

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-468

CHEMISTRY REVIEW(S)

Memorandum

To: NDA 22-468
From: Sarah Pope Miksinski, Ph.D.
Date: 9/22/2009
Re: Final CMC recommendation for NDA 22-468

NDA 22-468 was initially submitted on 24-MAR-2009 and was granted a priority review by the Agency. Chemistry Review #1 (08-SEP-2009) resulted in a recommendation for approval pending a determination of acceptability from the Office of Microbiology, and pending the receipt of an overall acceptable recommendation from the Office of Compliance. At the time of CMC review finalization, the microbiology review and overall compliance recommendation were still pending.

This memo serves to update that determination. The Office of Microbiology (Dr. S. Fong) issued a recommendation for approval in a review dated 09-AUG-2009. An overall acceptable recommendation was issued by the Office of Compliance on 18-SEP-2009.

In a review dated 18-SEP-2009, the Division of Medication Errors and Prevention Analysis (DMEPA) noted additional deficiencies with regards to the container/carton labeling. From a CMC perspective, the container/carton labels submitted on 04-SEP-2009 and specified in CMC Review #1 are acceptable. Further revisions recommended by DMEPA are currently ongoing and should be documented in the corresponding DMEPA review.

All CMC deficiencies have been resolved, and there are no outstanding issues with this NDA. Therefore, approval of NDA 22-468 is recommended from a CMC perspective.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22468

ORIG-1

ALLOS
THERAPEUTICS
INC

FOLOTYN

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/s/

Sarah Pope Miksinski
09/22/2009

ONDQA Division Director's Memo
NDA 22-468, Folutyn™ (pralatrexate injection) 20 mg per mL
Date: 08-SEP-2009

Introduction

Folutyn is a sterile, preservative-free injection of pralatrexate; an antineoplastic for the treatment of relapsed or refractory peripheral T-cell lymphoma. Two single-dose presentations are proposed; 1 mL/vial and 2 mL/vial (each at 20 mg/mL).

Administrative

The original submission of this 505(b)(1) NDA was received 23-MAR-2009 from Allos Therapeutics, Inc., Westminster, CO. The NDA is supported by IND 52,604Eight amendments were received and reviewed after the original submission; as late as 08-SEP-2009.

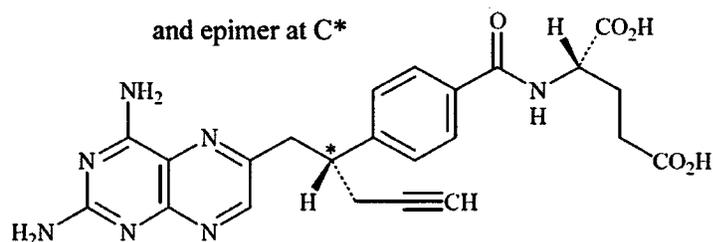
There are **no outstanding CMC deficiencies from ONDOA**. However, the Microbiology review and overall EES recommendation are pending as of this writing. Thus, **ONDOA's recommendation for APPROVAL is pending a satisfactory outcome from the Product Quality Microbiology review and EES.**

Drug Substance (pralatrexate)

(b) (4)

(b) (4) The

proposed retest period for the drug substance is (b) (4) when stored under refrigeration and protected from light.



Chemical formula C₂₃H₂₃N₇O₅
Molecular weight 477.48

Drug Product (Folotyn™)

The drug product contains 20 mg of pralatrexate drug substance in each mL of solution. Two single-dose presentations are proposed for commercial production: 1 mL/vial and 2 mL/vial. The solution contains sufficient quantity of sodium chloride to achieve an isotonic solution. The solution is adjusted to achieve and maintain a pH of 7.5-8.5 using sodium hydroxide (primarily) and hydrochloric acid (as needed).

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

Based on the stability data provided, a twelve (12) month drug product shelf life when stored at 5C in the approved container / closure system is assigned.

Rik Lostritto, Ph.D., Director, ONDQA Division III

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/s/

RICHARD T LOSTRITTO
09/08/2009



CMC REVIEW



NDA 22-468

**FolotynTM
(pralatrexate injection)**

Allos Therapeutics, Inc.

