight Variation)

C. Regarding the Reference Standards

   Provide information to show the equivalence of the Ph.Eur. and USP methotrexate reference standards. Provide the source of the impurity standards.

D. Regarding the acceptance testing for the syringes

1. Explain what an (b) (4) on the barrel is.
2. Explain how it is determined that an (b) (4) on the surface or inside the barrel does not lead to breakage or leakage.
3. For the tests where the Tolerance Accept is greater than 0 (table below), explain why these are considered acceptable.

Test number	Parameter
10.	Contamination on outer surface of syringe
11.	Presence of foreign contamination matter included in the glass
12.	(b) (4) on the surface or inside the barrel that does not lead to breakage or leakage
14.	Crack without leakage on the barrel (b) (4)
15.	Cracked, chipped. broken or deformed flanges or tip
16.	Deformed container→functionality affected
17.	Deformed container→functionality not affected
19.	Needle shield deformed or damaged. functionality affected
20.	Plastic Cap can be separated from rubber part
22.	Bent needle (>2.5")

4. Explain what the (b) (4) is that is referenced in the Visual Tests performed by (b) (4) on the COA for the syringes.
5. Explain how the AQLs in the Visual Tests performed by (b) (4) for the release of the syringes were calculated. We note that there is a discrepancy between many of

the values listed in the table and the values in [redacted]. For instance for the [redacted]

6. Provide the source and specifications for the needle shield.
7. Explain what the [redacted] is that is referenced in the Visual Tests performed by [redacted] on the COA for the syringes.

E. Regarding the stability

1. Explain why different protocols are used for stability studies for batches 000123, 000124, 000133, and 000134 compared with batches 000174, 000175, 000177, and 000179 (3.2.P.8.1 Table 5). We also note that the detailed protocols in Tables 7, 9, and 10 show differing protocols at different time points.
2. Your proposed expiration date of 24 months is acceptable, based on our analysis of the stability data for the appearance of Impurity [redacted]. We note that your calculation for the expiration date based on Impurity [redacted] used an acceptance criterion of NMT [redacted]% rather than the actual proposed Specification of NMT [redacted]%. You are advised that any future calculations be based on the acceptance criteria in the Specifications.
3. Explain whether the entire drug product may be removed from the market or a failing batch may be removed from the market if a batch fails Specification on stability.

F. Regarding the Drug Master Files

Information is being requested for DMF [redacted] and has been requested for DMF [redacted].

If you have any questions, contact Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
07/01/2013

Liu, Youbang

From: Liu, Youbang
Sent: Tuesday, June 11, 2013 4:33 PM
To: Kaushik Dave
Cc: 'Sthornton@antarespharma.com'
Subject: Information Request for NDA 204824, Otrexup

Antares Pharma, Inc.
Attention: Kaushik J. Dave, RPh., Ph.D, MBA
Executive Vice President, Product Development
100 Princeton South Corporate Center, Suite 300
Ewing, NJ 08628

Dear Dr. Dave:

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 204824, Otrexup™ (methotrexate) injection, received December 14, 2012. We acknowledge receipt of your amendment dated June 6, 2013. We have the following comments and information requests.

1. You state: "Antares has updated 3.2.P.3.4 to add an incoming identification test."

   Please specify the test that was added and why it was added at this time.

2. This amendment contains new information that was not in response to an information request. Specifically:
   - You have included a manual process (Process (b)(4)) for assembly of the autoinjector device in Section P.3.3 and state that this was used for the registration and clinical trial batches and may be used for the production of commercial batches.
   - You state that the semi-automated process for assembly of the autoinjector device previously submitted in Section P.3.3 is now called Proces (b)(4) and will be used for commercial batches.

We note that the process described in the Executed Batch Record (EBR) in the original submission in Section 3.1.R appears to correspond to the Process (b)(4) which was not in the original submission in P.3.3.

Please provide the following information:

1. Has Process (b)(4) been used to manufacture any batches of the drug product? If so please provide a copy of the EBR for that process. We note that the submission of new information late in the review cycle can affect the review clock.

2. If Process (b)(4) has not been used to manufacture any batches of drug product then we recommend that you withdraw this process.
   - Please provide the stability data for this NDA in tabular format so that our statistic reviewers can analyze the data.
   - Please provide the manufacturing process information and a flow chart.

Please provide the appropriate information as an amendment to the submission. In addition, a copy of your response submitted by e-mail (youbang.liu@fda.hhs.gov) will expedite the review of your request. In your cover letter refer to the date on which this information was requested.

Please acknowledge the receipt of this email and provide the response by June 20, 2013.

Sincerely,

Youbang Liu, Ph.D.
Regulatory Project Manager
Division III, ONDQA/OPS/CDER/FDA
10903 New Hampshire Avenue
Building 21, Room 2525
Silver Spring, MD 20993
Phone: (301) 796-1926

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/s/

YOUBANG LIU
06/11/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: June 7, 2013

To: Dr. Kaushik Dave
Executive Vice President, Product Development

Phone: (609) 359-3020

From: Sadaf Nabavian, Pharm.D.
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: Comments re: NDA 204824

Thank you.

NDA 204824
Methotrexate
Antares Pharma, Inc.

Dear Dr. Dave:

Your NDA submission dated December 14, 2012, is currently under review and we have the following comments and requests for information:

We note that the methodology section of Clinical Study Report MTX-11-002 indicates that the interval between Visit 1 and Visit 2 was dependent upon the date of the participant's last dose of methotrexate and a minimal interval of 7 days was required between administration of the participant's last dose of methotrexate and visit 2. Additionally, if the participant's last methotrexate dose was administered ≥7 days prior to Visit 1, eligible participants were permitted to proceed to Visit 2 procedures after enrollment.

1. Specify how many participants in the study were permitted to proceed to Visit 2 procedures directly after Visit 1. Also, indicate the decay time between training and self-injection for these participants.

2. Specify how many participants in the study did not proceed to Visit 2 procedures directly after Visit 1. Also, indicate the decay time between training and self-injection for these participants.

In order to facilitate the review of your NDA submission, submit your responses to me via telephone facsimile to 301-796-9728 or email at Sadaf.Nabavian@fda.hhs.gov by COB, Monday, June 10, 2013. Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Sadaf Nabavian, Regulatory Program Manager, at 301-796-2777.

Initial Draft: SNabavian/06.07.2013

Cleared: LJafari/06.07.2013

Finalized: SNabavian/06.07.2013

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/s/

SADAF NABAVIAN
06/07/2013

Background Memo for PeRC Meeting on June 5, 2013

NDA 204-824: Otrexup (methotrexate) Auto-Injector

Introduction and Background

This is a 505(b)(2) new drug application submitted by Antares Pharma, Inc. for a drug/device combination of Methotrexate (MTX) Injection, a folate analog metabolic inhibitor, in an auto-injector presentation consisting of a single-use, single-dose, pre-filled, auto-injector fitted with a 27-gauge, ½ inch needle [total length] that delivers a fixed volume of 0.4 mL per injection as a sterile, preservative-free solution. Antares proposes to market four different dosage strengths of the device containing MTX doses of 10, 15, 20, or 25 mg (concentrations of (b) (4) , respectively). The intended route of administration is via subcutaneous (SC) injection. The needle is protected before use by a needle safety guard and safety cap and after use by a soft needle shield, giving an exposed needle length of at least 2.5 mm.

Methotrexate Tablets have been marketed since December of 1953 (NDA 8085, Dava Pharms Inc.) when the product was approved for the treatment of acute leukemia in adults. In addition to tablets, MTX is approved as an injection (NDA 11-719; approved 1959; Hospira) for intramuscular (IM), intravenous (IV), subcutaneous (SC), intra-arterial, and intra-thecal administration. This application references Methotrexate Sodium Injection EQ 50 mg base/2mL (NDA 11-719; Hospira), which is listed in the Orange Book as a reference listed drug (RLD) and was the originator for the generic methotrexate injectable products.

MTX is currently approved for the following indications when administered by the routes as shown below:

- Neoplastic disease (oral, IM, IV, intra-arterial, intra-thecal)
- Adult rheumatoid arthritis (RA) (oral; doses starting at 7.5 mg/week, up to 15 mg/week)
- Polyarticular-course juvenile rheumatoid arthritis (JRA) (oral, IM, SC; dosing based on BSA from 10 mg/m^2/week to 30 mg/m^2/week)
- Adults with severe recalcitrant disabling psoriasis that is not adequately responsive to other forms of therapy (oral, IM, and IV; doses of 10 to 25mg/week).

The Pediatric Use sections for both the tablets and the injectable products state that "the safety and effectiveness [of methotrexate] in pediatric patients have been established only in cancer chemotherapy and in polyarticular course juvenile rheumatoid arthritis".

The Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) is triggered by this application for the indications of RA and psoriasis, for which this is a new route of administration. However, the addition of an auto-injector to an injectable methotrexate, making this a drug/device combination, does not trigger PREA as this change is not considered a new dosage form.

Because the product is an auto-injector intended for self or caregiver use in the home setting, the proposed indications for this product are appropriately limited to RA, pJIA, and psoriasis, and do not include treatment of neoplastic diseases. However, the applicant has proposed to extend the current indication for psoriasis from symptomatic control of severe, recalcitrant, disabling psoriasis to moderate psoriasis, which requires a risk/benefit assessment for the newly proposed dermatological indication beyond an assessment of risk/benefit for the use of methotrexate by the subcutaneous route in the home setting. Therefore, the application was administratively split to

provide for review in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) and the Division of Dermatology and Dental Products (DDDP).

The application includes literature reviews, two bioavailability and bioequivalence studies in adults, and two labeling and use studies. The results of the BE study shows that SC administration using this product in either the abdomen or the thigh is bioequivalent to similar doses using a needle and syringe by SC or IM administration. The results of the BA study supports the efficacy of SC dosing because, when compared to oral exposure, SC dosing yields higher systemic exposures, particularly after absorption is saturated at and above doses of 15 mg.

RA and pJIA Indications

The literature submitted to this application supports the safety and efficacy of methotrexate administered SC and IM in adults with RA and children with pJIA. Combined with the BA/BE information provided, the application supports approval for RA and pJIA.

The current labeling for MTX for RA in adults includes dosing via the oral but not the SC route, whereas the labeling for pJIA includes dosing via the oral, IM, and SC routes. (b) (4)

Because pJIA is considered the pediatric counterpart of adult RA, PeRC suggested that the product would not trigger PREA for the RA/pJIA indications because pJIA is already labeled for SC use. However, DPARP believes that the RA indication triggers PREA because the RA indication is not labeled for SC dosing. For a 505(b)(1) application, triggering of PREA would require a pediatric assessment in children with pJIA down to 2 years of age, the lowest age that pJIA can be diagnosed. However, for this 505(b)(2) application that relies on the Agency's previous findings of safety and effectiveness by the SC route in children with pJIA for the injectable formulation in pJIA, once the links are provided for this drug to the reference product, PREA is satisfied by the approved indication (pJIA) and route of administration (SC).

The applicant has asked for a waiver in children 0 to 17 years because the product does not present a meaningful therapeutic benefit over the available already marketed generic products. This waiver request is likely directed to psoriasis, which is discussed in the next section. Based on the discussion above, the Division does not agree that a waiver for the entire pediatric age group is appropriate.

Likewise, the applicant has also asked for a waiver for children ≤6 years because dosing is based on body surface area (BSA) and the proposed product cannot be varied in small dosing increments that would be required for dosing in pediatric patients according to BSA or weight. This is based on the fact that the lowest proposed dose for this product of 10 mg is only appropriate for children starting at about 7-8 years of age and around 28 kg (62 pounds). However, as discussed above, the Division disagrees with this waiver request as well, and will consider the pediatric assessment to be complete for patients 2 years of age and older.

On the other hand, it is true that the applicant has not provided doses that will be appropriate for children of all ages. A 2 year old weighing 10 kg (22 pounds) would require a dose of 5 mg. Therefore, dosing in children typically starts at 5 mg, and increases in increments of about 2.5 mg. Above, 10 mg, the Division believes that increments of 5 mg are acceptable. If PREA had not been satisfied by the Agency's previous findings, the Division would have proposed that the applicant be required under PREA to develop 5 and 7.5 mg doses, 2.5 mg dosing increments being about the smallest increment that are typically used in this age range, which happens to

also correspond to the smallest increment that we believe is reasonable for such a convenience product. However, since PREA is satisfied for this indication by the Agency's previous findings, we will have to be satisfied that younger children will not have this product available to them.

