

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-468

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 22-468

SUPPL #

HFD # 150

Trade Name Folutyn TM

Generic Name pralatrexate

Applicant Name Allos Therapeutics Inc.

Approval Date, If Known 9/24/09

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)(1)

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.

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?

5 years

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#

NDA#

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: Milinda Vialpando

Title: Regulatory Project Manager

Date: 9/24/09

Name of Office/Division Director signing form: Robert Justice, M.D., M.S.

Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

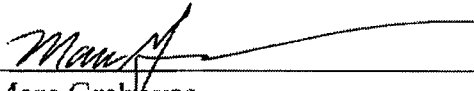
MILINDA F VIALPANDO
09/23/2009

ALICE KACUBA
09/24/2009

ROBERT L JUSTICE
09/24/2009

DEBARMENT CERTIFICATION

On behalf of Allos Therapeutics, Inc. ("Allos"), I hereby certify that Allos 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 New Drug Application for Pralatrexate Injection.



Marc Graboyes
Senior Vice President, General Counsel
Allos Therapeutics, Inc.

3/12/09

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22-468 BLA #	NDA Supplement # NME BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Folotyn™ Established/Proper Name: pralatrexate Dosage Form: injection		Applicant: Allos Therapeutics, Inc. Agent for Applicant (if applicable):
RPM:		Division:
<u>NDA's:</u> 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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		<u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review. ☐ No changes ☐ Updated Date of check: 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. On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.
❖ User Fee Goal Date Action Goal Date (if different)		9/24/09
❖ Actions		
• Proposed action		☐ AP ☐ TA ☐ AE ☐ NA ☒ CR
• Previous actions (specify type and date for each action taken)		☒ None
❖ Promotional Materials (accelerated approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received

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.

❖ Application Characteristics ²		
Review priority: ☐ Standard ☐ Priority Chemical classification (new NDAs only): ☐ 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 ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies Comments: _____		
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: _____	Orphan	
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	☐ Yes, date	
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No	
❖ Public communications (<i>approvals only</i>)		
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No (Liz H)	
• Press Office notified of action (by OEP)	☒ Yes ☐ No (Karen R)	
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Burst	

² All questions in all sections pertain 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
NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>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.</i>	☒ 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? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ 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? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ 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? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ 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)? <i>(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.)</i>	☒ 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). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i>	☐ N/A (no paragraph IV certification) ☐ Verified

- [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). <i>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).</i> <i>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.</i>	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	X
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Complete Response on 9/24/09
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	X
• Original applicant-proposed labeling	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☒ None
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A

³ Fill in blanks with dates of reviews, letters, etc.

Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	N/A
Original applicant-proposed labeling	N/A
Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
Most-recent division proposal for (only if generated after latest applicant submission)	
Most recent applicant-proposed labeling	X
❖ Proprietary Name - Review(s) (<i>indicate date(s)</i>) - Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)	8/7/09 Acceptable
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☐ RPM ☒ DMEPA 9/18/09 ☐ DRISK ☒ DDMAC 9/4/09 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	9/8/09
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant in on the AIP	☐ Yes ☒ No
- This application is on the AIP - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	☒ Included (ORPHAN-exempt)
❖ 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 (<i>include certification</i>)	☒ Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	X
❖ Internal memoranda, telecons, etc.	X
❖ Minutes of Meetings	
PeRC (<i>indicate date of mtg; approvals only</i>)	☒ Not applicable
Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>)	☒ Not applicable
Regulatory Briefing (<i>indicate date of mtg</i>)	☒ No mtg
Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg 7/16/08
EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg 2/6/06

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 8/26/09

• Other (e.g., EOP2a, CMC pilot programs)	N/A
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	9/2/09
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	X
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☐ None 9/21/09
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 9/24/09
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 9/12/09
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None 9/24/09
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	Concurred with MOR dated 9/17/09
• Clinical review(s) (<i>indicate date for each review</i>)	9/17/09
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	In MOR dated 9/17/09
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	6/29/09
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☐ None IRT 8/27/09
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ Not needed
❖ Risk Management - REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) - REMS Memo (<i>indicate date</i>) - Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	☐ None requested 8/26/09
Clinical Microbiology	☒ None
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None
Biostatistics	☐ None
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☒ None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☐ None 9/4/09
Statistical Review(s) (<i>indicate date for each review</i>)	☐ None 9/4/09 and 9/22/09
Clinical Pharmacology	☐ None

⁵ Filing reviews should be filed with the discipline reviews.

❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	☐ None Concluded with primary review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	☐ None Concluded with primary review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	☐ None 9/3/09
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	☐ None 9/14/09
• Supervisory Review(s) <i>(indicate date for each review)</i>	☐ None 9/8/09
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	☐ None 9/4/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	☒ None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	☐ None 9/8/09
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	☐ None 9/22/09
• Product quality review(s) <i>(indicate date for each review)</i>	☐ None 9/8/09
• ONDQA Biopharmaceutics review <i>(indicate date for each review)</i>	
• BLAs only: Facility information review(s) <i>(indicate dates)</i>	☒ None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i>	9/10/09 ☐ Not needed
• BLAs: Sterility assurance, product quality microbiology <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See CMC review dated 9/8/09
☐ Review & FONSI <i>(indicate date of review)</i>	N/A
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i>	Date completed: ☒ Acceptable ☐ Withhold recommendation

• BLAs: ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☒ Requested ☐ Not yet requested ☐ Not needed

Appendix A 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.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22468

ORIG-1

ALLOS
THERAPEUTICS
INC

FOLOTYN

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

/s/

MILINDA F VIALPANDO

09/25/2009

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-468 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Folutyn
Established Name: pralatrexate
Strengths: injection 20 mg/1 mL and 40 mg/2 mL

Applicant: Allos Therapeutics Inc.
Agent for Applicant (if applicable):

Date of Application: March 23, 2009

Date of Receipt: March 23, 2009

Date clock started after UN: N/A

Date of Filing Meeting: 4/24/09

Filing Date: May 23, 2009

Action Goal Date (optional): 9/14/09

User Fee Goal Date: 9/24/09

Indication(s) requested: Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL)

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)

Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☐
Resubmission after withdrawal? ☐
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.) Orphan

P ☒
Resubmission after refuse to file? ☐

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☐ Exempt (orphan, government) ☒
Waived (e.g., small business, public health) ☐

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☐
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐
- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
If no, explain:
- Was form 356h included with an authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐
2. This application is an eNDA or combined paper + eNDA YES ☐
This application is: All electronic ☒ Combined paper + eNDA ☐
This application is in: NDA format ☐ CTD format ☒
Combined NDA and CTD formats ☐

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fml.pdf>) YES ☒ NO ☐

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES ☒
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐
- Exclusivity requested? YES, X 5 Years NO ☐
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.
NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] 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." Applicant may not use wording such as "To the best of my knowledge . . ."
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES ☐ NO ☐
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☐ NO ☐
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒
If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ NO ☐
- PDUFA and Action Goal dates correct in tracking system? YES ☐ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 52,604
- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) 2/6/06 NO ☐
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 7/16/08 NO ☐
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) 7/28/06 NO ☐
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES ☒ NO ☐

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A ☐ YES ☐ NO ☐
- Risk Management Plan consulted to OSE/IO? N/A ☐ YES ☐ NO ☐
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
If EA submitted, consulted to EA officer, OPS? YES ☒ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☒
- If a parenteral product, consulted to Microbiology Team? YES ☒ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 24, 2009

NDA #: 22-468

DRUG NAMES: Folutyn (pralatrexate)

APPLICANT: Allos

BACKGROUND: This new NDA application is for a New Molecular Entity. The proposed indication for Folutyn is for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).

ATTENDEES: Shenghui Tang, Gene Williams, Terry Ocheltree, Ke Liu, Shakun Malik, Tony Murgo, Robert Young, Brian Booth, Sue-Ching Lin, Steven Fong.