Sue-Ching Lin

Review Chemist

**Office of New Drug Quality Assessment
Division of Pre-marketing Assessment and Manufacturing Science
Branch V**

**CMC REVIEW OF NDA
For the Division of Drug Oncology Products (HFD-150)**

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CMC Review Data Sheet

1. NDA 22-468
2. REVIEW #: 1
3. REVIEW DATE: 08-Sept-2009
4. REVIEWER: Sue-Ching Lin
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 52,604 submission	31-Jan-1997
Pre-NDA meeting (Clinical, non-clinical, and 2 CMC comments)	16-Jul-2008
CMC only pre-NDA meeting	19-Aug-2008
FDA response to sponsor's questions in 9/9/08 amendment	06-Nov-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS Sequence Number	Document Date	Stamp Date
Original NDA Submission	1	23-Mar-2009	24-Mar-2009
Amendment (BC) (Clarification of the manufacturer functions and addresses)	2	21-Apr-2009	21-Apr-2009
Amendment (BC) (Response to FDA request to merge DP sections)	8	03-Jun-2009	04-Jun-2009
Amendment (Response to FDA 7/21/09 CMC IR)	16	31-Jul-2009	03-Aug-2009
Amendment (container and carton labeling)	18	20-Aug-2009	21-Aug-2009
Amendment (Response to 8/14/09 telecon)	19	21-Aug-2009	24-Aug-2009
Amendment (Updated post-approval stability protocols for DS and DP -- response to 8/21/09 CMC request)	20	26-Aug-2009	27-Aug-2009
Amendment (Revised container and carton labeling)	22	01-Sep-2009	02-Sep-2009
Amendment (Revised container and carton labeling)	23	04-Sep-2009	08-Sep-2009



CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Allos Therapeutics, Inc.
Address: 11080 CirclePoint Road Suite 200
Westminster, CO 80020
Representative: Linnea Tanner, Senior Director, Regulatory Affairs
Telephone: 303-540-5340

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Folutyn™
- b) Non-Proprietary Name: pralatrexate injection
- c) Code Name/# (ONDQA only): PDX
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 1 (new molecular entity)
 - Submission Priority: P (priority review)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: antineoplastic (treatment of patients with relapsed or refractory peripheral T-cell lymphoma)

11. DOSAGE FORM: injection

12. STRENGTH/POTENCY: 20 mg/mL

13. ROUTE OF ADMINISTRATION: intravenous

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product



CMC Review Data Sheet

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

Chemical structure	<p>and epimer at C*</p>
Molecular formula	C ₂₃ H ₂₃ N ₇ O ₅
Molecular weight	477.48
United States Adopted Name (USAN)	pralatrexate
USAN chemical names	<i>L</i> -glutamic acid, N-[4-[1-[(2,4-diamino-6-pteridinyl)methyl]-3-butynyl]benzoyl]- <i>(2S)</i> -2-[[4-[(1 <i>R</i> ,5 <i>S</i>)-1-[(2,4-diaminopteridin-6-yl)methyl]but-3-ynyl]benzoyl]amino]pentanedioic acid
Company or laboratory code	PDX
Chemical Abstracts Service(CAS) registry number	146164-95-1

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	Date of this review	See section 3.2.P.7
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	Date of this review	See section 3.2.P.7
(b) (4)	III	(b) (4)	(b) (4)	3 & 4**	Adequate	14-Oct-208	Reviewed by Donald Klein**
(b) (4)	V	(b) (4)	(b) (4)	3	Adequate	21-Jan-2009	Reviewed by Steven P. Donald. See also microbiology review.

(b) (4)



CMC Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	52,604	PDX, pralatrexate

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	Pending	
Pharm/Tox	All impurities are qualified at the proposed acceptance criteria*.	9/4/09	William D. McGuinn
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA**	The proposed proprietary name Folutyn is acceptable.	8/7/09	Kellie A Taylor
EA	Categorical exclusion (see review)	Date of this review	Sue-Ching Lin
Microbiology	Pending	Pending	

* Dr. McGuinn confirmed in a 9/3/09 e-mail that all impurities are qualified at the proposed acceptance criteria in the drug substance and drug product. See Dr. McGuinn's e-mail on page 130 of this review, under the heading of "E-mail correspondences."

**DMEPA: Division of Medication Error Prevention and Analysis



Executive Summary Section

The CMC Review for NDA 22-468

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of chemistry, manufacturing, and controls, this NDA may be approved, pending “acceptable” overall recommendations from both the Office of Compliance and the Microbiology reviewer.

Based on the provided stability data, a 12-month expiration dating period is granted for the drug product when stored in the original carton under the proposed refrigerated condition.

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

The active ingredient is pralatrexate, which is a new molecular entity. Detailed information regarding the drug substance is provided in the NDA.

Pralatrexate is chemically synthesized as a mixture of two diastereomers. The C10 chiral center exists in the *RS*-configuration. The C19 chiral center is in *S*-configuration. Neither chiral center has demonstrated racemization or epimerization. The drug substance is an off-white to yellow solid. It is soluble in aqueous solutions at pH 6.5 or higher. It is slightly hygroscopic.

(b) (4)

The NDA has included a detailed report regarding the fate of potential related impurities. The critical operating parameters are identified and the reaction parameters are controlled to properly minimize the formation of the impurities.