Based on the above reasoning, DPARP proposes to waive the pediatric assessment for RA/pJIA in children below 2 years of age and consider the pediatric assessment complete for children 2 years of age and above. However, we will ask the applicant whether they would consider developing 5 and 7.5 mg doses that would be appropriate for use in younger children with pJIA.

Psoriasis

Methotrexate is currently approved for the indication of treatment of "severe recalcitrant disabling psoriasis that is not adequately responsive to other forms of therapy" administered by **oral**, **IM** or **IV** routes. As noted previously, safety and efficacy for this indication has not been established in children [although the only location where this is specified in the labeling for the oral tablets or the injectable solution is in the Precautions, Pediatric Use section].

The current application (Otrexup, NDA 20-4824) provides for the following changes for the psoriasis indication:

1. New route of administration: SC.
2. New indication: "Otrexup is indicated for treatment of **moderate** or severe **psoriasis**".

Because the applicant seeks approval for a new indication and new route of administration, this application is required under PREA to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The applicant has asked for a full waiver in children 0 to 17 years because the product does not present a meaningful therapeutic benefit over the available already marketed generic products. The Division agrees with granting of a waiver, but disagrees with the applicant's reasoning or justification.

Methotrexate has the potential for serious toxic reactions (which can be fatal). Methotrexate labeling carries Boxed WARNING for the following:

- METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS WITH SEVERE, RECALCITRANT, DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY.
- DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY, PSORIASIS, AND RHEUMATOID ARTHRITIS
- PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES
- Methotrexate causes hepatotoxicity, fibrosis and cirrhosis
- Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis which may occur at any time during therapy and at low doses.
- Hemorrhagic enteritis and death from intestinal perforation may occur
- Malignant lymphomas
- Occasionally fatal skin reactions
- Potentially fatal opportunistic infections

Further, it should also be noted that per current MTX labeling, periodic liver biopsy is recommended during the treatment of patient with psoriasis:

> "In psoriasis, liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) pretherapy or shortly after initiation of therapy (2 to 4 months), 2) a total cumulative dose of 1.5 grams, and 3) after each additional 1.0 to 1.5 grams."

Currently, there are several products approved for the treatment adult patients with moderate to severe or severe psoriasis: acitretin, cyclosporine, alefacept, infliximab, adalimumab, etanercept, ustekinumab. None of these products are approved for treatment of pediatric population with psoriasis because of increased risk of malignancies or serious adverse reactions.

Based on the above safety information for the use of methotrexate, the safety concerns posed by the drug outweigh the potential benefits of treatment in pediatric psoriasis. Therefore, it is the opinion of the Division that full waver of studies in pediatric population with psoriasis should be granted for safety reasons, and DDDP plans to label the product accordingly.

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/s/

PETER R STARKE
05/29/2013

SNEZANA TRAJKOVIC
05/30/2013

THERESA M MICHELE
05/30/2013

TATIANA OUSSOVA
05/30/2013

Liu, Youbang

From: Liu, Youbang
Sent: Friday, May 24, 2013 8:39 AM
To: 'Kaushik Dave'
Subject: Information Request for NDA 204824, Otrexup™

Antares Pharma, Inc.
Attention: Kaushik J. Dave, RPh., Ph.D, MBA
Executive Vice President, Product Development
100 Princeton South Corporate Center, Suite 300
Ewing, NJ 08628

Dear Dr. Dave:

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 204824, Otrexup™ (methotrexate) injection, received December 14, 2012. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your submission.

1. Please provide the stability data for this NDA in tabular format so that our statistic reviewers can analyze the data.

2. Please provide the manufacturing process information and a flow chart.

Please provide the appropriate information as an amendment to the submission. In addition, a copy of your response submitted by e-mail (youbang.liu@fda.hhs.gov) will expedite the review of your request. In your cover letter refer to the date on which this information was requested.

Please acknowledge the receipt of this email and provide the response by June 5, 2013.

Sincerely,

Youbang Liu, Ph.D.
Regulatory Project Manager
Division III, ONDQA/OPS/CDER/FDA
10903 New Hampshire Avenue
Building 21, Room 2525
Silver Spring, MD 20993
Phone: (301) 796-1926

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/s/

YOUBANG LIU
05/24/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: May 17, 2013

To: Dr. Kaushik Dave
Executive Vice President, Product Development

Phone: (609) 359-3020

From: Sadaf Nabavian, Pharm.D.
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: Comments re: NDA 204824

Thank you.

NDA 204824
Methotrexate
Antares Pharma, Inc.

Dear Dr. Dave:

Your NDA submission dated December 14, 2012, is currently under review and we have the following comments and requests for information:

1. Did the commercial-ready device used for all participants in the summative usability study contain placebo solution?

2. If so, was any placebo solution noted on the site of injection for any of the close call participants who injected with inadequate force to fully retract the needle shield and for those participants that held for less than 3 seconds?

3. Where there any cases of accidental firing of the device noted during the study?

In order to facilitate the review of your NDA submission, submit your responses to me via telephone facsimile to 301-796-9728 or email at Sadaf.Nabavian@fda.hhs.gov by COB, Friday, May 24, 2013. Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Sadaf Nabavian, Regulatory Program Manager, at 301-796-2777.

Initial Draft: SNabavian/05.17.2013

Cleared: LJafari/05.17.2013

Finalized: SNabavian/05.17.2013

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/s/

SADAF NABAVIAN
05/17/2013

Liu, Youbang

From: Liu, Youbang
Sent: Monday, May 06, 2013 10:39 AM
To: 'Kaushik Dave'
Subject: Information Request for NDA 204824, Otrexup™

Antares Pharma, Inc.
Attention: Kaushik J. Dave, RPh., Ph.D, MBA
Executive Vice President, Product Development
100 Princeton South Corporate Center, Suite 300
Ewing, NJ 08628

Dear Dr. Dave:

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 204824, Otrexup™ (methotrexate) injection, received December 14, 2012. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your submission.

1. Your application states that you purchase drug product sterilizing (b) (4). You also provide some information on production parameters and validation studies for (b) (4) sterilization, but more information is needed. Address the following points:
   a. State the site at which (b) (4) sterilization occurs.
   b. Describe dose mapping studies (b) (4).
   c. Describe routine dosimetry that takes place (b) (4).
   d. Describe the dose auditing schedule and methods (b) (4).

2. You describe annual requalification of (b) (4), and provide requalification data from 2011. More recent data are needed. Provide your most recent requalification data for this (b) (4)e.

Please acknowledge the receipt of this email and provide the amendment submission by May 20, 2013.

Regards,

Youbang Liu, Ph.D.
Regulatory Project Manager
Division III, ONDQA/OPS/CDER/FDA
10903 New Hampshire Avenue
Building 21, Room 2525
Silver Spring, MD 20993
Phone: (301) 796-1926

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/s/

YOUBANG LIU
05/06/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: April 30, 2013

To: Dr. Kaushik Dave
Executive Vice President, Product Development

Phone: (609) 359-3020

From: Sadaf Nabavian, Pharm.D.
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: Comments re: NDA 204824

Thank you.

NDA 204824
Methotrexate
Antares Pharma, Inc.

Dear Dr. Dave:

Your NDA submission dated December 14, 2012, is currently under review and we have the following comments and requests for information:

1. Provide six samples of the proposed trainer devices and the actual devices.

2. Provide details regarding whether the trainer device has been modified to provide a "click" similar to that of the actual device.

3. Provide the following information for study MTX-11-004:

    a. The training script used in Session 1.
    b. The medical training and experience of the professional caregivers.

4. Provide a copy of your test method for residual solvents in the drug substance, MA-0144.

5. During OSE's evaluation of your proposed proprietary name Otrexup, they noted that the proposed product is integrated with a device. They also noted that you have referred to the device component (b) (4) in the IFU. Although not currently a part of your proposed proprietary name, OSE acknowledges that the naming convention of adding a modifier to represent a specific device has been used before. Please clarify if you intend to use a modifier that refers to the name of the delivery device in which the medication is fully integrated or you intend to pursue only the root name Otrexup without the modifier (b) (4) for this product.

    Thus, taking the above into consideration, would you like OSE to continue with their proprietary name evaluation or would you like to withdraw your current request for proprietary name review and submit a new request for a proposed proprietary name review that includes a modifier for the device? (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

In order to facilitate the review of your NDA submission, submit your responses to me via telephone facsimile to 301-796-9728 or email at Sadaf.Nabavian@fda.hhs.gov by COB, Tuesday, May 7, 2013. Your responses (except item no. 1) will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Sadaf Nabavian, Regulatory Program Manager, at 301-796-2777.

Initial Draft: SNabavian/04.30.2013

Cleared: LJafari/04.30.2013

Finalized: SNabavian/04.30.2013

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/s/

SADAF NABAVIAN
04/30/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204824/Original 1
NDA 204824/Original 2

ADVICE

Antares Pharma, Inc.
100 Princeton South Corporate Center
Suite 300
Ewing, NJ 08628

Attention: Kaushik J. Dave, RPh., Ph.D, MBA
Executive Vice President, Product Development

Dear Dr. Dave:

Please refer to your New Drug Application (NDA) submitted section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Otrexup™ (methotrexate) injection.

NDA 204824 provides for the use of methotrexate injection for the following indications which, for administrative purposes, we have designated as follows:

- NDA 204824/Original 1 – rheumatoid arthritis and juvenile rheumatoid arthritis
- NDA 204824/Original 2 – moderate to severe psoriasis

NDA 204824/Original 1 will be reviewed by the Division of Pulmonary, Allergy, and Rheumatology Products and NDA 204824/Original 2 will be reviewed by the Division of Dermatology and Dental Products.

All future submissions to your NDA should specify the NDA number and all Original numbers to which each submission pertains.

If you have any questions, contact the following individuals:

For NDA 204824/Original 1 - Sadaf Nabavian, Senior Regulatory Project Manager at (301) 796-2777
For NDA 204824/Original 2 - Barbara Gould, Chief Project Management Staff at (301) 796-4224

Sincerely,

{See appended electronic signature page}

Sadaf Nabavian, Pharm.D.
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SADAF NABAVIAN
03/21/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204824

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Antares Pharma, Inc.
100 Princeton South Corporate Center
Suite 300
Ewing, NJ 08628

ATTENTION: Kaushik J. Dave, R.Ph., Ph.D., MBA
EVP Product Development

Dear Dr. Dave:

Please refer to your New Drug Application (NDA) dated December 14, 2012, received December 14, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Methotrexate Injection, 10 mg/0.4 mL, 15 mg/0.4 mL, 20 mg/0.4 mL, and 25 mg/0.4 mL.

We also refer to your December 19, 2012, correspondence, received December 19, 2012, requesting review of your proposed proprietary name, Otrexup. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Otrexup, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your December 19, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Sadaf Nabavian, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
03/13/2013

Liu, Youbang

From: Liu, Youbang
Sent: Saturday, March 02, 2013 4:39 PM
To: 'kdave@antarespharma.com'
Subject: Information Request for NDA 204824

Antares Pharma, Inc.
Attention: Kaushik J. Dave, RPh., Ph.D, MBA
Executive Vice President, Product Development
100 Princeton South Corporate Center, Suite 300
Ewing, NJ 08628

Dear Dr. Dave:

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 204824, Otrexup™ (methotrexate) injection, received December 14, 2012. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your submission.

1. Your application describes (b) (4) studies for container closure integrity testing performed on the primary container closure system. Please address the following points:
   a. Provide a justification for using (b) (4) testing as opposed to a more rigorous test such as (b) (4).
   b. Provide a justification for the use of "opened" syringes as positive controls in these tests. An example of a more appropriate positive control for a container closure of this type would consist of a container breached with a small gauge needle prior to exposure to test conditions.

2. Your application describes annual requalification studies for (b) (4). Describe the culturing and handling of these biological (b) (4).

3. Your application describes media fill simulations performed on the drug product filling line. Describe the environmental monitoring methods, schedule, and alert/action limits for these simulations, or state if they are the same as used in production.

Please acknowledge the receipt of this email and provide the time line of the amendment submission.

Regards,

Youbang Liu, Ph.D.
Regulatory Project Manager
Division III, ONDQA/OPS/CDER/FDA
10903 New Hampshire Avenue
Building 21, Room 2649
Silver Spring, MD 20993
Phone: (301) 796-1926

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/s/

YOUBANG LIU
03/02/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204824

FILING COMMUNICATION

Antares Pharma, Inc.
100 Princeton South Corporate Center
Suite 300
Ewing, NJ 08628

Attention: Kaushik J. Dave, RPh., Ph.D, MBA
Executive Vice President, Product Development

Dear Dr. Dave:

Please refer to your New Drug Application (NDA) dated December 14, 2012, received December 14, 2012, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Otrexup™ (methotrexate) injection.