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization

Reviewer

Medical:	Shakun Malik
Secondary Medical:	
Statistical:	Qiang (Casey) Xu
Pharmacology:	William Mc Guinn
Statistical Pharmacology:	
Chemistry:	Sue-Ching Lin
Environmental Assessment (if needed):	
Biopharmaceutical:	Gene Williams
Microbiology, sterility:	Stephen Langille
Microbiology, clinical (for antimicrobial products only):	
DSI:	Robert Young
OPS:	
Regulatory Project Management:	Milinda Vialpando
Other Consults: DDMAC	Karen Rulli

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

• Clinical site audit(s) needed? YES ☒ NO ☐
If no, explain:

• Advisory Committee Meeting needed? YES, date if known Sept 2, 2009 NO ☐

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS

FILE ☒

REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed?
YES

☐ NO ☒

PHARMACOLOGY/TOX

N/A ☐

FILE ☒

REFUSE TO FILE ☐

- GLP audit needed?

YES ☐ NO ☒

CHEMISTRY

FILE ☒

REFUSE TO FILE ☐

- Establishment(s) ready for inspection?
- Sterile product?
- If yes, was microbiology consulted for validation of sterilization?

YES ☒ NO ☐

YES ☒ NO ☐

YES ☒ NO ☐

ELECTRONIC SUBMISSION:

Any comments: EDR link does not work for the clinical section.

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- ☐ The application is unsuitable for filing. Explain why:
- ☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Milinda Vialpando
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and,
- (3) **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) 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, or
- (3) 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 Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☐

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES ☐ NO ☐

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES ☐ NO ☐

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES ☐ NO ☐

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(*Pharmaceutical alternatives* are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

If "Yes," to (c), proceed to question 7.

NOTE: If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☐

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☐

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? YES ☐ NO ☐
(This is different from the patent declaration submitted on form FDA 3542 and 3542a.)
13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- ☐ Not applicable (e.g., solely based on published literature. See question # 7)
- ☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- ☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- ☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- ☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- ☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- ☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- ☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.
- ☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☐ NO ☐

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

MILINDA F VIALPANDO
09/04/2009

ALICE KACUBA
09/08/2009



ALLOS™
THERAPEUTICS

20 September 2009

Robert Justice, MD
Director, Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Subject: **NDA 22-468 (022468-0027)** **AMENDMENT No. 27**
FOLOTYN™ (pralatrexate injection) Post-Marketing Commitments

Dear Dr. Justice:

Reference is made to NDA 22-468 for FOLOTYN™ (pralatrexate injection) in the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL) that was received at the Agency on 24 March 2009 and formally accepted for filing on 22 May 2009. Reference is also made to the teleconferences held on 03 September 2009, 09 September 2009, and 18 September 2009 between the Division of Drug Oncology Products and Allos Therapeutics, Inc. (Allos) regarding post-marketing requirements and commitment.

Based on the FDA recommendations for post-marketing requirements and commitment, below are the Allos post-marketing requirements and commitment, description of each of these post-marketing studies that Allos agrees to conduct, and major milestones for completing these studies.

Postmarketing Requirements Under 21 CFR 314.510 (Subpart H)

1. A randomized trial of maintenance treatment with pralatrexate in previously untreated patients with PTCL who have demonstrated a response to CHOP or a CHOP-like regimen.

Description of trial/study: This will be a Phase 3 multi-center, randomized clinical study of sequential FOLOTYN versus observation in patients with newly diagnosed aggressive peripheral T-cell lymphoma who have responded following initial treatment with CHOP-based chemotherapy. The primary endpoint will be progression-free survival (PFS). The study will also be sized to detect a realistic difference in survival. Patients will be enrolled prior to initiation of the CHOP-based regimen. Patients responding (CR or PR) after CHOP-based treatment will then be randomized 2:1 to FOLOTYN versus observation.

