CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204824Orig2s000

CHEMISTRY REVIEW(S)

Chemistry Review Cover Sheet

NDA 204824
OTREXUP®
(METHOTREXATE INJECTION)

Arthur B. Shaw, Ph.D.
DNDQA III/Branch VIII/DPARP

Table of Contents

Chemistry Review Data Sheet

1. NDA 204824

2. REVIEW #:2

3. REVIEW DATE: September 10, 2013

4. REVIEWER: Arthur B. Shaw, Ph.D.

5. PREVIOUS DOCUMENTS:

Document	Document Date	Comment
Original	2012-12-14	
Consult to CDRH	2013-01-13	
Chem review #1	2013-09-09	

Chem Review #1 September 9, 2013

6. SUBMISSION(S) BEING REVIEWED:

Document	Document Date	Comment
CDRH Consult review	2013-09-10	Device acceptable

7. NAME & ADDRESS OF APPLICANT:
Antares Pharma Inc.
100 Princeton South Corporate Center
Suite 300
Ewing NJ 08628

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Proposed: Otrexup
   b) Non-Proprietary Name (USAN): Methotrexate
   c) Code Name/# None
   d) Chem. Type/Submission Priority
      - Chem. Type: 5 (new manufacturer)
      - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: folate analog metabolic inhibitor

11. DOSAGE FORM: Solution; injection

12. STRENGTH/POTENCY: 10 mg, 15 mg, 20 mg and 25 mg/0.4 ml

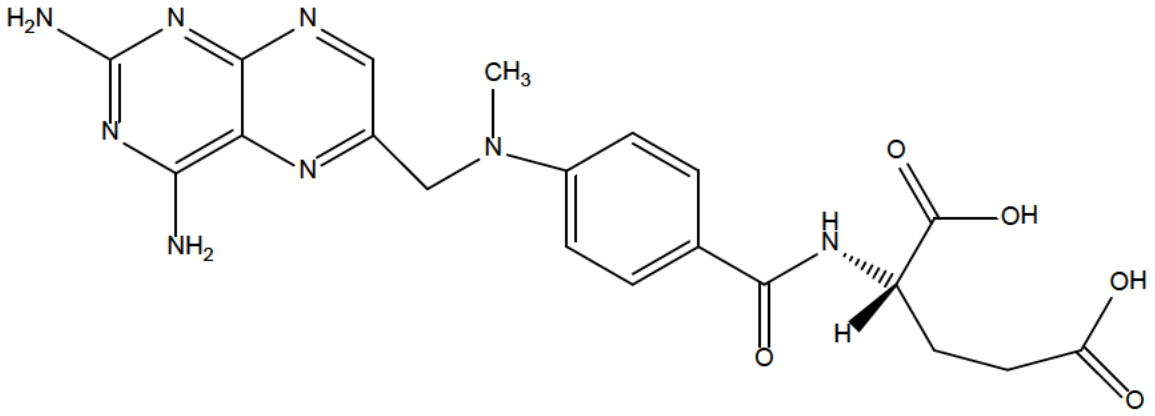
13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

l-Glutamic acid, N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-;



$C_{20}H_{22}N_8O_5$

MW= 454 (b) (4)

CAS RN N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-(+)-glutamic acid (IUPAC, CAS)

N-[p-[(2,4-diamino-6-pteridinylmethyl)methylamino]benzoyl]-L-(+)-glutamic acid (WHO)

4-amino-10-methylpteroyl-glutamic acid

4-amino-10-methylfolic acid

CAS Registry Number:

59-05-2

Company or Laboratory Code(s):

CL-14377

NSC-740

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED
(b) (4)	II	(b) (4)	Methotrexate	Acceptable	07/22/2013
	III		(b) (4)	Acceptable	07/22/2009
	III			Acceptable	07/29/2013
	V			Adequate	5/23/2013
	V			Adequate	3/18/2013

B. Other Documents: None

18. STATUS OF CONSULTS/ CMC RELATED REVIEWS

	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	05/23/2013	N/A
EA	Categorical Exclusion granted	No review needed	N/A
Microbiology	Acceptable	07/29/2013	Erika Pfeiler
Statistics	Recommend (b) (4) month expiry Additional data supports 33 month expiration	06/26/2013	Meiyu Shen
Device	Acceptable	09/10/2013	Jacqueline Ryan
Methods Validation	Acceptable	07/22/2013	Mike Trehy