We also refer to your amendment dated January 25, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**.

Therefore, the user fee goal date is October 14, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 17, 2013.

During our filing review of your application, we identified the following potential review issue:

1. We note that you have proposed labeling for moderate psoriasis. As a 505(b)(2) application, the indication for your product should match that for the reference product.

We are providing the above comment to give you preliminary notice of a potential review issue. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. Provide revised labeling that matches the labeled indication for psoriasis for the listed product.

2. Submit a copy of a Letter of Authorization from (b) (4) for Drug Master File (b) (4) containing specific references (e.g., dates of submission, page numbers) to the syringe for review in support of your New Drug Application. See the Guideline for Drug Master Files Section V.A. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073164.htm

3. Provide placebo samples of the drug product.

Also, during our preliminary review of your submitted labeling, we have identified the following labeling format issues in the package insert:

1. Highlight (HL) Section

   - For the Initial U.S. Approval date, use the original date of approval of the active ingredient
   - White space must be present before each major heading in the HL section
   - In the Highlights Limitation Statement, the name of the drug product must be in upper case
   - In the Boxed Warning
     - All text must be bolded
     - The word "Warnings" must be replaced with "Warning" and be bolded in the center heading with the subject(s) of the Warning
   - In the Dosage and Administration
     - Indicate administration (subcutaneous)
   - Dosage Forms and Strengths
     - A concise summary of dosage forms and strengths including any appropriate subheadings (e.g., injection)

2. Table of Contents (TOC)

   - The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI

- The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in upper-case letters and bolded
- Do not include FDA-approved patient labeling as a subsection heading in the TOC
- There should be no periods after the numbers for the section and subsection headings

3. Full Prescribing Information (FPI) Section

- Boxed Warning
  - All text should be bolded
  - The word "Warnings" must be changed to "Warning" and be bolded in the center heading with the subject(s) of the Warning
- When post-marketing adverse reaction data is included, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

  "The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

- There should be no periods after the numbers for the section or subsection headings

- Dosage and Administration

  - Provide basic dosing information first, followed by other information relevant to dosage and administration. The sequence of information should reflect the relative importance of the information to safely and effectively administer the drug. In unusual circumstances, certain dosage or administration information may be so important that it should precede the basic dosage information (e.g., for subcutaneous use only). This critical information should be placed in the first subsection heading under DOSAGE AND ADMINISTRATION (e.g., 2.1 Important Administration Instructions) that identifies the critical nature of the information.

- Patient Counseling Information
  - Reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

    "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

- Post-marketing Experience subsection
  - Include the following statement (or appropriate modification) preceding the presentation of AR: "The following adverse reactions have been identified during post approval use of methotrexate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

In addition, we have the following comments pertaining to the package insert and carton/container labels:

- The "how supplied" section should also describe the appearance of the drug product for identification.
- The "description" section should specify the dosage form and route of administration.
- The name of the drug product should include "injection" in all labels and labeling.
- Carton labels should include the inactive ingredients.

We request that you resubmit labeling that addresses these issues by March 12, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), patient package insert (PPI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient package insert (PPI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Sarah Yim, M.D.
Associate Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SARAH K YIM
02/26/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204824

NDA ACKNOWLEDGMENT

Antares Pharma, Inc.
100 Princeton South Corporate Center
Suite 300
Ewing, NJ 08628

Attention: Kaushik J. Dave, RPh., Ph.D, MBA
Executive Vice President, Product Development

Dear Dr. Dave:

We have received your New Drug Application (NDA) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Methotrexate Injection

Date of Application: December 14, 2012

Date of Receipt: December 14, 2012

Our Reference Number: NDA 204824

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 12, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory

registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 204824** submitted on December 14, 2012, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and
Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me, Regulatory Project Manager, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Sadaf Nabavian, Pharm.D.
Regulatory Project Manager
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SADAF NABAVIAN
12/27/2012

IND 103738

MEETING MINUTES

Antares Pharma, Inc.
Princeton Crossroads Corporate Center
Phillips Boulevard, Suite 290
Ewing, NJ 08618

Attention: Kaushik J. Dave, R.Ph., Ph.D., MBA
Executive Vice President, Product Development

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (b) (4) Methotrexate Autoinjector.

We also refer to the meeting between representatives of your firm and the FDA on November 02, 2012. The purpose of the meeting was to discuss the filing of your application as a 505(b)(2) for treatment of rheumatoid arthritis and psoriasis.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Sadaf Nabavian, Pharm.D.
Regulatory Project Manager
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B Meeting
Meeting Category:	Pre-NDA
Meeting Date and Time:	November 02, 2012, from 11:00-12:30 p.m. EST
Meeting Location:	Conference Room 1417
Application Number:	IND 103738
Product Name:	(b) (4) Methotrexate
Indication:	Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, (b) (4) and Severe Psoriasis
Sponsor/Applicant Name:	Antares Pharma, Inc.

FDA ATTENDEES

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sarah Yim, M.D., Associate Director, DPARP
Banu Karimi-Shah, M.D., Clinical Team Leader, DPARP
Deborah Seibel, M.D., Clinical Reviewer, DPARP
Prasad Peri, Ph.D., Chief, Branch VIII, Division of New Drug Quality Assessment III, ONDQA
Sheetal Agarwal, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II, OCP
Suresh Doddapaneni, Ph.D., Clinical Pharmacology Acting Team Leader, Division of Clinical Pharmacology II, OCP
Carol Rivera-Lopez, Ph.D., Pharmacology/Toxicology Reviewer, DPARP
Marcie Wood, Ph.D., Acting Team Leader, Pharmacology/Toxicology, DPARP
Mahesh Ramandham, Pharm.D., M.B.A, Acting Team Leader, DGMPA, OMPQ
Nichelle Rashid, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)
Carolyn Yancey, M.D., Safety Evaluator, OSE
Yongman Kim, Ph.D., Biostatistical Reviewer, Division of Biometrics II, OB
Jaqueline Ryan, M.D., Team Leader, Center of Devices and Radiological Health (CDRH)
Sadaf Nabavian, Pharm.D., Regulatory Project Manager, DPARP

SPONSOR ATTENDEES

Kaushik J. Dave, R.Ph., PhD, MBA, Executive Vice President, Product Development, Antares Pharma, Inc.
Gerald J. Orehostky, Vice President Quality and Regulatory Affairs, Antares Pharma, Inc.
Jonathan Jaffe, MD, Vice President Clinical Development, Antares Pharma, Inc.
Patrick Madsen, Vice President and General Manager Parenteral Products, Antares Pharma, Inc.
Susan Thornton, MS, Director of Regulatory Affairs, Antares Pharma, Inc.
(b) (4)

1.0 BACKGROUND

Antares Pharma, Inc. submitted a meeting request dated August 17, 2012, for a Pre-NDA Meeting to discuss the filing of (b) (4) MTX as a 505(b)(2) application for the proposed indications of rheumatoid arthritis, juvenile rheumatoid arthritis, (b) (4) and psoriasis. Upon review of the briefing package, the Division provided the preliminary comments on November 01, 2012. Any discussion that took place at the meeting is captured in the discussion sections. Antares' questions are in ***bold italics***; FDA's response is in *italics*; discussion is in normal font.

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

2. DISCUSSION

Questions and *Responses*

2.1. Clinical /Clinical Pharmacology/Statistics

Question 1:

Does the Agency agree that the clinical development program designed and executed by Antares and represented herein, is appropriate to support a fileable 505(b)(2) NDA for the currently approved MTX Injection, USP label indications for the treatment of:

- ***Rheumatoid Arthritis, including Polyarticular-Course Juvenile Rheumatoid Arthritis (JRA)*** (b) (4)
- ***Severe Psoriasis***

FDA Response:

In general, the summary of your clinical development plan in support of a 505(b)(2) NDA submission for (b) (4) *MTX is consistent with the advice provided by the Division during our End-of-Phase 2 (EOP2) meeting on September 13, 2011, and in our written responses dated February 10, 2012. Therefore, it appears that your clinical program is generally acceptable to support filing pending full review of the submission. In addition to the information provided, the following aspects should be addressed in the NDA and/or label:*

- *PK differences in patients with different body weights (see response to Q5)*
- *Data pertaining to dosing in special populations such as renal and hepatic impairment, elderly patients etc. seem to be available in the public domain. We encourage you to undertake a literature search to check if some of the known information is of sufficient quality to be incorporated into the product label.*

In addition, we do not agree that your data will necessarily be adequate to support an indication in (b) (4)*, which is currently not an approved indication. To support a new indication in* (b) (4)*, you will need to provide substantial evidence of efficacy of MTX in* (b) (4)*.*

It is questionable whether you will find compelling evidence in the literature, as a recent randomized, double-blind, placebo-controlled trial showed no effect of MTX in improving (b) (4) *You may submit the evidence and a final determination will be made after review of the data. Your efficacy argument must address the concerns raised by the* (b) (4) *study.*

Discussion:

The Sponsor acknowledged the Division's responses and stated that they will be taken into consideration and re-visited at a later time.

Question 2:

The clinical studies' datasets, studies MTX-11-001 and MTX-11-003, used in statistical evaluation of study outcomes will be provided in CDISC SDTM model 3.1.2 with Amendment I format and study reports in Module 5.3.1.2, for MTX-11-002 and MTX-11-004, will be provided in PDF format in Module 5.3.5.4 of the NDA.

a. ***Does the Agency agree with the proposed dataset format of the individual studies?***
b. ***Does the Agency agree with the proposed Module 5 location of the individual studies?***

FDA Response to 2a and 2b:

Yes, we agree.

Discussion:

No discussion occurred.

Question 3:

Does the Agency agree that the clinical studies summaries from the literature will be appropriate to support a fileable 505(b)(2) NDA for the current approved MTX label indications, via the subcutaneous route of administration, for the treatment of:

- ***Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis (JRA)*** (b) (4)
- ***Severe Psoriasis***

FDA Response:

As discussed at the September 13, 2011, End-of-Phase 2 (EOP2) meeting, in our post- meeting comments, and in our February 10, 2012, written responses, clinical summaries from the literature may support fileability of a 505(b)(2) application for your subcutaneous methotrexate product, pending full review of the submission. See our response to Question 1 with respect to the proposed indication in (b) (4) (b) (4)

Discussion:

No discussion occurred.

Question 4:

Does the Agency agree with the recommendation to provide the White Paper in Module 5.3.5.3?

FDA Response:

Yes, we agree.

Discussion:

No discussion occurred.

Question 5:

Does the Agency agree that the summary of the patient body weights obtained in study MTX-11-003 adequately covers the expected spectrum of body weights?

FDA Response:

You enrolled subjects ranging between 52-132 kg in your completed study MTX 11-003, which seems like a reasonable range to evaluate differences in absorption, if any, across various spectrums in this weight range. Acknowledging that the number of subjects in each of these suggested weight range categories may not be high, you should compare drug absorption using weight-normalized doses in 3 groups: subjects on the lower end of the spectrum (e.g. < 60 kg), subjects at the higher end of the spectrum (e.g. > 100 kg) and subjects in the more general weight range expected in the adult group (e.g. 60-100 kg). This comparison should be made within each of the 2 injection site groups, i.e., abdomen and thigh dosing groups, separately.

Discussion:

The Sponsor agreed to the Division's recommendations and stated that they plan to provide the data analysis in the NDA submission.

2.2. Chemistry, Manufacturing, and Controls and Office of Compliance

Question 6:

Does the Agency agree that the proposed documentation, as outlined above, is sufficient to support the approval of the alternative drug substance supplier when submitted Post-Approval as a CBE-0?

FDA Response:

A change in the drug substance manufacturer may involve multiple changes (e.g., process, equipment, facility). The significance of these changes, the compliance status of the firm, and the need for inspection will be evaluated upon submission of the supplement. A current and acceptable compliance status is required for approval. It is premature to discuss any post-approval supplements when the NDA is not approved.

Please find more information in the Guidance for Industry "Changes to an Approved NDA or ANDA"

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM077097.pdf

Discussion:

The Sponsor asked the Division about the need to conduct stability studies for the proposed multiple strengths and stated that all four strengths are very similar except for the difference in the amount of drug that gets added to each one. The Sponsor proposed to place two batches on stability: one for the lower strength (10 mg) and one for the higher strength (25 mg) to bracket the intermediate strength.

The Division replied that the Sponsor's proposal seemed reasonable, but that the evaluation of the data would occur during NDA review. The Division also recommended that the Sponsor submit the data for all four strengths as a CBE-30 for review.