Final Protocol Submission: By: December 23, 2009
Trial/Study Completion: By: December 31, 2016
Final Report Submission: By: June 30, 2017

2. A randomized trial comparing pralatrexate in combination with systemic bexarotene versus systemic bexarotene alone in patients with cutaneous T-cell lymphoma (CTCL) who are refractory to at least one prior systemic therapy.

Description of trial/study: This will be a Phase 3 multi-center, randomized clinical study in patients with CTCL. The primary endpoint will be progression-free survival (PFS). Response rate will be a secondary endpoint. Prior to initiation of the Phase 3 study, a Phase 1 study will be conducted to determine the maximum tolerated dose (MTD) of the combination.

Submission of Phase 1 pralatrexate and systemic bexarotene protocol: By:
November 15, 2009

(b) (4)

Phase 1 Study completion: By: August 31, 2011
Final Phase 3 Protocol Submission: By: September 30, 2011
Trial/Study Completion: By: March 31, 2015
Final Report Submission: By: September 30, 2015

Postmarketing Requirements Under 505(O):

3. A clinical trial in patients with renal impairment to include patients with severe renal impairment.

Description of trial/study: This will be a Phase 1 clinical study to evaluate the pharmacokinetics of pralatrexate in relapsed/refractory lymphoma patients (B-cell, T-cell, and Hodgkin's Lymphoma) with mild to severe renal impairment. Three cohorts (N=6 per cohort) will be enrolled in this study for a total of 18 patients. Cohorts will be based on the severity of renal impairment, ie, cohort A = severely impaired ($\text{Crea}_{\text{CL}}^{\text{CG}} < 30 \text{ mL/min}$), cohort B = moderately impaired ($\text{Crea}_{\text{CL}}^{\text{CG}} = 30\text{-}50 \text{ mL/min}$), and cohort C = mildly impaired patients ($\text{Crea}_{\text{CL}}^{\text{CG}} = 50\text{-}80 \text{ mL/min}$). The pralatrexate dose for cohorts A and B will be determined based on the pharmacokinetics experience from the PROPEL study. Cohort C will be dosed at the recommended dose (30 mg/m^2) since patients with mild renal impairment were included in the PROPEL study. Patients will undergo extensive plasma and urine collections following the first dose of FOLOTYN.

Final Protocol Submission: By: January 31, 2010
Trial/Study Completion: By: June 30, 2012
Final Report Submission: By: January 31, 2013

4. Completion of the planned mass balance trial, and contingent on FDA review of the mass balance results, a trial in patients with hepatic impairment.

Description of trial/study: This is an ongoing Phase 1 mass balance clinical study to evaluate the excretion and metabolic profile of pralatrexate. Patients will receive a fixed dose of 225 mg radio-labeled pralatrexate. Patients will undergo intense sampling of blood, urine, feces, expired air, and other incidental excreta as needed for up to 7 days. Analysis of the samples will be done by liquid scintillation counting for mass balance determination and HPLC for metabolite profiling. Pralatrexate diastereomer concentrations in plasma and urine will be determined in parallel using a validated LC-MS/MS method.

Final Protocol Submission: By: October 29, 2008
Trial/Study Completion: By: June 30, 2010
Final Report Submission: By: December 31, 2010

Post-marketing Commitment

Allos agrees to conduct the following postmarketing commitment, with milestones.

1. Perform *in vitro* studies to determine if transporters are involved in the elimination of pralatrexate.

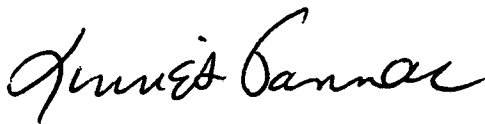
Description of trial/study: This will be an *in vitro* study to determine whether pralatrexate is a substrate for the OAT family, in particular OAT1 and OAT3¹, and whether drugs that interfere with or compete for these transporters (eg, acyclovir, probenecid, NSAIDS) have an effect on pralatrexate transport.

¹ Takeda M et al. Characterization of methotrexate transport and its drug interactions with human organic anion transporters. *Journal of Pharmacological and Experimental Therapeutics* (2002).