The Chemistry Review for NDA 204824

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved from a CMC point of view.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

None

II. Summary of Chemistry Assessments

1. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance

Methotrexate is a yellow to orange, [redacted] insoluble in water. It was first approved as a treatment for cancer in 1959 and is cytotoxic, which requires care in handling. There are a number of approved tablets and injections using methotrexate and the indication has been expanded to include treatment of forms of arthritis and psoriasis. The current application is a 505(b)(2). The CMC information for methotrexate is covered in DMF [redacted], which has been reviewed many times and has been found acceptable. A recent amendment contains a number of changes in the manufacturing which have been reviewed and found acceptable. The specifications and testing for the drug substance are provided in the NDA, both in terms of COAs from the supplier and in terms of complete testing by the manufacturer of the drug product. The testing conforms to both the USP and the Ph.Eur. All process-related impurities are well-controlled and degradation is minimal. Note that the major degradant, [redacted], is a metabolite of methotrexate and has no additional toxicity. The applicant has proposed a reduced testing program for release of the drug substance by the drug product manufacturer after the first commercial batches. This is acceptable.

The drug substance is manufactured at [redacted] which has a satisfactory CGMP status as of [redacted]. The retest date of [redacted] months is supported by data in the DMF.

2. Drug Product

The drug product is formulated by titrating with sodium hydroxide to a neutral pH, [redacted] methotrexate. No preservatives are added, since the drug product is intended for single use in a custom injector. The drug product solution is sterile [redacted] glass syringes and closed with a plunger with a rubber stopper. No leachables have been observed from the packaging

components in direct contact with the drug product. The preparation, including sterilization, of the syringes and the plunger are covered in DMFs which have been reviewed by the Microbiology Staff and found acceptable. The sterility aspects of the drug product manufacturing have been reviewed by the Microbiology Staff and found acceptable. The drug is formulated at four different strengths to be delivered at a fixed volume of 0.4 mL by the device.

The drug product specifications are adequate to support different expiration dates for different strengths. 24 months for 10 mg/0.4 mL and 15 mg/0.4 mL and 33 months for 20 mg/0.4 mL and 25 mg/0.4 mL. The controlling parameter is the appearance of the degradant (b) (4), which is controlled at NMT (b) (4)%. This level of the impurity has been found acceptable by the pharm/tox reviewer. The unusual expiration date of 33 months is acceptable because that is one of the "pull dates" specified in the stability protocol.

The pre-filled syringes (PFS) are loaded manually into a custom device, covered by a device master file. The device along with the syringe inside is the to-be-marketed product, a drug-device combination. The device incorporates a number of features. It is designed to deliver a fixed volume with no measuring by the patient. The needle is completely covered when not in use so that the chances of accidental injection or exposure to the needle are minimized. When the device is activated by the force of delivery is controlled by a spring in the device, not the patient. The needle is the correct length to ensure that the drug is administered subcutaneously. After the device is actuated there is no drug remaining in the syringe and there are no exposed needles so that safe disposal is not an issue. A review (09/10/2013) of the Device Master File (MAF (b) (4)) found no deficiencies in the description or performance of the Autoinjector device..

The prefilled syringe manufacturer is (b) (4) which was found satisfactory from a cGMP point of view as of (b) (4)

The site for assembly, packaging and labeling of the combination product is (b) (4) which was found satisfactory from a cGMP point of view as of (b) (4).

A demonstration device, containing no drug, will be supplied by the company to health-care professionals to train patients in the use of the product

2. Description of How the Drug Product is Intended to be Used

The drug is intended to be used by patients with rheumatoid arthritis including polyarticular-course, juvenile rheumatoid arthritis, and moderate to severe psoriasis on a weekly basis after instruction by a doctor or other health care professional. The drug is injected subcutaneously in a fixed dose. Different strengths are available to permit a range of doses.

3. Basis for Approvability or Not-Approval Recommendation

The drug substance and drug product are manufactured and controlled adequately to deliver the labeled dose of the drug.