Executive Summary Section

Fates of each starting material and the impurities in each starting material were provided in details in section 3.2.S.3.2. (b) (4)

The proposed acceptance criteria for these impurities are below the qualified levels and are based on the manufacturing capabilities.

The applicant provides long-term (5°C) primary stability data (up to 18 months for two batches and up to 12 months for one batch) for pralatrexate manufactured at the proposed commercial manufacturing site. The applicant also provides 6 months of accelerated (25°C/60% RH and 40°C/75% RH) stability for these three batches. Up to 36 months stability data are submitted as supporting data for a batch manufactured at an earlier stage of development. The submitted stability data support the proposed retest period of (b) (4) for the drug substance when stored under refrigerated (at 5°C) conditions in the commercial container closure system and protected from light.

(2) Drug Product

The drug product is a sterile, preservative-free aqueous solution containing 20 mg of pralatrexate drug substance in each mL of solution. Two single-dose sizes are proposed for commercial production: 1 mL/vial and 2 mL/vial.

The solution contains sufficient quantity of sodium chloride to achieve an isotonic solution. The solution is adjusted to achieve and maintain a pH of 7.5-8.5 using sodium hydroxide (primarily) and hydrochloric acid (as needed).

(b) (4)

Two manufacturing sites, (b) (4), are proposed for the manufacture of the drug product. The original NDA submission contains two complete drug product sections (section 3.2.P), each for the drug product manufactured at respective sites. The two separate drug product sections had created confusions and difficulties for the CMC review. Consequently,

Executive Summary Section

the applicant was requested by the FDA during the May 21, 2009 teleconference to merge the drug product information into one 3.2.P section for both manufacturers. In response, the company submitted the June 3, 2009 amendment with a combined 3.2.P section.

The primary stability data include 9-month stability results for 3 batches of the drug product packaged in 1-mL and 2-mL fill sizes and stored under 5°C (long-term) and 25°C/60%RH (accelerated) conditions. Supportive data include 4 batches of the drug product packaged in 4-mL or 5-mL fill sizes. Three months of stability are provided for a batch of the drug product to support a change to the (b) (4). Since all batches show apparent trends of degradation under accelerated storage condition of 25°C/60%RH, the shelf life may be granted up to 3 months beyond the period covered by long-term data, according to the principles outlined in section 2.5.1.1 of ICH Q1E, "Evaluation of Stability Data," for drug products intended for storage in a refrigerator. Therefore, based on the 9-month primary stability data and the supportive data, a 12-month expiration dating period is granted.

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

The drug product Folutyn is indicated for the treatment of patients with relapsed or refractory peripheral T cell lymphoma (PTCL). Folutyn should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents.

Folutyn is administered by intravenous (IV) push over 30 seconds to 5 minutes via the side port of a free flowing 0.9% Sodium Chloride Injection, USP IV line. The recommended dose of Folutyn is 30 mg/m² once weekly for 6 weeks in 7-week cycles until progressive disease or unacceptable toxicity. Patients should take low-dose (1.0 - 1.25 mg) oral folic acid on a daily basis. Patients should also receive a vitamin B₁₂ (1 mg) intramuscular injection no more than 10 weeks prior to the first dose of Folutyn and every 8-10 weeks thereafter.

Folutyn vials must be stored refrigerated at 2-8°C (36-46°F) (see USP Controlled Cold Temperature) until use. Vials contain no preservatives and are intended for single use only. After withdrawal of dose, discard vial including any unused portion.

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been provided for the manufacture and controls of the drug substance and drug product.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Folutyn. The CMC revisions of the package insert have been incorporated into the revised labeling during the internal labeling

Executive Summary Section

meetings of the NDA. This reviewer had shared the labeling comments regarding container labels and carton labeling with the DMEPA reviewers before the labeling comments were conveyed to the applicant on August 27, 2009. The revised container labels and carton labeling, as amended by the applicant on September 4, 2009, are acceptable.

As of the date of this review, the microbiology review and the inspection for the drug product manufacturing facilities are still pending. This NDA is recommended for **approval pending "acceptable" overall** recommendations from the Office of Compliance and the Microbiology reviewer.

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Sue-Ching Lin, M.S., R.Ph., Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Terrance Ocheltree, R.Ph., Ph.D., Acting Pharmaceutical Assessment Lead, Branch V, ONDQA

Sarah Pope Miksinski, Ph.D., Branch Chief, Branch V, ONDQA

C. CC Block: entered electronically in DARRTS

125 Pages Withheld
as Trade Secret/
Confidential b(4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22468	ORIG-1	ALLOS THERAPEUTICS INC	FOLOTYN
NDA-22468	ORIG-1	ALLOS THERAPEUTICS INC	FOLOTYN
NDA-22468	ORIG-1	ALLOS THERAPEUTICS INC	FOLOTYN
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09/08/2009

TERRANCE W OCHELTREE
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