Study Start: December 1, 2009
Study Completion: By: January 31, 2011
Final Report Submission: By: July 31, 2011

If you have any questions regarding this submission, please do not hesitate to contact me.

Sincerely,



Linnea Tanner, M.S., R.A.C.
Senior Director, Regulatory Affairs
(720) 540-5340 – direct line
(720) 540-5476 – fax

Kacuba, Alice

From: Kacuba, Alice
Sent: Wednesday, September 16, 2009 2:41 PM
To: 'Tanner, Linnea'
Cc: Vialpando, Milinda
Subject: RE: NDA 22-468; FOLOTYN; Request Feedback on Proposed Printed Format of PI and Patient Information
Importance: High
Attachments: 9-16-09-Request-for-PMC&dates-for-PMR.doc

Tracking:

Recipient	Read
'Tanner, Linnea'	
Vialpando, Milinda	Read: 9/16/2009 2:41 PM

Hi,

In preparation for our tcon on Friday, please find attached. We will need you to fill in the "description" and "milestone dates" for PMRs.

For the PMC, fill in "description" and "milestone dates" along with a commitment to conduct. The PMRs will be mandatory so no need to provide written agreement to those.

I attempted to copy what dates I could from your recent submission, but check them closely.

Dates must be Month, day, year--in the format I provided.

You may want to wait until after our tcon Friday to return the information so as to have any of your questions clarified. If you change any wording, please use track changes. Our safety team is also reviewing so we may have additional revisions. If so, I will send along ASAP.

Any questions, I need to leave at 3:30 today but may be on line later this evening and will be in my office Thursday AM.

Thank you.

Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-1381
(f)301-796-9845
alice.kacuba@fda.hhs.gov

9/17/2009

Your response should include the proposed schedule for conducting the study/clinical trial, including all major milestones for the study/clinical trial, e.g., submission to the FDA of the finalized protocol, completion of the study/clinical trial, and submission of the final report. Dates must include month, day, year as indicated below.

Provide a description of the study and fill in milestones for Postmarketing Requirements.

Postmarketing Requirements Under 21 CFR 31.510 (Subpart H)

1. A randomized trial of maintenance treatment with pralatrexate in previously untreated patients with PTCL who have demonstrated a response to CHOP or a CHOP-like regimen.

Description of trial/study:

Final Protocol Submission: By: December __, 2009
Trial/Study Completion: By: ____, 2010
Final Report Submission: By: ____, 2017

2. A randomized controlled trial of single agent pralatrexate vs. an appropriate control in patients with relapsed or refractory PTCL.

Description of trial/study:

Final Protocol Submission: By: _____
Trial/Study Completion: By: _____
Final Report Submission: By: _____

Postmarketing Requirements Under 505(O):

3. A clinical trial in patients with renal impairment to include patients with severe renal impairment, and

Description of trial/study:

Final Protocol Submission: By: January __, 2010
Trial Completion: By: June __, 2010
Final Report Submission: By: January __, 2013

4. Completion of the planned mass balance trial, and contingent on FDA review of the mass balance results, a trial in patients with hepatic impairment.

Description of trial/study:

Final Protocol Submission: By: October 29, 2008
Trial Completion: By: May 18, 2009
Final Report Submission: By: December __, 2010

Postmarketing Commitment:

Please submit a written agreement to conduct the following postmarketing commitment, with milestones.