III. Administrative

A. Reviewer's Signature See DARRTS

B. Endorsement Block: See DARRTS

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/s/

ARTHUR B SHAW
09/11/2013
Incorporates CDRH review.

PRASAD PERI
09/11/2013
I concur

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Chemistry Review Data Sheet

1. NDA 204824
2. REVIEW #:1
3. REVIEW DATE: August 9, 2013
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

Document	Document Date	Comment
Original	2012-12-14	
Consult to CRDH	2013-01-13	
Filing review CMC	2013-02-12	Fileable
Filing review Micro	2013-02-11	Fileable
Filing Issues Letter	2012-10-12	Fileable Micro issues identified
Micro IR	2013-03-02	Not in DARRTS. Additional Micro requests
Amendment	2013-03-14	Response to 3/02 micro IR
IR Letter	2013-04-30	Request for residual solvents method
Micro IR	2013-05-06	Additional Micro requests
Amendment	2013-05-07	Residual solvents method provided
Amendment	2013-05-17	Response to 05/06micro IR
IR Letter	2013-05-24	Request for stability data in tabular format and batch records
Amendment	2013-06-06	Response to 5/24 IR letter
IR letter	2013-06-11	Request for additional clarification regarding manufacturing
Amendment	2013-06-19	Response to 06/11 IR letter
IR Letter	2013-07-01	Questions from initial draft CMC review
Amendment	2013-07-22	Response to 07/01 IR letter
IR Letter	2013-07-29	Questions about MBR and Stability Protocols
Amendment	2013-08-09	Response to 7/29 IR

7. NAME & ADDRESS OF APPLICANT:

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

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Proposed: Otrexup
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   c) Code Name/# None

d) Chem. Type/Submission Priority
- Chem. Type: 5 (new manufacturer)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

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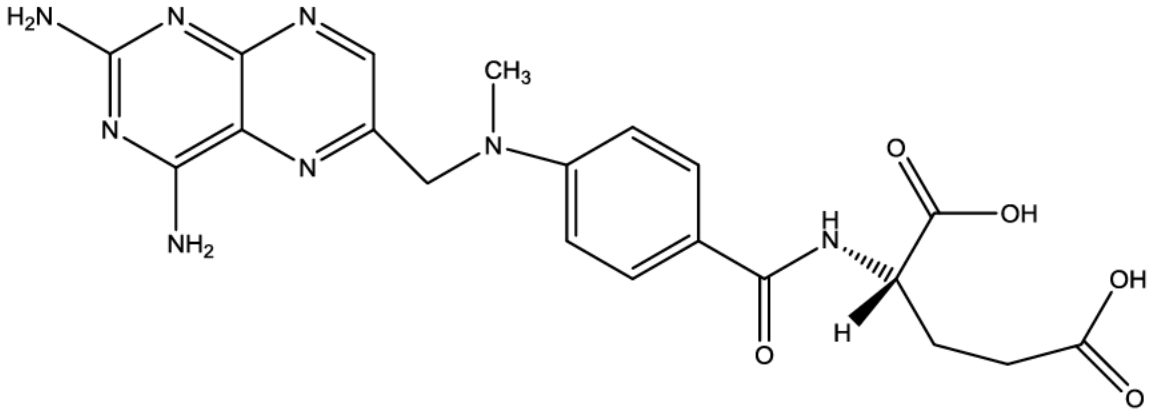

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B. Other Documents: None

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Microbiology	Acceptable	07/29/2013	Erika Pfeiler
Statistics	Recommend (b) (4) month expiry Additional data supports 33 month expiration	06/26/2013	Meiyu Shen
Device	Filing review No major deficiencies identified	1/28/2013 (not filed)	Jacqueline Ryan
Methods Validation	Acceptable	07/22/2013	Mike Trehy

The Chemistry Review for NDA 204824

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved from a CMC point of view, pending a final review from CDRH of the device.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