Question 7:

Does the Agency agree that results from the (b) (4) MTX stability program for the eight (8) product registration lots and for the storage durations described above are sufficient for the Agency to assess product stability and render a decision with regard to (b) (4) MTX 24 month proposed shelf-life?

FDA Response:

Yes, we agree, provided all the appropriate parameters including leachables are reported in your NDA.

Additional Comment (nonclinical)

- *Provide structures of any impurities and degradants of the drug substance and drug product in your submission. Refer to ICH Guidances [ICH Q3A(R) and ICH Q3B] for possible qualification requirements. We remind you that impurities or degradants of active ingredients that are identified as structural alerts should be at or below acceptable qualification thresholds to support an NDA, as described in the draft FDA Guidance for Industry Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (December 2008).*

Discussion:

No discussion occurred.

Question 8:

As noted above, Antares respectfully requests allowance for submission of limited additional stability results during the NDA review cycle, but not to surpass, the sixth month of the review cycle (e.g., not later than the six (6) months after the Agency's filing of the NDA). Does the Agency agree with this approach?

FDA Response:

No. We expect a complete application at the time of submission to grant a reasonable shelf life.

Discussion:

No discussion occurred.

Question 9:

Does the Agency agree that the stability data for the four (4) additional strengths, (b) (4) (b) (4) stored at both 25°C/60%RH and 30°C/65%RH for up to 3 months, are sufficient for review of these additional strengths during the NDA review cycle?

FDA Response:

No. It is premature to comment on the acceptability of stability data for review of these additional strengths, when we have not evaluated the NDA.

Discussion:

No discussion occurred.

Question 10:

Does the Agency agree that Antares may assign the same proposed 24 month expiration date for the four (4) additional strengths, (b) (4) as the four original strengths, 10 mg/0.4 mL, 15 mg/0.4 mL, 20 mg/0.4 mL and 25 mg/0.4 mL, provided the 3 months of stability results at both 25°C/60%RH and 30°C/65%RH conditions meet shelf-life specifications and demonstrate stability profiles consistent with the four (4) primary product strengths evaluated through 24-months?

FDA Response:

Although we do not usually extrapolate the 3 months data to assign a 24 month shelf life, in theory your proposal may be reasonable. However we cannot comment on the acceptability of the shelf life of the original strength products since we have not reviewed the data (for all parameters including leachables) as yet. We note that the lowest strength (b) (4) is not bracketed in your original strengths.

Discussion:

No discussion occurred.

Question 11:

Commercial Process Validation Plan:

The manufacturing processes for all strengths of the (b) (4) MTX product differ only with regard to the formula (i.e. amount of excipients and drug substance weighed) (b) (4) . All strengths utilize the (b) (4) for fill volume and packaging. Therefore, Antares proposes to validate the (b) (4) MTX manufacturing process utilizing one (1) lot of each strength (10 mg/0.4mL, 15 mg/0.4mL, 20 mg/0.4mL and 25 mg/0.4mL) which will be defined in the commercial manufacturing process validation protocol. Antares has provided in Attachment 8 of this Briefing Package an outline of our Commercial Process Validation Plan to further support our proposal. This proposal provides for 4 lots to be manufactured which should be more than sufficient to confirm robustness of the manufacturing process.

Does the Agency agree with the proposed Commercial Manufacturing Process Validation Plan?

FDA Response:

It is your responsibility to conduct all studies necessary to assure that the commercial manufacturing process is capable of consistently delivering quality product. The number of lots for each strength included in a validation plan is not a performance criterion. We do not approve process validation plan, protocols, or specific batches used in process validation studies. The actual protocols, acceptance criteria and study outcomes will be evaluated during an inspection.

FDA requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)] but does not prescribe how that is to be accomplished as it will depend on multiple factors, some of which are specific to the complexity of the product and process.

We also refer you to the Guidance for Industry, Process Validation: General Principles and Practices (January 2011).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf

Discussion:

The Sponsor sought guidance on the validation process plans based on PDUFA V. The Sponsor proposed to submit data for the lower and higher dosage strengths (as noted above), with the parameter and sensitivity data as required for NDA submission, since the manufacturing of all fours strengths will be similar, (b) (4) The Division responded that the design of the process validation studies is at the discretion of the Sponsor, with the Division providing recommendations based on the results.

Question 12:

Does the Agency agree that the safety data obtained from Antares' four clinical studies along with the MTX safety literature to be summarized in our proposed White Paper is sufficient to support a fileable 505(b)(2) NDA for (b) (4) MTX from a safety perspective?

FDA Response:

Based on your summary information, your proposal appears to be sufficient to support a fileable 505(b)(2) NDA.

Discussion:

No discussion occurred.

Question 13:

Does the Agency agree that a REMS is not required for our (b) (4) MTX NDA?

FDA Response:

We acknowledge the white paper you submitted entitled, "Position Paper re: REMS Requirement for (b) (4) MTX" and, specifically, Section 9 (of this white paper) entitled, "Rationale for Why a REMS Should Not Be Required for (b) (4) MTX."

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your NDA.

Discussion:

No discussion occurred.

Question 14:

Does the Agency agree with Antares' plan to include, in the proposed (b) (4) ***MTX Package Insert,*** (b) (4) ***?***

FDA Response:

No, we do not agree. The issue of higher bioavailability of MTX delivered subcutaneously via the autoinjector as compared to the oral MTX product, can be communicated through relevant PK information in the package insert (b) (4)

Discussion:

The Sponsor acknowledged the Division's comments and replied that they plan to address these issues at the time of NDA submission.

Question 15:

Does the Agency agree that the current approved Hospira and Bedford Package Inserts, along with our IFU, White Paper and clinical and safety data may be used as a basis for creating the (b) (4) ***MTX Package Insert?***

FDA Response:

The currently approved Hospira and Bedford Package Inserts, along with your IFU, supportive data from the literature, and clinical and safety data may be used as a starting point for creating the (b) (4) *MTX package insert. However, we remind you that the package insert for your product will be expected to conform to the Physician's Labeling Rule (PLR).*

Discussion:

No discussion occurred.

Question 16:

Does the Agency agree that this 505(b)(2) application from a clinical perspective, (b) (4) ***?***

FDA Response:

(b) (4)

Discussion:

No discussion occurred.

Question 17:

Does the Agency agree that the (b) (4) ***MTX 505(b)(2) NDA is considered under the PDUFA to be a human drug application requiring clinical data for approval?***

FDA Response:

We have previously discussed our expectations for your application. (b) (4) (b) (4)

Also, additional general comments regarding filing of 505(b)(2) applications are provided below:

- *FDA recommends that sponsors considering submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54 and FDA's Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf. In addition, the FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408, available at http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf.*
- *If you intend to submit a 505(b)(2) application that relies on approval of FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a bridge (e.g., via a relative bioavailability study) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference, but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.*
- *If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not*

limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies. The use of labeling statements taken from the labeling of other drug products may cause those products to also be listed drugs. It is important to identify all listed drugs at the time of the initial 505(b)(2) NDA submission.

- *Circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product was approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.*

Discussion:

The Sponsor inquired as to whether PDUFA fees could be reduced, since no clinical data will be submitted with the application. The Division replied that we are unable to answer user fee questions at this time, but would provide contact information in a post-meeting note.

Post-Meeting Note:

For any user fee question, contact either Bev Friedman or Mike Jones at 301-796-3602.

Question 18:

Does the Agency agree that a full waiver for the requirement to provide pediatric information to the NDA for the proposed indications: RA, JRA, (b) (4) and Psoriasis is acceptable?

FDA Response:

No, we do not agree. Because an application for a new route of administration would trigger a requirement for pediatric assessments under the Pediatric Equity Research Act (PREA), a plan for addressing PREA requirements would need to be submitted with the NDA. It is unlikely that you would receive a full waiver for JRA studies.

It is possible that a pediatric assessment for the efficacy and safety of SC MTX in a pediatric population could be largely derived from the literature. However, additional clinical data may be necessary to support the efficacy and safety of your product in pediatric patients. For example, it may be necessary to perform a study in the smallest/youngest pediatric patients to provide evidence that the available presentations are appropriate and safe in the pediatric population.

Discussion:

The Sponsor sought clarification regarding the Division's comments on PREA requirements and (b) (4) and stated that they do not believe that MTX SC is a new route of administration since the SC route is already approved and part of the MTX current label. The Sponsor furthermore indicated that the label has information on the pediatric population ages 2-16 years old. The Sponsor then commented that they feel strongly that a pediatric waiver should be applicable in this scenario. The Division replied that the label does not include SC administration in RA patients, thus triggering PREA requirements. The Division clarified that the intent of our comment was as guidance, so that the Sponsor would address the pediatric plan at the time of NDA submission, and not to imply that pediatric studies would definitely be required. The Sponsor should submit what they feel to be an appropriate proposal to address PREA in the

NDA submission (which may include literature support, prior labeling, etc). The proposed pediatric plan would then be presented to the Pediatric Review Committee (PeRC), and based on their guidance, the Division would then decide on the acceptability of the proposed plan. The Division also provided some highlights regarding PeRC, and explained to the Sponsor the review process, communications that occur, and the timelines of the review.

(b) (4)

Question 19:

Considering the nature of this NDA 505(b)(2) submission, does the Division agree that an ISS is not required for this NDA?

FDA Response:

No, we do not agree. The ISE and ISS are detailed integrated analyses of all relevant data from clinical study reports, are required by the regulations, and would be located in Module 5. However, if you believe section 2.7.3 (Summary of Clinical Efficacy) and section 2.7.4 (Summary of Clinical Safety) would be sufficiently detailed to serve as the narrative portion of the ISE and ISS, respectively, then you may place the narrative portion of your integrated assessment in Module 2 and place the appendices of tables, figures, and datasets in section 5.3.5.3. In this case, an explanation should be placed in both Module 2 and in Module 5.

Discussion:

No discussion occurred.

Question 20:

Again, due to the nature of this NDA 505(b)(2) submission, does the Division agree that an ISE is not required for this NDA?

FDA Response:

No, we do not agree. Refer to our response to Question 19.

Discussion:

No discussion occurred.

Question 21:

Does the Agency agree that the appropriate RLD for citation in our NDA is Hospira NDA# 011719, Methotrexate Sodium Preservative Free, approved on August 19, 1959?

FDA Response (clinical):

If a 505(b)(2) application seeks to rely on the Agency's previous finding of safety or efficacy for a product, then that product should be identified as a listed drug. In some cases, more than one listed drug may be applicable; for example, your application may list both Hospira's NDA 011719 (IM MTX) and Dava's NDA 008085 (Oral MTX) as reference products.

2.3. Center for Devices and Radiological Devices (CDRH)

Discussion:

No discussion occurred.

Question 22:

Does the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) agree that the separate MAF is not required to be provided for the NDA to be able to provide demo devices to physicians commercially?

FDA Response:

If there is no MAF, then CDRH requires that data comparable to what would be submitted to a MAF be submitted to the NDA for a demo device. Preliminary performance data should be documented and formative design validation studies should be completed before demo devices are provided commercially.

Discussion:

The Sponsor sought further clarification from CDRH regarding the demo device and MAF. The Sponsor stated that the meeting that took place with CDRH on April 2012 was very productive, with clear guidance being provided with respect to the MAF and other device-related issues.

The Sponsor added that during their meeting with CDRH, a discussion took place regarding the demo device in which Antares' communicated their intent for practitioners to use the demo device to demonstrate proper use to their patients. The Sponsor assured the Division that the demo device will not have any commercial value and it will contain neither drug nor an attached syringe. Based on this clarification, CDRH stated that it will not require the Sponsor to submit a separate MAF for the demo device.

Question 23:

Antares requests the Agency's guidance pertaining to the information, including labeling, required to be provided in the NDA to be able to provide demo devices to physicians commercially.

FDA Response:

The device should be clearly labeled " Not FDA cleared or approved, Not for Human Use."

Discussion:

No discussion occurred.

Question 24:

Antares requests the Agency's guidance pertaining to the information, including labeling, required to be provided in the NDA to be able to allow consumer to ship used devices to Antares's designated facility for appropriate disposal of used devices.

FDA Response:

You will need to check each State's requirements for disposal of household medical waste as well as the requirements of the US Postal Service or any other potential shipper.

Discussion:

No discussion occurred.

3.0 PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

4.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

5.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

6.0 ATTACHMENTS AND HANDOUTS

None

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

/s/

SADAF NABAVIAN
11/28/2012

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: May 23, 2012

To: Kaushik Dave	**From:** Ladan Jafari
Company: Antares Pharma	Division of Pulmonary, Allergy and Rheumatology Products
Email: Kaushik Dave [kdave@antarespharma.com]	**Fax number:** 301-796-9728
Phone number: 609-359-3020	**Phone number:** 301-796-1231

Subject: IND 103738

Total Number of Pages Including Cover: 4

Comments: CMC comments

Document to be mailed: YES ☑ NO

Dear Dr. Dave:

In response to your email inquiry dated May 14, 2012, we have the following comments. Your questions are noted below in Italics followed by our response in normal font.