1. Perform *in vitro* studies to determine if transporters are involved in the elimination of pralatrexate.

Description of trial/study:

Final Protocol Submission: By: November __, 2009
Study Completion: By: _____
Final Report Submission: By: July __, 2011

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22468

ORIG-1

ALLOS
THERAPEUTICS
INC

FOLOTYN

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

/s/

ALICE KACUBA
09/17/2009



ALLOS™
THERAPEUTICS

22 September 2009

Robert Justice, MD
Director, Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Subject: **NDA 22-468 (022468-0031)** **AMENDMENT No. 31**
FOLOTYN™ (pralatrexate injection) Post-Marketing Commitments

Dear Dr. Justice:

Reference is made to NDA 22-468 for FOLOTYN™ (pralatrexate injection) in the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL) that was received at the Agency on 24 March 2009 and formally accepted for filing on 22 May 2009. Reference is made to the teleconferences held on 03 September 2009, 09 September 2009, and 18 September 2009 between the Division of Drug Oncology Products and Allos Therapeutics, Inc. (Allos) regarding post-marketing requirements and commitment. Reference is also made to the e-mail dated 22 September 2009 from Alice Kacuba, Chief, Project Management Staff, Division of Drug Oncology Products, in which FDA provided comments to the post-marketing requirements and commitment submitted in Amendment 27 on 20 September 2009.

Based on the FDA recommendations for post-marketing requirements and commitment, below are the Allos post-marketing requirements and commitment, description of each of these post-marketing studies that Allos agrees to conduct, and major milestones for completing these studies.

Postmarketing Requirements Under 21 CFR 314.510 (Subpart H)

1. A randomized trial of maintenance treatment with pralatrexate in previously untreated patients with PTCL who have demonstrated a response to CHOP or a CHOP-like regimen.

Description of trial/study: This will be a Phase 3 multi-center, randomized clinical study of sequential FOLOTYN versus observation in patients with newly diagnosed aggressive peripheral T-cell lymphoma who have responded following initial treatment with CHOP-based chemotherapy. The primary endpoint will be progression-free survival (PFS). The study will also be sized to detect a realistic difference in survival. Patients will be enrolled prior to initiation of the CHOP-based regimen. Patients responding (CR or PR) after CHOP-based treatment will then be randomized 2:1 to FOLOTYN versus observation.

Final Protocol Submission: By: December 23, 2009
Trial/Study Completion: By: December 31, 2016
Final Report Submission: By: June 30, 2017

2. A randomized trial comparing pralatrexate in combination with systemic bexarotene versus systemic bexarotene alone in patients with cutaneous T-cell lymphoma (CTCL) who are refractory to at least one prior systemic therapy.

Description of trial/study: This will be a Phase 3 multi-center, randomized clinical study in patients with CTCL. The primary endpoint will be progression-free survival (PFS). Response rate will be a secondary endpoint. Prior to initiation of the Phase 3 study, a Phase 1 study will be conducted to determine the maximum tolerated dose (MTD) of the combination.

Submission of Phase 1 pralatrexate and systemic bexarotene protocol: By: November 15, 2009

(b) (4)

Phase 1 Study completion: By: August 31, 2011
Final Phase 3 Protocol Submission: By: September 30, 2011
Trial/Study Completion: By: March 31, 2015
Final Report Submission: By: September 30, 2015

Postmarketing Requirements Under 505(O):

3. A clinical trial in patients with renal impairment to include patients with severe renal impairment.

Description of trial/study: This will be a Phase 1 clinical study to evaluate the pharmacokinetics of pralatrexate in relapsed/refractory lymphoma patients (B-cell, T-cell, and Hodgkin's Lymphoma) with mild to severe renal impairment. Three cohorts (N=6 per cohort) will be enrolled in this study for a total of 18 patients. Cohorts will be based on the severity of renal impairment, ie, cohort A = severely impaired ($\text{Crea}_{\text{CL}}^{\text{CG}} < 30 \text{ mL/min}$), cohort B = moderately impaired ($\text{Crea}_{\text{CL}}^{\text{CG}} = 30\text{-}50 \text{ mL/min}$), and cohort C = mildly impaired patients ($\text{Crea}_{\text{CL}}^{\text{CG}} = 50\text{-}80 \text{ mL/min}$). The pralatrexate dose for cohorts A and B will be determined based on the pharmacokinetics experience from the PROPEL study. Cohort C will be dosed at the recommended dose (30 mg/m^2) since patients with mild renal impairment were included in the PROPEL study. Patients will undergo extensive plasma and urine collections following the first dose of FOLOTYN.