None

II. Summary of Chemistry Assessments

1. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance

Methotrexate is a yellow to orange, (b) (4), insoluble in water. It was first approved as a treatment for cancer in 1959 and is cytotoxic, which requires care in handling. There are a number of approved tablets and injections using methotrexate and the indication has been expanded to include treatment of forms of arthritis and psoriasis. The current application is a 505(b)(2). The CMC information for methotrexate is covered in DMF (b) (4), which has been reviewed many times and has been found acceptable. A recent amendment contains a number of changes in the manufacturing which have been reviewed and found acceptable. The specifications and testing for the drug substance are provided in the NDA, both in terms of COAs from the supplier and in terms of complete testing by the manufacturer of the drug product. The testing conforms to both the USP and the Ph.Eur. All process-related impurities are well-controlled and degradation is minimal. Note that the major degradant, (b) (4), is a metabolite of methotrexate and has no additional toxicity. The applicant has proposed a reduced testing program for release of the drug substance by the drug product manufacturer after the first commercial batches. This is acceptable.

The drug substance is manufactured at (b) (4) which has a satisfactory CGMP status as of (b) (4). The retest date of (b) (4) months is supported by data in the DMF.

2. Drug Product

The drug product is formulated by titrating with sodium hydroxide to a neutral pH, (b) (4) methotrexate. No preservatives are added, since the drug product is intended for single use in a custom injector. The drug product solution is sterile (b) (4) glass syringes and closed with a plunger with a

rubber stopper. No leachables have been observed from the packaging components in direct contact with the drug product. The preparation, including sterilization, of the syringes and the plunger are covered in DMFs which have been reviewed by the Microbiology Staff and found acceptable. The sterility aspects of the drug product manufacturing have been reviewed by the Microbiology Staff and found acceptable. The drug is formulated at four different strengths to be delivered at a fixed volume of 0.4 mL by the device.

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The prefilled syringe manufacturer is (b) (4), which was found satisfactory from a cGMP point of view as of (b) (4)

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III. Administrative

A. Reviewer's Signature See DARRTS

B. Endorsement Block: See DARRTS

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/s/

ARTHUR B SHAW
09/09/2013

PRASAD PERI
09/09/2013
I concur

Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

APPLICATION INFORMATION

1. NEW DRUG APPLICATION NUMBER: 204824

2. Drug Name: Otrexup (methotrexate)
(Single-use prefilled autoinjector)
(Strength: final delivered doses of 10, 15, 20 or 25 mg methotrexate per 0.4 ml)

Route of administration: subcutaneous

Indication: rheumatoid arthritis, polyarticular-course juvenile rheumatoid arthritis, moderate or severe psoriasis

Applicant: Antares Pharma Inc. (Ewing, NJ 08628)

3. RECEIVED DATE: 12/14/2012

4. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
MAF (b) (4)		Antares	device	(b) (4)	this is a Device Master File (not a DMF)
	II	(b) (4)	methotrexate		This DMF was reviewed on 2/08/2013 and found to be adequate for an

					injection drug product. Numerous changes are discussed.
(b) (4)	III			(b) (4)	
	III				
	III				
	III				

b. Recommended Consults

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	X	☐	There is a statistical analysis of the stability data provided in a shelf life analysis.
Clin Pharm	☐	X	
EES	X		EES entered on January 30, 2013
Pharm/Tox	☐	☐	This is to be a review decision, as methotrexate is not a new drug. The applicant claims four potential drug product degradation products, i.e., impurities (b) (4) (see 3.2.P.5.6). Shelf life acceptance criteria for related substances are said to be based on the British Pharmacopeia monograph for methotrexate injection. The leachables data may not need pharm/tox consult, because of the very low levels observed. This should be verified with the pharm/tox reviewer.
Methods Validation	☐	?	This will be a review decision, if there is a special reason to have the FDA St. Louis laboratory perform validation or verification on one or more methods.
EA	☐	X	The categorical exclusion claim is to be evaluated by

			the reviewer. The applicant in 1.12.14 claims that this action (i.e., NDA approval) would not increase the use of the active moiety. No extraordinary circumstances are known to the applicant.
New Drug Micro	X	☐	
CDRH	X	☐	This may not be necessary as this device may be the same as was approved for epinephrine. However, note that DPARP has requested a consult from the Office of Combination Products (OCP).
Other	☐	☐	

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND		103738	methotrexate

d. Previous Communications with the Applicant to note (if any)*:

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
meeting minutes	11/28/12	IND 103738	some CMC issues, including, e.g., stability
responses (CMC)	5/23/12	IND 103738	
EOP2 meeting minutes	10/13/11	IND 103738	includes CMC issues
pre-NDA prelim. comments	11/1/12	IND 103738	includes CMC issues
pIND meeting minutes	3/05/09	IND 103738	includes CMC issues

*See also Module 1.6 for other correspondence, including pre-IDE meeting minutes.