> *Our intent was to obtain agency concurrence on our approach on qualifying an alternative methotrexate (API) supplier, not only for inclusion in our IND but also our NDA which we plan to file shortly. Methotrexate is compendial grade material (USP grade) and hence Antares Pharma intends to execute the following qualification activities:*

- *Obtain and review three (3) recent Certificates of Analysis from the supplier to verify conformance to the USP monograph for methotrexate*

- *Analyze sample from at least one (1) lot of methotrexate supplied by* (b) (4) *to verify conformance to the USP monograph for methotrexate,*

- *Obtain a Letter of Authorization from* (b) (4) *to permit access to their DMF in association with Antares IND 103,738 and forthcoming NDA.*

Kindly let us know whether the agency concurs with our proposal.

We provided the following feedback to you on May 22, 2012, and notified you that additional feedback would be forthcoming:

We find your approach reasonable. Please note that we also need release and stability data on drug product lots manufactured with the new source of drug substance as well.

We have the following additional comments:

The Chemistry, Manufacturing, and Controls (CMC) information for the drug substance to be used in Phase 3 trials, whether from your current supplier or from a new supplier, should follow the recommendations in the "Guidance for Industry: INDs for Phase 2 and Phase 3 Studies, Chemistry, Manufacturing, and Controls Information" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070567.pdf . Reference to USP testing is not sufficient. If a DMF is referenced, whether form the existing supplier or a new supplier, it will be reviewed to determine whether the information in the DMF is acceptable to support the Phase 3 trials. If a new supplier of the drug substance is used for the Phase 3 trials or for the NDA, the drug substance will have to be qualified in terms of its effect on the quality of the drug product. The information expected to be provided is similar to the information recommended for a post-approval supplement when a new supplier is added e.g., release and stability data for the drug product (including a complete impurity profile) manufactured using the additional source of methotrexate.

See the Guidance for Industry: Changes to an Approved NDA or ANDA.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf

Alternatively you may add the new supplier after approval of the NDA as a supplement.

I may be reached at 301-796-1231 for any questions.

Ladan Jafari
Chief, Project Management Staff

Drafted by: LJ/5-2312

Initialed by: Peri/5-23-12

Filename: I103738 CMC Comments.doc

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

/s/

LADAN JAFARI
05/23/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 103738

MEETING REQUEST-
Written Response

Antares Pharma, Inc.
250 Phillips Boulevard
Suite 290
Ewing, NJ 08618

Attention: Kaushik J. Dave, RPh, PhD, MBA
Executive Vice President Product Development

Dear Dr. Dave:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (b) (4) Methotrexate.

We also refer to our November 18, 2011, communication notifying you that we would provide written responses to the question included in your November 08, 2011, meeting request within 60 days after receiving the briefing materials. The briefing materials were received on December 16, 2011.

Our responses to your questions are enclosed. If you have any questions, you must submit a new meeting request.

If you have any questions, call me at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Sadaf Nabavian, Pharm.D.
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II/Office of New Drugs
Center for Drug Evaluation and Research

Enclosure

Question 1:
Does the Agency concur with the revised design of the in vivo local tolerance study?

FDA Response:
We concur with your revised design. However, after review of the information submitted in your December 16, 2011, briefing document, we have determined that the available clinical data using Subcutaneous (SC) methotrexate (MTX) are sufficient to assess safety of the SC injection. If you have not conducted this nonclinical study, note that it is not considered necessary. However, if you have completed the study, submit the data to the IND for review.

Question 2:
The (b) (4) MTX Clinical Development Plan, as discussed during the 13 September 2011 EOP-2 Meeting, summarizes the clinical steps necessary to achieve a successful NDA submission. This Clinical Development Plan was developed based on the recommendations provided by the Agency in the EOP-2 Meeting and is provided in Attachment 1 of the Briefing Document for the Agency review and feedback.
Does the Agency agree with the proposed plan to support a successful NDA submission for (b) (4) MTX or have any further feedback?

FDA Response:
In general, the summary of your proposed clinical development plan in support of an NDA submission for (b) (4) MTX is consistent with the advice provided by the Division during our End-of-Phase 2 (EOP2) meeting on September 13, 2011. Details regarding the Summative Usability Study are being addressed via correspondence with CDRH, and specific questions regarding your Actual Human Use (AHU) study are provided below.

Based on the limited information in the briefing document, your proposed relative bioavailability study would include three treatment arms: 1) oral methotrexate, 2) SC methotrexate delivered via the Vibex device, and 3) SC methotrexate via a vial and syringe presentation. In your e-mail dated January 30, 2012, you inquire regarding the suitability of substituting the commercially unavailable Bedford MTX with Hospira's MTX for the third treatment arm. As you have already performed a PK study assessing the relative bioavailability of (b) (4) MTX Autoinjector SC vs. IM MTX and SC MTX, that study could be used to support arguments that 1) your device does not negatively impact subcutaneous delivery, and 2) your drug/device combination product results in exposures that are no greater than exposures that would be achieved with approved IM MTX administration of the same dose. The purpose of a relative bioavailability to oral methotrexate would be to allow for bridging to the oral dosing information for MTX in rheumatoid arthritis (RA). Therefore, we do not believe it is necessary to include an arm with a different company's MTX for SC administration in this study. We remind you that this protocol should include study of the relative bioavailability of your product in RA over a spectrum of body weights. Although bioequivalence is not expected to be demonstrated in light of the different routes of administration, we suggest that you use the BE criteria to analyze the data.

Question 3:
AHU study will assess the performance of the device, clarity of Instruction for Use (IFU), and local injection site reaction(s) in patients with rheumatoid arthritis (RA). Antares proposes to perform this study in RA patients; therefore, the AHU study will only evaluate 10, 15, 20 and 25 mg doses and will not evaluate placebo.
Does the Agency concur?

FDA Response*:*
In general, your currently proposed AHU study is acceptable. The AHU study should also capture actual use of the device over the proposed shelf-life of your product. While the proposed AHU study is reasonable, we remind you that the actual use of your product by patients will consist of chronic, repeat-dosing, in an outpatient environment. As a result, your NDA submission should include safety information, which provides justification for chronic, repeat, subcutaneous dosing of methotrexate. This information may be provided from the literature, including the use of SC MTX in indications other than RA**.**

Question 4:
AHU study will evaluate 10, 15, 20, and 25 mg (b) (4) ***MTX dose in a total of 100 RA patients. Inclusion criteria for distribution of the subjects across these four (4) doses will be not less than 20 patients in each dose level.***
Does the Agency concur?

FDA Response*:*
Your proposal is acceptable.

Question 5:
The primary objective is to assess the safe usability of the VIBEX MTX device for SC self injection with MTX in adult patients with RA after standardized training by site personnel and review of written instructions.
Does the Agency concur with the primary objective?

FDA Response*:*
The primary objective is acceptable.

Question 6:
The secondary objectives of the study include evaluation of the reliability and robustness of the VIBEX MTX device performance; assessing the safety and local tolerance of an SC self injection with MTX using the VIBEX MTX device; and evaluation of the effectiveness and ease of use of the VIBEX MTX device patient education tools, including written instructions for use and SC self-injection training administered by site personnel.
Does the Agency concur that this is appropriate?

FDA Response*:*
The secondary objectives are acceptable. However, we remind you that evaluation of the reliability and robustness of your device in the AHU study should take place after validation of the device with thorough bench testing. In addition, you should perform a risk analysis of user tasks to establish risk-related priority prior to performing the simulated use testing and having patients use the product for actual treatment. Your evaluation should include performance and subjective data on critical/essential tasks and follow up on any observed or reported difficulty or incident related to use of the device to determine its cause and to obtain the perspective of the study participant regarding the difficulty/incident.

Question 7:
The primary endpoint for determination of safe usability is successful SC self-injection using the VIBEX MTX device. Successful SC self-injection will be defined by patient report and inspection of the used device by site personnel to confirm delivery of study drug.
Does the Agency concur?

FDA Response*:*
Your proposal is acceptable**.**

Question 8:
Secondary endpoints include ease of use questionnaire scores for the VIBEX MTX device; ease of use and training confirmation questionnaire scores for written patient instructions and SC self-injection training; self-reported Visual Analog Scale (VAS) questionnaire scores for pain at the injection site; and injection site assessment numerical grades.

Additional safety evaluations will include adverse events and vital signs.
Does the Agency concur?

FDA Response:
Your proposal is acceptable.

Question 9:
Only safety evaluation in the AHU study will be local injection site reactions.
Does the Agency concur?

FDA Response*:*
Your proposal is acceptable. However, all adverse events should be recorded and included with your NDA submission.

Question 10:
AHU study is a safety study and Antares proposes to submit the study results within the 120 day safety reporting period post NDA submission.
Does the Agency concur?

FDA Response:
We do not concur. The AHU study provides important data regarding the use of your device by patients. Your NDA should be complete with the results of the AHU study at the time of the NDA submission.

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

/s/

SADAF NABAVIAN
02/10/2012

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: October 13, 2011

To: Gerald J. Orehostky, V.P. Qualilty and Regulatory Affairs	From: CDR Sadaf Nabavian Regulatory Project Manager
Company: Antares Pharma, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 609-359-3015	Fax number: 301-796-9718
Phone number: 609-359-3020	Phone number: 301-796-2777
Subject: IND 103738 /Final Meeting Minutes	
Total no. of pages including cover: 21	

Comments: Please confirm receipt.

Document to be mailed: YES xNO

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	Type B Meeting
Meeting Category:	IND
Meeting Date and Time:	September 13, 2011 at 9:00 A.M.-10:30 P.M.
Meeting Location:	Conference Room 1313
Application Number:	IND 103738
Product Name:	(b) (4) Methotrexate (b) (4)
Received Briefing Package	August 08, 2011
Sponsor Name:	Antares Pharma, Inc.
Meeting Requestor:	Gerald J. Orehostky Ph.D. V.P., Quality and Regulatory Affairs
Meeting Chair:	Badrul A. Chowdhury, M.D., Ph.D. Division Director
Meeting Recorder:	Sadaf Nabavian, Pharm.D. Regulatory Management Officer

Meeting Attendees:

FDA Attendees

Division of Pulmonary and Allergy Products

Badrul A. Chowdhury, M.D., Ph.D., Division Director of Pulmonary, Allergy, and Rheumatology Products (DPARP)-via phone
Deborah Seibel, M.D., Clinical Reviewer, DPARP
Sarah Yim, M.D., Clinical Team Leader, DPARP
Sally Seymour, M.D., Deputy Director for Safety, DPARP
Joan Buenconsejo, Ph.D., Acting Biotatistical Team Leader, Division of Biometrics II, OB
Prasad Peri, Ph.D., Chief, Branch, Division of Premarketing Assessment III, Brach VIII, ONDQA
Carol Rivera-Lopez, Ph.D., Pharmacology/Toxicology Reviewer
Cathy Miller, MPH, BSN, Safety Evaluator, DMEPA
Robin Duer, R.N., MBA, Senior Patient Labeling Reviewer, OSE
Nichelle Rashid, Safety Regulatory Project Manger, OSE
Molly Topper, Ph.D., Pharmacology/Toxicology Supervisor
Suresh Doddapaneni, Ph.D., Clinical Pharmacology Acting Team Leader, Division of Clinical Pharmacology 2, Office of Clinical Pharmacology

QuynhNhu Nguyen, LT, USPHS, Biomedical Engineer/Injection Systems Human Factors Specialist, Human Factors Pre-Market Evaluation Team, CDRH
Sadaf Nabavian, Pharm.D., Regulatory Management Officer, DPARP

Sponsor Attendees

Gerald Orehostky, Ph.D., V.P., Quality and Regulatory Affairs
(b) (4)

1.0 BACKGROUND

Antares Pharma, Inc. submitted a meeting request dated May 24, 2011, for a Type B End-of-Phase 2 Meeting to discuss their proposed development plan to support the registration of (b) (4) Methotrexate in the treatment of rheumatoid arthritis. Upon review of the briefing package, the Division provided the preliminary comments on September 09, 2011. Any discussion that took place at the meeting is captured in the discussion sections. Antares' questions are in ***bold italics***; FDA's response is in *Italics*; discussion is in normal font.