Final Protocol Submission: By: January 31, 2010
Trial/Study Completion: By: June 30, 2012
Final Report Submission: By: January 31, 2013

4. Completion of the planned mass balance trial, and contingent on FDA review of the mass balance results, a trial in patients with hepatic impairment.

Description of trial/study: This is an ongoing Phase 1 mass balance clinical study to evaluate the excretion and metabolic profile of pralatrexate. Patients will receive a fixed dose of 225 mg radio-labeled pralatrexate. Patients will undergo intense sampling of blood, urine, feces, expired air, and other incidental excreta as needed for up to 7 days. Analysis of the samples will be done by liquid scintillation counting for mass balance determination and HPLC for metabolite profiling. Pralatrexate diastereomer concentrations in plasma and urine will be determined in parallel using a validated LC-MS/MS method.

Final Protocol Submission:	By: October 29, 2008
Trial/Study Completion:	By: June 30, 2010
Final Report Submission:	By: December 31, 2010

Post-marketing Commitment

Allos agrees to conduct the following postmarketing commitment, with milestones.

1. Perform *in vitro* studies to determine if transporters are involved in the elimination of pralatrexate.

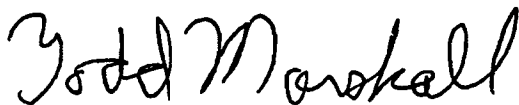
Description of trial/study: This will be an *in vitro* study to determine whether pralatrexate is a substrate for the organic anion transporter (OAT) family, including but not limited to OAT1 and OAT3¹, and whether drugs that interfere with or compete for these transporters (eg, acyclovir, probenecid, NSAIDS) have an effect on pralatrexate transport.

¹ Takeda M et al. Characterization of methotrexate transport and its drug interactions with human organic anion transporters. Journal of Pharmacological and Experimental Therapeutics (2002).

Study Start:	December 1, 2009
Study Completion:	By: January 31, 2011
Final Report Submission:	By: July 31, 2011

If you have any questions regarding this submission, please do not hesitate to contact me.

Sincerely,



Todd Marshall
Director, Regulatory Affairs
(720) 540-5256 – direct line
(888) 351-3712 – fax

From: Kacuba, Alice [mailto:Alice.Kacuba@fda.hhs.gov]
Sent: Tuesday, September 22, 2009 10:08 AM
To: Tanner, Linnea
Cc: Vialpando, Milinda
Subject: RE: NDA 22-468; FOLOTYN; Confirm if there any FDA comments to the PI
Importance: High

Hi,

Getting there....

The team has reworded the PMC. Please review and send in written agreement to conduct this PMC.

Perform *in vitro* studies to determine if transporters are involved in the elimination of pralatrexate.

Description of study: This will be an *in vitro* study to determine whether pralatrexate is a substrate for the organic anion transporter (OAT) family, including but not limited to OAT1 and OAT3, and whether drugs that interfere with or compete for these transporters (e.g., acyclovir, probenecid, NSAIDS) have an effect on pralatrexate transport [Takeda M *et al.* Characterization of methotrexate transport and its drug interactions with human organic anion transporters. Journal of Pharmacological and Experimental Therapeutics (2002)].

Study Start Date: December 1, 2009

Study Completion Date: January 31, 2011

Final Report Submission Date: July 31, 2011

Thank you.

Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-1381
(f)301-796-9845
alice.kacuba@fda.hhs.gov

From: Kacuba, Alice
Sent: Tuesday, September 22, 2009 11:52 AM
To: Kacuba, Alice; 'Tanner, Linnea'
Cc: Vialpando, Milinda
Subject: RE: NDA 22-468; FOLOTYN; Confirm if there any FDA comments to the PI
Importance: High

Hi,

You can send in "final agreed to labeling" if you agree to the revisions. We will need a WORD version to attach to action letter.

I am still working on labels.