OVERALL PRODUCT QUALITY CONCLUSIONS AND RECOMMENDATIONS

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
X	☐	1.

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?
Yes (minor): Please obtain a copy of a Letter of Authorization from (b) (4) for DMF (b) (4) containing specific references (e.g., dates of submission, page numbers) to the syringe to be reviewed to support this application. See the Guideline for Drug Master Files Section V.A. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073164.htm

Preliminary labeling comments:

- 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.

Provide placebo samples of the drug product.

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?		
Yes	No	Biopharmaceutics Filing Issues
☐	☐	1. Biopharmaceutics is not included in this review.

Are there potential biopharmaceutics review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
☐	☐	Biopharmaceutics is not included in this review.

Does the submission contain any of the following elements?

	Yes	No	Comments
Botanical Products	☐	X	
Combination Products	X	☐	
Nanotechnology	☐	X	
PAT	☐	X	
QbD Elements	☐	X	
SPOTS	☐	X	

Is a team review recommended?

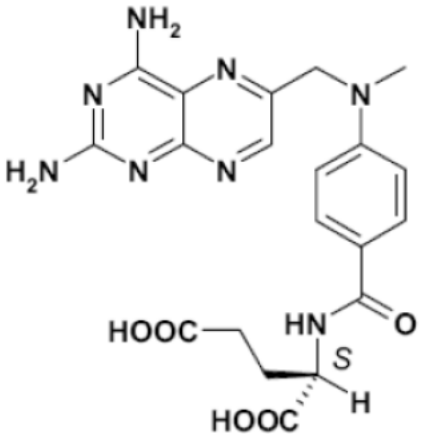
Yes	No	Suggested expertise for team
☐	X	

CMC Summary:
Critical Issues and Complexities

(This section is formatted to expand as far as needed by author.)

Drug substance:

- The referenced DMF [redacted] (b) (4) was previously reviewed and found adequate on 2/08/13 for methotrexate drug substance.
- The drug substance solid state form is said to resemble the [redacted] (b) (4) of about [redacted] (b) (4).
- Chemical structure:



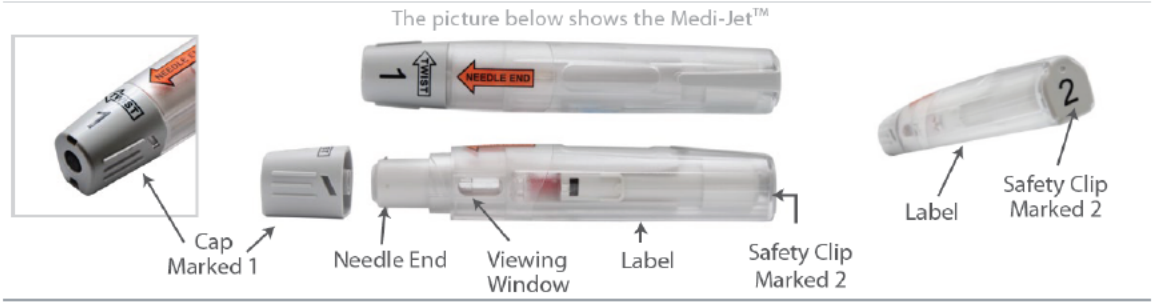
Drug product:

- Sterile solution without preservative. Sterilization is performed by (b) (4)
- Intended for single use. Autoinjector delivers entire dose (0.4 mL) at once.
- Four different concentrations, with NaCl added (b) (4)
- Strengths: 10, 15, 20 and 25 mg (each per 0.4 mL)
- Proposed dose is once weekly subcutaneous administration.