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

2. DISCUSSION

QUESTIONS *and RESPONSES*

We have the following Introductory Comments regarding your development program.

1. *Your development program does not address dosing information for the subcutaneous route of administration. Your completed PK study does not provide information that informs the dosing for subcutaneous methotrexate (MTX).*

2. *Your program should include a bioavailability comparison of subcutaneous* (b) (4) *methotrexate and oral methotrexate. This information is necessary because patients may be transitioned from oral MTX to subcutaneous MTX.*

3. *The bioavailability of your product could vary based on the site of injection. Your proposed instructions for use propose injections in the abdomen or thigh; however, your completed PK study did not include both sites of injection with your device. You should address this inconsistency, or provide data to support the proposed injection sites.*

4. *You will need to evaluate device reliability and robustness with additional patient use data, including collection and evaluation of devices after actual use in patients, e.g.100 patients.*

5. *We recommend that you fully develop the device component, conduct verification and validation testing including a summative Human Factors study, before conducting your pivotal clinical program.*

6. *Regarding the device, you should initially demonstrate thorough bench testing that the autoinjector is safe and effective for its intended use. Specifically, you should ensure that the device conforms to the ISO Standard ISO 11608-1, Pen-Injectors for Medical Use – Part 1: Pen Injectors – Requirements and Test Methods, and ISO 11608-2, Pen-Injectors for Medical Use – Part 2: Needles – Requirements and Test Methods. You should also ensure that the autoinjector adheres to the recommendations within FDA's Draft Guidance, Technical Considerations for Pen, Jet and Related Injectors Intended for Use with Drugs and Biological Products. Regarding the prefilled syringe that contains the methotrexate drug product, you should ensure that this syringe conforms to the ISO 11040-4, Prefilled Syringes – Part 4: Glass Barrels for Injectables.*

   Also, it appears that your autoinjector contains a Sharps Injury Prevention Feature, in that there is a safety mechanism that deploys post injection to prevent inadvertent needle stick injuries. The FDA has a guidance regarding demonstrating the safety and effectiveness of this feature titled, Medical Devices with Sharps Injury Prevention Features, (August 9, 2005). Per this guidance, you should perform 500 activations of your autoinjector and demonstrate that there

are zero (0) failures of the sharps injury prevention mechanism within these 500 activations. This demonstrates that you have achieved a 99% confidence interval in demonstrating the safety and effectiveness of this element of the autoinjector.

Additionally, you stated the device is designed to deliver the medication in less than (b) (4) Submit device performance data to demonstrate that the device as designed can deliver the medication in less than (b) (4). You also stated that this device is intended for subcutaneous injection. You should provide the performance data to demonstrate that the needle penetration depth is consistent with the typical depth for a subcutaneous injection.

7. *We suggest that you request a meeting with CDRH, regarding the development of the device, especially if you plan to submit a 510K application or device master file for the device.*

Discussion:

The sponsor opened the discussion noting that they plan to follow- up on the suggestion to have a meeting with CDRH.

With regards to introductory comments 1 and 2, the sponsor stated that they strongly believe that their current proposed bridging study would be adequate to submit a 505(b)(2) application and that the reliance listed drug is the IM route with the supportive data as it was recommended by the Division during the Pre-IND meeting dated February 05, 2009.

The sponsor proceeded by projecting the labeling of the package insert for methotrexate injection, NDA 011719 and ANDA 089340 (enclosed), as a reference and for further points of discussion. The sponsor noted that the original RLD does have dosing information for the parenteral route of administration.

The Division noted that the dosing information proposed by the sponsor in the reference label is not clear and appears to be for polyarticular-course juvenile rheumatoid arthritis patients. The Division does not want to perpetuate ambiguous labeling. Because of the lack of clear dosing information for the parenteral route, the sponsor will need to provide information to support the proposed dosing for the subcutaneous product to label the product appropriately. Since oral dosing information is available and patients may be transitioned from oral to subcutaneous route of administration, linking the subcutaneous product to the oral product is a path forward.

The sponsor shared their frustration with the Division and elaborated that from the Pre-IND meeting the sponsor had planned to bridge the SQ to both the IM and PO routes of administration. But based on the Pre-IND meeting discussion they understood the necessary comparison was between the IM and SC routes. The Division clarified that in the Pre-IND meeting the Division's recommendation was that bridging to IM was necessary for toxicity studies. However, they also need to bridge to the PO route of

administration if they want to link to the efficacy, safety, and dosing for oral methotrexate.

The Sponsor asked if a pharmacokinetic link to the oral product was sufficient to bridge the efficacy, safety, and dosing information for the oral and subcutaneous product. There was some discussion regarding the term "bioequivalent" and the fact that it does not apply in this case because it means the product is pharmaceutically equivalent and interchangeable. Instead the phrase "equal in exposure to the RLD" may be more applicable. The Division noted that pharmacokinetic data could bridge to the pharm/tox data. However, further internal discussion was necessary to determine whether a PK bridging study comparing the oral and subcutaneous routes of administration was sufficient to support link to the efficacy, safety, and dosing for the oral product. The Division had considered an efficacy, safety, and PK study comparing the two routes of administration. This would provide useful information to inform the product label and practitioners and to obtain patient use information as well. The Division further commented for the sponsor to keep in mind that the methotrexate label from the past reflects the period during which it was approved. The RLD label does not reflect the information that would be required today so the Sponsor has the opportunity to provide useful information to update the label.

The sponsor further elaborated on a proposed PK study bridging 4 doses of SC and PO medication. The Sponsor asked if the Division expects an efficacy trial as well. The Division committed to discuss the need for the sponsor to conduct another efficacy trial and the response will be provided in the post-meeting comments.

The sponsor further elaborated on the following proposed programs. The Sponsor stated that one proposal would be an Actual Human Use Study to evaluate the safety aspects of the device (e.g. adverse reaction on site of injection, device performance, etc.) and also to conduct a Comparative Exposure Study, which would be a small PK study of anywhere from 15-30 patients comparing oral dosing to SQ at doses of 10, 15, 20, 25, and 25 mg as a two-way cross-over single dose PK study, the results of which will allow for links between each oral dose to the SC. In regards to the Actual Human Use Study, it will be conducted open label in which the results will demonstrate the device performance, evaluate the instruction for use, and any reactions that may occur at the injection site.

1. BA study with oral and subcutaneous-single dose BA study is acceptable
2. Human Factors/Usability Validations:
    a. Simulated Human Factors validation (summative) study (with placebo and injection pads), and
    b. Actual Human Use Study (with placebo and actual injection into skin)

Post-meeting comment: for clarity purposes the Division recommends specific terms for studies evaluating different aspects of "usability." For the usability validation where subjects are performing actual injections to themselves, the term "Usability Study" is changed to "Actual Human Use Study".

The Sponsor questioned whether a single dose BA study is sufficient to compare the oral and subcutaneous MTX and the Division found this acceptable. The Division stated that for the Actual Human Use Study they need active patients with RA with active drugs and need adequate number of patients (e.g. at least 100 patients) to use and collect the data, independent of strengths. The Human Factors study can be conducted with placebo. The Division committed to discussing the above program internally and addressing in a post-meeting note comment.

Post-meeting comments: It may be sufficient to provide a pharmacokinetic bridge between the oral and subcutaneous product and rely on the finding of safety and efficacy of the oral methotrexate product, such that a separate efficacy study would not be necessary.

With regards to the proposed Actual Human Use studies, the proposal for an actual use study and a Human factors study are consistent with the Division recommendations; however, without details of the overall program and proposed studies, the Division cannot comment regarding the adequacy of the proposal. The Division suggests that the Sponsor provide more details regarding the proposed program in a submission with request for feedback.

With regards to introductory comment 3 regarding the sites of injection, the sponsor proposed to (b) (4) noted in the IFU. The Division noted this was one approach and the sponsor would have to provide data to support the site of injection(s).

The Sponsor questioned whether the PK study could be submitted as an SPA. The Division noted that a PK study is not appropriate for submission as an SPA.

Clinical

Question 1:

Based on the results of the recently completed PK study does the Agency concur with our conclusion of bioequivalence?

FDA Response:

We do not agree. Refer to our Introductory Comments regarding the link to oral PK data. Pending thorough review, based on the top level results of the bridging Study MTX-10-001 you submitted, the systemic exposure (in terms of Cmax and AUC) of your proposed product is similar to the IM and SC route of methotrexate administration of the reference product administered without an autoinjector.

Discussion:

No discussion occurred.

Question 2:

Does the Agency concur that the efficacy evidentiary requirement for MTX delivered subcutaneously is fulfilled by the published clinical literature?

FDA Response:

We do not agree. You seek to meet the evidentiary requirement for efficacy of subcutaneous MTX utilizing published trials. You provided a summary of the literature and the most applicable study would be the 2008 Arthritis & Rheumatism article comparing oral vs. subcutaneous MTX in patients with active RA. However, to consider this trial as supportive for efficacy, complete access to the data would be necessary. A determination of the adequacy of this trial to support the efficacy of subcutaneous MTX can only be made after review of the submitted data.

One option may be to conduct an adequate and well-controlled clinical trial in patients with RA comparing subcutaneous (b) (4) *MTX to oral MTX and include efficacy, safety, patient use, and PK assessments to address the concern above and concerns outlined in the introductory comments.*

Discussion:

No discussion occurred.

Question 3:

Based on the preceding conclusion, does the Agency concur that the published clinical literature of subcutaneous MTX can be utilized to meet the evidentiary requirement to fulfill Phase 3 efficacy and safety requirement for (b) (4) ***MTX 505(b)(2) New Drug Application?***

FDA Response:

No, we do not agree. Refer to our response to Question 2 and our Introductory Comments.

Discussion:

No discussion occurred.

Question 4:

Does the Agency agree that based on Antares' data and conclusions described in Questions #1, #2 and #3 above, all the clinical efficacy and safety requirements for filing a NDA have been met?

FDA Response:

No, we do not agree. Refer to our responses to Questions 2 and 3.

Discussion:

No discussion occurred.

Question 5:

Due to a potential patent infringement issue, does the Agency concur that in lieu of injecting 0.4 mL of the (b) (4) concentration to achieve a 20 mg dose we can inject (b) (4) concentration to achieve the same dose.

FDA Response:

From a clinical perspective, it is acceptable to use the smaller volume (b) (4) of the (b) (4) concentration to achieve a 20 mg dose. Based on the results of PK Study MTX-10-001, the proposed volume difference is unlikely to affect the bioavailability of the product. However, you should address any accommodations necessary for the smaller injected volume in the device.

Discussion:

No discussion occurred.

General

Question 6:

Does the Agency concur that the proposed Instructions for Use (IFU) complies with all the Office of Surveillance and Epidemiology (OSE) requirements?

FDA Response:

We do not concur. The proposed IFU does not comply with current patient labeling standards. We have provided high level patient labeling comments below.

- *Patient labeling materials should meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).*
- *Patient labeling materials should utilize simple wording and clear concepts where possible and should be consistent with the Prescribing Information.*
- *To enhance comprehension and readability, patient labeling materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at*

least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

- *Patient labeling materials should be in fonts such as Verdana, Arial or APHont at font size 11 or greater to make medical information more accessible for patients with vision loss. We recommend Verdana 11 point font.*
- *Do not use all capital letters in patient labeling as people with low vision have difficulty reading them.*
- *IFUs are generally organized as follows:*
    - *Standard header and introductory paragraph*
    - *Bulleted list of all the supplies needed to complete the task.*
    - *Patient instructions that are not sequential should be bulleted.*
    - *Patient instructions that are sequential should be noted as "**Step 1, Step 2**" etc.*
    - *Figures (photos and /or diagrams) should accompany all numbered steps as appropriate and should be placed immediately adjacent to the related step. The figures should be labeled as "**Figure A, Figure B**" etc.*
    - *Within the figures there should be detailed labeling for each part of the device that the patient expected to become familiar with.*
    - *Storage information as stated in the Prescribing Information (PI)*
    - *Disposal information as stated in the PI*
    - *Other pertinent miscellaneous instructions to the patient*
    - *Manufacturer name and address*
    - *Add the statement "This Instructions for Use has been approved by the U.S. Food and Drug Administration."*
    - *Approved Month/Year*

- *Additional Recommended revisions to draft IFU*
    - *As the auto-injector contains glass, add a warning statement such as: Do not use if the autoinjector appears cracked or broken; if dropped on a hard surface, the autoinjector may have broken and a break my not be visible; Contact XXX or call XXX for assistance.*
    - *Add: Do not remove the cap until you are ready to use the product*

We also have the following additional comments:

1. *The IFU references the (b) (4)' but it appears that after the (b) (4) 'Cap' and (b) (4) 'Safety' are removed from each end, both ends are (b) (4). We recommend: -Differentiating colors for each end of the auto-injector*

-Making the text ' (b) (4) *' displayed on the auto-injector needle more prominent in size*

2. *Your Usability Study should capture all medication errors and adverse events, as well as:*

    a. *Malfunctioning of the auto-injector during administration*

    b. *Patient Misuse of the auto-injector, including patients attempting to inject the wrong end of the injector, including a needle sticks that occur as a result of this misuse*

    c. *Reports of breakage or leakages during use (if the auto-injector contains glass).*

3. *Your training script and device in the Usability Study should be the versions planned for marketing.*

Discussion:

The Division clarified that the comment provided above is derived from concerns that have arisen with other autoinjectors in the post-marketing period, and is intended to encourage pre-market identification of issues that could lead to misuse or medication errors. The Division asked if the sponsor is aware of any other potential safety issues, as assessment of these should be incorporated in the Actual Human Use Study as well. The Division accepted the source of the different databases that the sponsor offered (e.g. MDR, etc.) in order to obtain and provide the requested information.