Drug product container closure system (device):

- Pre-filled (b) (4) glass syringe with a (b) (4) gray plunger. (b) (4)
- Vibex Assembly: single-use, pressure-assisted mini-needle injection device prefilled for subcutaneous self-administration
- Needle is ½ inch, 27 gauge.

Illustration of the device:



The following drug product leachables were found after 18 and 24 months on stability: (b) (4) ; all other organic leachables were below the LOD (b) (4) syringe). These may not need pharm/tox evaluation due to their low levels (b) (4) each per syringe) and limited use of the product. Nevertheless, this should be discussed with the pharm/tox reviewer.

Table 3: Effect of Formulation Variables on Methotrexate Solution Stability

Experimental Variable	Result
Temperature	• The main degradant was (b) (4); all other degradation products were (b) (4)%. • (b) (4) levels increase with time on stability at both 25°C/60% RH and 40°C/75% RH • Methotrexate degradation is significantly increased at 40°C/75% RH for all study formulations at all stability timepoints
Methotrexate Concentration	• Slightly higher levels of (b) (4) were observed for the low concentration study formulations
pH 7-9	• (b) (4) levels were independent of formulation pH
All Variables	• Maximum level of (b) (4) was below the proposed shelf-life acceptance limit of (b) (4)% for the study duration

The clinical studies are indicated to have used the same drug product doses, formulations and autoinjector device as proposed for the commercial product.

There are separate specifications for prefilled syringes and for the combination product (assembled autoinjector). Both release and shelf life acceptance criteria are listed with the specifications; it should be clarified that the shelf life specification is the regulatory specification. This will require some modification of the specifications since tests for identification are only listed with the release specifications. There is no drug product specification for osmolarity, but there is an in process control for osmolarity (230-320 mOsmol/L). Leachables may not need to be included in specifications based on low levels observed on stability.

Drug product stability: there are 8 primary stability batches: one batch each at all strengths (including both the prefilled syringe and the autoinjector device), and two batches (including or not including the autoinjector device, depending upon the attribute tested) at both the highest and lowest strengths. The latter 4 batches only included the autoinjector device for the following attributes: autoinjector functionality, volume in container and uniformity of dosage unit. It should be determined what constitutes a batch of the autoinjector devices and what constitutes a batch of the prefilled syringe, and the commercial batch sizes of each of these components. It should be determined whether there is a system involving batch numbers to track both the prefilled syringe batch and the autoinjector device batch for a batch of drug product. Stability data at 40°C/75%RH are not provided due to product instability under these storage conditions.

Refer also to the notes in the filing table later in this review.

Description of Facility Related Risks or Complexities (i.e. foreign sites, large number of sites involved, etc.)
See EES for complete list of facilities related to this application.
Drug substance and drug product are manufactured by other companies (neither is manufactured or tested by the applicant) which also perform some testing. A number of other companies are involved with drug substance and drug product testing.

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
1.	Is the CMC section organized adequately?	X	☐	☐	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X	☐	☐	
3.	Are all the pages in the CMC section legible?	X	☐	☐	
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	☐	☐	☐	This is in part a review decision. Any potential filing concerns involving the device master file would be identified by CDRH; it does not appear at this time that there are any. As far as potential CMC filing issues are concerned, FDA requested extractables and leachables studies for the device and there are reports provided that address these issues. MAF (b) (4) is referenced by the applicant for the device, and the NDA does list device changes made during drug development.

B. FACILITIES*					
	Parameter	**Yes**	**No**	**N/A**	**Comment**

5	Is a single, comprehensive list of all involved facilities available in one location in the application?	X	☐	☐	
6	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**	☐	☐	X	
7	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	note that contact person, telephone number and e-mail address for each site is included in 3.2.S.2.1 and 3.2.P.3.1.

8	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	note that contact person, telephone number and e-mail address for each site is included in 3.2.S.2.1 and 3.2.P.3.1.
9	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	DMFs and MAF (for device) are listed separately.
1	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X	☐	☐	This readiness for inspection is indicated in check boxes on Form FDA 356h and its continuation sheets, for each facility.

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X	☐	☐	categorical exclusion is claimed based on 21 CFR 25.31(a). They claim that there are no extraordinary circumstances.

D. MASTER FILES (DMF/MAF)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X	☐	☐	*See table on cover page.* There are references to a MAF for the device, and DMFs for the drug substance, syringe and rubber components.

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

NDA # 204824 Received Date: 12/14/12

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
13.	Does the section contain a description of the DS manufacturing process?	X	☐	☐	Only a synthetic flow diagram is provided. DMF (b) (4) is referenced for full details.
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters?	☐	X	☐	Key intermediates are listed but not critical steps. DMF (b) (4) is referenced for full details.
15.	Does the section contain information on impurities?	X	☐	☐	
16.	Does the section contain information regarding the characterization of the DS?	X	☐	☐	elucidation of structure is discussed.
17.	Does the section contain controls for the DS?	X	☐	☐	DMF (b) (4) is referenced for current specifications of drug substance at (b) (4) (d.s. manufacturer). Information is provided for specifications and analytical methods at both (b) (4) and at (b) (4) (drug product manufacturer, which also tests d.s.)
18.	Has stability data and analysis been provided for the drug substance?	☐	X	☐	The NDA only contains results of stress testing. DMF (b) (4) is referenced for full details.
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	☐	X	☐	None mentioned in the NDA. This is an older DMF (submitted 1995).
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	X	☐	None mentioned in the NDA
21.	Does the section contain container and closure information?	☐	X	☐	Only very briefly summarized, details are referenced to DMF (b) (4)

F. DRUG PRODUCT (DP)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
22.	Does the section contain quality controls of excipients?	X	☐	☐	All excipients are compendial. Specifications/acceptance criteria are provided and CoAs (b) (4)
23.	Does the section contain information on composition?	X	☐	☐	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X	☐	☐	A description is provided in P.3.3 and there are master batch records (dual language: French and English) for each strength, for bulk solution and for filling. Master batch records for labeling and final assembly of the product & packaging are not found. Executed batch records for the d.s. "will be provided on request." Drug product executed batch records are provided for each strength, at least through applying labels to bags of filled syringes, placing them in shippers and labeling the shippers. Executed batch records are also provided for assembly of the final product ("packaging batch record"). Some photodegradation is possible for the drug product, therefore there are safeguards to control this in the manufacturing process.
25.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X	☐	☐	
26.	Is there a batch production record and a proposed master batch record?	X	☐	☐	See #24 above.
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X	☐	☐	Investigational formulations (phase 2) are indicated in P.2.2 (pp. 8-9).

28.	Have any biowaivers been requested?	☐	X	☐	not found
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	X	☐	☐	Note that the autoinjector device is referenced to MAF (b) (4). The NDA in section P.7 (pp. 17-18, Table 7) provides a brief summary of the history of the device changes over drug development. It needs to be determined whether this is discussed in more detail in MAF (b) (4).
30.	Does the section contain controls of the final drug product?	X	☐	☐	
31.	Has stability data and analysis been provided to support the requested expiration date?	X	☐	☐	Data are provided at 25°C/60% RH (18-24 months) and at 30°/65%RH (12 months). A statistical analysis is provided. Primary stability data include two lots of the 10 mg strength, two lots of the 25 mg strength, and one lot each for the 15 and 20 mg strengths. Accelerated stability at 40°C/75%RH has not been tested: the explanation for the omission this study is that specification limits would not be met at 6 months under these storage conditions.
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	☐	X	☐	
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	X	☐	

G. METHODS VALIDATION (MV)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
34.	Is there a methods validation package?	X	☐	☐	The MV "package" is a page of references to information elsewhere in the NDA. It is missing a tabular listing of all samples to be submitted. The applicant states that they will provide samples along with CoA and MSDS information upon request.

H. MICROBIOLOGY					
	Parameter	**Yes**	**No**	**N/A**	**Comment**

35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	X	☐	☐	see P.2.5

I. LABELING					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
36.	Has the draft package insert been provided?	X	☐	☐	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.
37.	Have the immediate container and carton labels been provided?	X	☐	☐	See above pertaining to the name of the drug product. Carton labels should include the inactive ingredients.
38.	Does section contain tradename and established name?	X	☐	☐	See item #36 above.