Question 7:

Does the Agency agree to provide feedback on the Pivotal Summative Usability protocol as part of a Special Protocol Assessment (SPA)? If so, what are the procedural steps for a combination product necessary to accomplish this under a SPA?

FDA Response:

We do not agree. A Human Factors study would generally not be considered appropriate for a Special Protocol Assessment as it is not the primary basis for an efficacy claim.

With regards to the review of the Summative Usability protocol, the Agency has the following General Comments:

- *The purpose of a design validation (human factors) study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users. Tasks included in the study should be those identified through completion of a risk assessment of hazards that may be*

associated with use-related problems and represent greater than minimal risk to users. The study should collect sufficient and appropriate data to facilitate identification and understanding of the root causes of any use failures or problems that do occur. The causes may be related to the design of the device, the device labeling (including instructions for use), and/or the training of test participants. The test report should present a summary of your test results, data analysis, and conclusions regarding safe and effective use and including whether any modifications are indicated; if they are, these modifications should be described and if significant, the modifications should also be validated.

Your validation study protocol should include a clear description of the items listed below.

1) Devices and Labeling Used and Training
For design validation, the devices used in your testing should represent the final design, which includes the commercial device version, final instructions for use, or any other labeling materials.

In addition, the proposed device comes in four package strengths:
- *10 mg in 0.4 mL (4 auto-injectors to a carton)*
- *15 mg in 0.4 mL (4 auto-injectors to a carton)*
- *20 mg in 0.4 mL (4 auto-injectors to a carton)*
- *25 mg in 0.4 mL (4 auto-injectors to a carton)*

Discuss if the intended users will be prescribed to a particular strength/dose.

The extent of training should be based on the analysis of the intended users and the use of product. The level of training provided during a validation study should be realistic, and representative of actual use, specifically the different levels of training described in the protocol, and how they will be implemented in actual use. Furthermore, although realistic time periods for "training decay" are difficult to build into a testing approach, please allow some period of time to elapse between training and testing (e.g., a minimum time might be a "lunch break."). Also, address the following concerns:

- *Assess the adequacy of the user instructions for your device as either part of your Human Factors/Usability effort or in a separate study in which representative users review the instructions for use and assess it for clarity and its ability to support their safe and effective use of your device. The adequacy of the labeling on the device itself is evaluated as part of the Human Factors/Usability validation study to the extent that if it is inadequate, this will be evidenced by subjective user feedback and possible failures. If a separate study has been conducted on the finalized IFU and labeling, please submit the results to the Agency.*

- *If you decide to include the assessment of clarity of instructions for use and training as part of the validation study, the Agency expects that the results*

demonstrating effectiveness of your training and instructions for use are analyzed separately from the results of use performance.

2) *Device user interface (UI)*
To establish the scope and facilitate understanding of the testing you perform, please provide a graphical depiction of the user interface for your device. Also explain the overall interaction between users/user groups and the UI and refer to it as necessary when discussing task priority, specific test results or residual risk.

3) *Use-Related Risks Analysis*
FDA expects to see a clear description of how you determined which user tasks would be included in the testing. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user. Provide use-related risks analysis.

4) *User Tasks and Tasks Priority*
The Agency needs to understand that you have conducted a comprehensive analysis of user tasks and as part of this analysis have established relative priority of the tasks you selected for testing in terms of the potential clinical impact of inadequate performance (e.g., "task failure") for each. You have not provided any discussion of user task analysis, task priority, nor was a testing protocol developed from these analyses provided. If you have performed this work, submit it to the IND for the Agency to review or initiate the development of a human factors/usability evaluation, development, and validation testing protocol. Note that human factors/usability is most effectively applied to the design of the device user interface when it is initiated early in the design process. Also provide a rationale for the tasks you include in your testing and their relative priority. In addition, describe all activities in which your test participants will engage during the test.

5) *Comprehensiveness of task set*
For human factors/usability validation testing, the Agency needs to understand that the tasks you chose to test represent the extent of the tasks that could lead to use-related failures that could have an undesirable clinical impact. Provide a rationale for the completeness of the user tasks you include in your Human Factors/Usability validation testing.

6) *Use Environment and Conditions*
You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.

Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting,

noisy situations, etc., should be included in your testing. Evaluate use of your device under whatever conditions you identify as potentially occurring and hazardous.

Describe the testing environment and realism of the simulated use in sufficient detail for us and justify how they were appropriate for validation testing.

7) *Study Participants*

The protocol stated that 30 participants will be recruited for the study. Half of the participants will have HAQ (Health Assessment Questionnaire) scores between 1 and 1.5 and half between 1.5 and 2.0. It is not clear how these scores equate to the intended patient population i.e. "selected adults with severe, active rheumatoid arthritis (ACR criteria) – page 6 of TR # 658). It is not clear how each participant's level of severity of the disease would be identified. It is not clear if the study participants will include only those with severe RA. Please provide an analysis of the intended users, and provide a justification for why the participants who will be recruited for the study are representative of intended users.

In addition, you indicated on page 13 of TR#658 that the intended user population consisted of a patient or a caregiver. However, the study protocol specifies that 30 users – only patients – will be recruited in the study.

You should include as many representative users in your human factors/usability validation as your analysis indicates are necessary to achieve a reasonable validation. If users fall into distinct groups that are expected to interact differently with the device or carry different risk profiles (e.g. different specialties that are more or less knowledgeable of diabetes treatment, physicians vs. nurses, etc.) then the testing should include representative samples from each of these groups, divided roughly evenly but where the total could be no less than 25. Regardless of the number of groups you test, please provide a rationale that these groups are representative the overall population of users for your device.

For devices sold in the United States, FDA has consistently requested that the participants in a validation test to be representative of the U.S. population and to reside in the U.S.. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing.

8) *Data Collection*

Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. FDA expects you to collect both empirical and qualitative data in a design validation study.

Empirical Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as

successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants' adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.

Qualitative Data – The Agency expects you to ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

Note that results of your validation studies should capture user performance failures, where failure of a task is defined as an action or lack of action on the part of the user that could lead to clinical harm to the patient. Test results (see "Report" below) should include success and failures for all critical tasks. In addition, and even if performance of all tasks is acceptable, the output that establishes critical treatment parameters resulting from the interaction for each use scenario should be evaluated for adequacy. Each instance of task or overall scenario failure should be evaluated to determine its cause. This evaluation should include subjective feedback concerning the cause of the failure from the perspective of the test participant involved and obtained immediately following the test scenario. Every test participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant. Finally, your protocol should enable identification and capture of unanticipated task failures and not be limited to pre-established failure modes.

In addition, please note the following comments regarding "data coding" (page 12 of the summative protocol). The data coding categories will require some additional information/clarification. In particular, the "resolved", "assisted", and "unresolved" categories. Please note that any form of guidance provided to the participants should be considered as a "failure." This should apply to all three categories. Failures of critical tasks will require further review and investigation to identify root causes, and determine whether or not and the extent to which failures found are due to aspects of the design of the device, its labeling/IFU, the content or proximity of training, and whether modifications are necessary.

9) <u>Report</u>
The Agency expects to review a report of the human factors/usability evaluation and validation testing. The report should begin with a conclusion that the device is reasonably safe and effective for the intended users, uses and use conditions. A summary of relevant portions of preliminary analyses, evaluations, the validation testing should be used as support of this conclusion. The test results, and particularly

failures or patterns of subjective reports of difficulty with the use of the device should be discussed with respect to whether they were caused by aspects of the design of the device, its labeling, the content or proximity of training and whether modifications are required. Residual risk associated with use that cannot be further reduced through modifications of training, labeling, or modifications to the design of the UI should be discussed and rationale provided for why it cannot be further reduced. Note that stated plans to modify design flaws that could result in clinical impact on patients in future versions of the device are generally unacceptable.

10) Prior Usability Studies/Assessments
You provided in Attachment 11 various usability assessments that were conducted during the development of this product. Note that the Agency considers these assessments as formative usability studies. While this information is helpful, the Agency's Human Factors review focus will be on the results of the summative study. However, to facilitate this review, please provide a discussion/rationale of how these tests were used to modify the design of the pens, the IFU or packaging and how they were used to identify critical user tasks and guide the design of the summative validation protocol. You may provide this discussion in the form of a table that outlines all the studies conducted, resulting changes to either the device and/or labeling, and how each study's results were used to identify critical tasks and guide the design of the summative validation protocol.

11) Device Samples
Provide a device sample that was used for the pilot assessment, and a device sample that will be used in the summative study.

We strongly recommend that you submit your revised draft protocol in advance for us to review in order to ensure that your methods and the resulting data will be acceptable. Guidance on human factors procedures to follow can be found in Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm.

Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, Applying Human Factors and Usability Engineering to Optimize Medical Device Design and can be found online at:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm.

Discussion:

The sponsor stated that they will take all of the HF comments from the Agency into consideration. The sponsor sought clarification on comment No. 7 regarding the severity of the disease for the inclusion criteria and asked for the Division's feedback on which tool they think would best meet the purpose. The Division responded that there is not

necessarily one best instrument to identify disease severity, and that the sponsor should provide justification for the instrument selected.

The Division also added that the caregivers should be included in a realistic setting with the use of the actual product. Although efficacy data is not required from the Actual Human Use Study, it would be helpful to generate this information. The Division closed the discussion by stating that the Actual Human Use Study will be expected to have data on medication errors, any adverse events and reports on any misuse of the device.

Question 8:

Does the Agency concur with the proposed approach to develop a PI for (b) (4) ***MTX?***

FDA Response:

We do not agree. While discussion of labeling is premature given that your development program is uncertain, we provided some general labeling comments. Your label would need to be presented in the PLR format. It is unclear how you plan to address the Dosage and Administration (2), Adverse Reactions (6), and Clinical Studies (14) sections based upon the development program you outlined.

Discussion:

No Discussion occurred.

Nonclinical

Question 9:

Does the Agency concur that the mini-pig would be a suitable alternative animal model for evaluating local tolerance of subcutaneous MTX?

FDA Response:

We agree that the mini-pig appears to be an appropriate alternative model for evaluating local tolerance.

Discussion:

No discussion occurred.

CMC

Question 10:

Does the Agency concur that the proposed release tests including functional testing for (b) (4) methotrexate drug product are adequate to support the filing of the NDA?

FDA Response:

No, we do not agree. Sterility testing per USP is required.

Refer to our Introductory Comments for additional information regarding the device.

Discussion:

The Division stated that in order for the results to be acceptable the Drug Product Specification criteria should agree per the USP Sterility Testing. The sponsor agreed with Division's recommendation.

Question 11:

Does the Agency agree that the stability regimen described will be sufficient to establish an assignable shelf-life supported by available data utilizing the FDA proposed model of shelf-life determination at the time of filing?

FDA Response:

While the matrix/bracket approach is generally acceptable, two additional batches at the highest and lowest strengths should be tested for Related Substances.

Discussion:

The sponsor stated that they have placed their finished batches on stability and that 3 batches are of low strength, 1 batch is of intermediate strength and 3 batches are of high strength that will be tested for all attributes including related substance, and that the data will be available in the NDA.

Question 12:

Does the Agency agree with the proposed approach to establishing release and shelf life specification limits for (b) (4)?

FDA Response:

From the nonclinical perspective, we do not agree. The toxicological assessment provided in your package is inadequate to support safety of (b) (4) at your proposed specification limits up to (b) (4)%. We recommend that you lower the specification

limits or qualify this impurity at the proposed levels. Refer to ICH Guidance Q3B(R2) "Impurities in New Drug Products" and CDER Guidance for Industry "ANDAs: Impurities in Drug Products" for qualification requirements.