J. FILING CONCLUSION					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
39.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X	☐	☐	
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	☐	☐	☐	
41.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X	☐	☐	Please obtain a copy of a Letter of Authorization from (b) (4) for DMF (b) (4) containing specific references (e.g., dates of submission, page numbers) to the syringe to be reviewed by to support this application. See the Guideline for Drug Master Files Section V.A. Preliminary labeling comments: – 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.

REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

CMC Lead
Branch Chief

{See appended electronic signature page}

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

/s/

ALAN C SCHROEDER
02/21/2013

PRASAD PERI
02/22/2013
I concur

NDA 204824

Otrexup

(methotrexate injection)

Single use, prefilled autoinjector

Antares Pharma Inc.

Original NDA receipt date: 12/14/2012

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
1.	Is the CMC section organized adequately?	X	☐	☐	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X	☐	☐	
3.	Are all the pages in the CMC section legible?	X	☐	☐	
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	☐	☐	☐	This is in part a review decision. Any potential filing concerns involving the device master file would be identified by CDRH; it does not appear at this time that there are any. As far as potential CMC filing issues are concerned, FDA requested extractables and leachables studies for the device and there are reports provided that address these issues. MAF (b) (4) is referenced by the applicant for the device, and the NDA does list device changes made during drug development.

B. FACILITIES*					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
5	Is a single, comprehensive list of all involved facilities available in one location in the application?	X	☐	☐	

6	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**	☐	☐	X	
7	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	note that contact person, telephone number and e-mail address for each site is included in 3.2.S.2.1 and 3.2.P.3.1.

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1	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X	☐	☐	This readiness for inspection is indicated in check boxes on Form FDA 356h and its continuation sheets, for each facility.

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X	☐	☐	categorical exclusion is claimed based on 21 CFR 25.31(a). They claim that there are no extraordinary circumstances.

D. MASTER FILES (DMF/MAF)					
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12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X	☐	☐	*See table on cover page.* There are references to a MAF for the device, and DMFs for the drug substance, syringe and rubber components.

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24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X	☐	☐	A description is provided in P.3.3 and there are master batch records (dual language: French and English) for each strength, for bulk solution and for filling. Master batch records for labeling and final assembly of the product & packaging are not found. Executed batch records for the d.s. "will be provided on request." Drug product executed batch records are provided for each strength, at least through applying labels to bags of filled syringes, placing them in shippers and labeling the shippers. Executed batch records are also provided for assembly of the final product ("packaging batch record"). Some photodegradation is possible for the drug product, therefore there are safeguards to control this in the manufacturing process.
25.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X	☐	☐	
26.	Is there a batch production record and a proposed master batch record?	X	☐	☐	See #24 above.
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X	☐	☐	Investigational formulations (phase 2) are indicated in P.2.2 (pp. 8-9).
28.	Have any biowaivers been requested?	☐	X	☐	not found

29.	Does the section contain description of to-be-marketed container/closure system and presentations?	X	☐	☐	Note that the autoinjector device is referenced to MAF (b) (4). The NDA in section P.7 (pp. 17-18, Table 7) provides a brief summary of the history of the device changes over drug development. It needs to be determined whether this is discussed in more detail in MAF (b) (4).
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G. METHODS VALIDATION (MV)					
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	Parameter	**Yes**	**No**	**N/A**	**Comment**
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	X	☐	☐	see P.2.5

I. LABELING					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
36.	Has the draft package insert been provided?	X	☐	☐	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.
37.	Have the immediate container and carton labels been provided?	X	☐	☐	See above pertaining to the name of the drug product. Carton labels should include the inactive ingredients.
38.	Does section contain tradename and established name?	X	☐	☐	See item #36 above.

J. FILING CONCLUSION					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
39.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X	☐	☐	
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	☐	☐	☐	
41.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X	☐	☐	Please obtain a copy of a Letter of Authorization from (b) (4) for DMF (b) (4) containing specific references (e.g., dates of submission, page numbers) to the syringe to be reviewed by to support this application. See the Guideline for Drug Master Files Section V.A. Preliminary labeling comments: – 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.

CMC lead/reviewer: Alan Schroeder
2/12/2013

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

/s/

ALAN C SCHROEDER
02/12/2013
Filing review only

PRASAD PERI
02/12/2013
I concur