Discussion:

The sponsor stated that they currently have a specification of (b) (4)% for (b) (4) at release and (b) (4)% on stability and asked whether that would be acceptable to the Division. The Division stated that they need concrete data to support safety of the (b) (4)% specification to qualify this impurity, which will require review. The Division referred the sponsor to the guidances available. Additionally, the Division advised the sponsor to either conduct a side by side comparison assay with the reference product to demonstrate that their impurity level is similar to the approved product's level or by providing data from literature to support safety of (b) (4) at the proposed level. The Division acknowledged the toxicology summary provided in the briefing document but informed the sponsor that the summary did not provide data to support their contentions.

The Division also stated that, if the sponsor chooses to do the side by side comparison with the reference product, data from different batches at different time points are needed for an adequate comparative assessment.

Question 13:

Does the Agency agree that the proposed plan to qualify the change from (b) (4) to (b) (4) for the 20 mg dose is acceptable?

FDA Response:

Yes, we agree.

Discussion:

No discussion occurred.

Exclusivity

Question 14:

(b) (4)

(b) (4)

Discussion:

No discussion occurred.

Question 15:

(b) (4)

Discussion:

No discussion occurred.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

4.0 ATTACHMENTS AND HANDOUTS

Enclosed

Draft: SNabavian/10.04.2011

Initialed: DSeibel/10.11.2011
SSeymour/10.12.2011
SYim/10.12.2011; 10.13.2011
JBuenconsejo/10.05.2011
CRivera-Lopez/10.06.2011; 10.12.2011
MTopper/10.06.2011; 10.12.2011
SDoddapaneni/10.12.2011
PPeri/10.11.2011
QNugyen/10.11.2011
CMiller/10.05.2011
RDuer/10.05.2011
BAChowdhury/10.13.2011

Finalized: SNabavian/10.13.2011

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

SADAF NABAVIAN
10/13/2011

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Attention: Kaushik Dave, R.Ph., Ph.D., MBA
Vice President of Clinical and Regulatory Affairs

Dear Dr. Dave:

Please refer to your Pre-Investigational New Drug Application (PIND) file for the mini-needle methotrexate injection device product.

We also refer to the meeting between representatives of your firm and the FDA on February 5, 2009. The purpose of the meeting was to obtain guidance on the 505(b)(2) regulatory pathway for the mini-needle methotrexate injection product.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 5, 2009

TIME: 12:00 PM – 1:00 PM (EST)

LOCATION: Food and Drug Administration, Bldg. 22, Room 1313

APPLICATION: PIND 103,738

PRODUCT: mini-needle methotrexate injection device product

INDICATION: treatment of rheumatoid arthritis

SPONSOR: Antares Pharma

TYPE OF MEETING: Pre-IND, Type B

MEETING CHAIR: Sarah Okada, MD
Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

MEETING RECORDER: Jessica Benjamin, Regulatory Project Manager

FDA Attendees	**Title**
Rigoberto Roca, MD	Deputy Director (Rheumatology Team)
Sarah Okada, MD	Clinical Team Leader
Keith Hull, MD	Clinical Reviewer
Adam Wasserman, PhD	Pharmacology/Toxicology Supervisor
Lei Zhang, PhD	Clinical Pharmacology Reviewer
Danae Christodoulou, PhD	Pharmaceutical Assessment Lead, ONDQA
Patricia Love, MD, MBA	Office of Combination Products, Associate Director
Alan Stevens	Combination Product Team Leader, ODE/CDRH
Kathleen Davies, MS	Regulatory Health Project Manager
Jessica Benjamin	Regulatory Health Project Manager
Antares Pharma	**Title**
Dario Carrara, PhD	Managing Director and SVP Pharma Division
Peter Sadowski, PhD	VP Medical Devices Division
John Hayes	VP Corporate Marketing
[redacted]	(b) (4)

BACKGROUND:
Antares Pharma requested a Type B meeting (Pre-IND) to obtain guidance on the 505(b)(2) regulatory pathway for the mini-needle methotrexate injection product.

Each of the Sponsor's questions is presented below in italics, followed by the Division's response in bold. A record of the discussion that occurred during the meeting is presented in normal font. The Division provided written responses to the Sponsor on February 4, 2009.

Question 1. *Does the Agency agree that Antares can reference safety and efficacy data available to the Agency for its prior approval of methotrexate for the treatment of adult rheumatoid arthritis when administered by oral and parenteral routes?*

FDA Response:
Although methotrexate is approved for rheumatoid arthritis (RA) via oral administration, and this information is in the approved injectable methotrexate labels, the label does not contain dosing information for parenteral routes of administration, nor does it contain route-specific efficacy and safety information. Therefore, you will need to take this into account in your clinical development program. In addition to referencing the approved oral methotrexate for RA, you will need to provide substantial evidence of efficacy for the parenteral routes for which you plan to seek approval. Because oral methotrexate is already approved for RA, the additional evidence that would be expected for the NDA would include data from at least one adequate and well-controlled trial of subcutaneously administered methotrexate. Based on your description of the available literature in the briefing package, you may be able to meet this evidentiary requirement utilizing published trials.

You should be aware that an application for a new route of administration would trigger a requirement for pediatric assessments under the Pediatric Research Equity Act (PREA). A plan for addressing PREA requirements would need to be submitted with the NDA. You may be able to address PREA requirements by including JRA patients (ages 0-16 years) in a PK/bioavailability study.

Discussion:
The Sponsor confirmed that they will submit their analysis of the available literature to determine their clinical development plan. They plan on submitting this information prior to the End-of-Phase 2 meeting for review. The Division will try to review it depending on available time and resources.

The Division explained that the entire age range, 0-16 years, will need to be addressed under PREA requirements. However, the Sponsor can submit a rationale for why certain age groups should not be studied. For the design of the PK study in children, the Division clarified that demonstration of bioequivalence to a reference drug is not needed. A bioavailability study to characterize the PK of methotrexate in JRA patients would suffice. The results of the study should then be used for dose selection in pediatric patients. The Division commented that the number of patients needed for a bioavailability study should be based on inter-subject variability of relevant methotrexate PK parameters (e.g., apparent clearance and volume of distribution) and local toxicity issues may require further exploration in a larger number of patients.

The Division also noted that although one appropriately designed and well-controlled trial may be sufficient for approval of SC MTX for the RA indication, an application intended to seek comparative or superiority claims, e.g., that SC MTX is superior to oral MTX, would need to provide independent substantiation of results to support that claim from at least 2 adequate and well-controlled trials. This topic can also be discussed at an End-of-Phase 2 meeting.

Post-meeting note:

(b) (4)

Question 2. *Does the Agency agree that Antares can incorporate, by reference, CMC information in their NDA from a Drug Master File based on an appropriate Letter of Authorization?*

FDA Response:
Yes, incorporating CMC information from a Drug Master File with a Letter of Authorization is acceptable. Provide the drug substance specifications and manufacturer qualifying criteria in the NDA. Include the names, addresses and cGMP status of all drug substance manufacturing facilities in the NDA.

Discussion:
There was no further discussion of this point.

Question 3. *Does the Agency agree that Antares can incorporate, by reference, information on the Vibex RA device (used for self administration of methotrexate), in their NDA from the Device Master File (see Attachment 2, Section 8.2) based on an appropriate Letter of Authorization?*

FDA Response:
Yes, incorporating information on the Vibex RA device from the Device Master File with a Letter of Authorization is acceptable. However, it is not clear that your proposed device is the same as the Vibex Master File device. Identify any modifications and provide any data verifying the performance of the modified device. In addition, provide a brief description with a diagram of the device in the IND. Provide controls to demonstrate consistent performance of the device and dose delivery. If this is an approved device, provide information on the comparisons of the parameters of the approved range of operation versus your proposed range. In addition, provide stability data to demonstrate compatibility of your device with the drug product. At the NDA stage, provide a complete leachables/extractables evaluation. Refer to non-clinical safety comments regarding leachables/extractables characterization.

Discussion:
The Division reiterated that any modifications and any data verifying the performance of the modified device will need to be submitted with the NDA.

The Sponsor plans to include a listing of impurities and level of excipients with NDA. The Division referred the Sponsor to the inactive ingredient guide which gives maximum limits for daily exposure. The Division also stated that nonclinical studies will need to be done with the drug product. The mini-pig is a common species for these studies, but a rationale for the use of a mini-pig will be needed.

The Office of Combination Products strongly recommended that the final studies for quality and test data for the combination product as a whole be performed with the actual methotrexate product. Data on the depth and reliability of the delivered dose should be documented in different [subcutaneous] areas of the body and in different age groups, as appropriate. Human factors trial design should consider such things as the dexterity of the patient population. FDA encourages submission of human factors protocol for intercenter review (e.g., by the review divisions and human factors consultants) before study implementation. The Sponsor indicated that they may submit a protocol for a human factors trial for review.

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).

Discussion:
There was no further discussion of this point.

Question 5. *Does the Agency agree that a single-dose crossover-design pharmacokinetic study in approximately 54 adult rheumatoid arthritis patients at doses of 15 mg, 20 mg, and 25 mg comparing the bioavailability of this novel dosage from with RLD when administered orally and IM allows for the demonstration that this novel dosage form is safe and effective for the treatment of adult rheumatoid arthritis? Furthermore, does the Agency agree that the range studied in the proposed bioavailability study is adequate to demonstrate comparability of the investigational novel dosage form with the RLD?*

FDA Response:
As noted in the response to question 1, you will need to provide substantial evidence of the effectiveness of subcutaneously administered methotrexate for RA. Your bioavailability study should be designed to be able to serve as a bridging study to demonstrate that methotrexate administered via the Vibex RA device would be similar to methotrexate administered subcutaneously without the device, with respect to pharmacokinetics and local tolerability. Your protocol needs to clearly state the BE criteria for comparing PK across the proposed treatments. Additionally, to allow bridging to nonclinical data in support of prior parenteral approval of the RLD you will need to include the IM route and establish that SC administration using your product provides a methotrexate exposure that is within that allowed with IM use in the approved indications. Your protocol also needs to clarify the site of injection via Vibex RA device and IM route.

Discussion:
There was no further discussion of this point.

Question 6. *Antares believes that evaluation of the local injection site following a single SC administration using the investigational novel dosage form in this study exposing approximately 54 patients will be sufficient to determine whether it will result in any local inject site reaction. Specifically, Antares plans to include a statement in the label to instruct patients to vary the location of the injection during their weekly methotrexate administration. Dose the Agency concur that assessment of potential local injection site reactions under the single administration dose conditions in this study will be sufficient, assuming that there are no findings of concern, that safety of the proposed route of administration will be comparable to the RLD?*

FDA Response:

See response to Questions 1 and 5.

Discussion:
There was no further discussion of this point.

Question 7. *Does the Agency agree that no further studies are required to support the efficacy and safety of the product if it can be demonstrated that the relative bioavailability of methotrexate with this novel dosage form is comparable to the RLD?*

FDA Response:
See response to Questions 1 and 5.

Discussion:
There was no further discussion of this point.

Question 8. *Does the Agency agree that the information available from the published clinical studies, when supported by the information from the proposed bioavailability comparison study, should be sufficient to support labeling that recommends physicians consider relative bioavailability when switching a patient from an oral to the same dose of this novel SC dosage form?*

FDA Response:
It is premature to discuss potential labeling at this time. What type of wording is supported by the data is determined after review of the data submitted in the application.

Discussion:
There was no further discussion of this point.

Question 9. *Based on the proposed conversion factor and user data collected in the clinical trial, Antares plans to demonstrate that the SC route of administration achieved by Vibex RA will provide a safe and reliable use of methotrexate by the patient for self administration of the methotrexate.* (b) (4)

FDA Response:

(b) (4)

(b) (4)

The Sponsor may submit a Special Protocol Assessment (SPA) to discuss a pivotal clinical trial design. The Division reiterated that the Sponsor should have an End-of-Phase 2 meeting before submitting an SPA as outlined in the following guidance document: Guidance for Industry: Special Protocol Assessment (May 2002) which is available on the CDER web page at the following http://www.fda.gov/cder/guidance/3764fnl.pdf

ACTION ITEMS:

1. Prior to the End-of-Phase 2 meeting, the Sponsor will submit an analysis of available literature to support their clinical development plan.

2. Sponsor will decide whether they will submit a protocol for review for a human factors trial.

Linked Applications	Sponsor Name	Drug Name / Subject
IND 103738	Antares Pharma, Inc	METHOTREXATE

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/s/

JESSICA M BENJAMIN
03/05/2009