From: Kacuba, Alice
Sent: Tuesday, September 22, 2009 11:44 AM
To: 'Tanner, Linnea'
Cc: Vialpando, Milinda
Subject: RE: NDA 22-468; FOLOTYN; Confirm if there any FDA comments to the PI
Importance: High

Hi,

Minor requests for revision. See attached. Also, team requests that you revise all table titles to Times New Roman font.

Serious Adverse Events

Forty-four percent of patients (n = 49) experienced a serious adverse event while on study or within 30 days after their last dose of FOLOTYN. The most common serious adverse events (> 3%), regardless of causality, were pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea and thrombocytopenia. One death from cardiopulmonary arrest in a patient with mucositis and febrile neutropenia was reported in this trial. Deaths from mucositis, febrile neutropenia, sepsis, and pancytopenia occurred in 1.2% of patients treated on all FOLOTYN trials at doses ranging from 30 to 325 mg/m².

Thank you.

Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-1381
(f)301-796-9845
alice.kacuba@fda.hhs.gov

From: Tanner, Linnea [mailto:ltanner@ALLOS.com]
Sent: Tuesday, September 22, 2009 11:01 AM
To: Kacuba, Alice
Cc: Vialpando, Milinda
Subject: NDA 22-468; FOLOTYN; Confirm if there any FDA comments to the PI

Alice,

Would you confirm whether there will be any additional FDA recommendations to the PI? We are now in the process of coordinating submissions to DDMAC and would like to send a final agreed PI, if possible.

Regards,
Linnea

Linnea Tanner, M.S., RAC
Senior Director, Regulatory Affairs
Allos Therapeutics, Inc.
11080 CirclePoint Road
Westminster, CO 80020
Telephone: 720-540-5340
Fax: 303.412.9160
e-mail: ltanner@ALLOS.com

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computer.

From: Vialpando, Milinda
To: "Marshall, Todd":
cc: Kacuba, Alice; Tanner, Linnea;
Subject: RE: Comments to Folotyn Labels and Labeling
Date: Thursday, September 24, 2009 10:44:30 AM

Todd,

Please send a courtesy e-mail copy for all of the completed labels that will be submitted officially to the NDA today.

Thanks,
Milinda

From: Marshall, Todd [mailto:tmarshall@ALLOS.com]
Sent: Thursday, September 24, 2009 8:59 AM
To: Vialpando, Milinda
Cc: Kacuba, Alice; Tanner, Linnea
Subject: RE: Comments to Folotyn Labels and Labeling

Milinda,

Thank you for your prompt response. We intend to provide these label mock-ups that we've emailed to you in an NDA Amendment today.

Todd

From: Vialpando, Milinda [mailto:Milinda.Vialpando@fda.hhs.gov]
Sent: Thursday, September 24, 2009 6:53 AM
To: Marshall, Todd
Cc: Kacuba, Alice; Tanner, Linnea
Subject: RE: Comments to Folotyn Labels and Labeling

Todd,

The labeling looks acceptable.

Milinda

From: Marshall, Todd [mailto:tmarshall@ALLOS.com]
Sent: Thursday, September 24, 2009 8:24 AM
To: Vialpando, Milinda
Cc: Kacuba, Alice; Tanner, Linnea
Subject: RE: Comments to Folotyn Labels and Labeling
Importance: High

Dear Milinda and/or Alice:

I am just checking on the status of our carton and vial labeling, especially those for the 40 mg/2 mL presentation that I provided yesterday afternoon.

Todd

From: Vialpando, Milinda [mailto:Milinda.Vialpando@fda.hhs.gov]
Sent: Wednesday, September 23, 2009 2:05 PM
To: Marshall, Todd
Cc: Kacuba, Alice; Tanner, Linnea
Subject: RE: Comments to Folotyn Labels and Labeling

Todd,

I will get back to you as soon as I can.

Milinda

From: Marshall, Todd [mailto:tmarshall@ALLOS.com]
Sent: Wednesday, September 23, 2009 3:53 PM
To: Vialpando, Milinda
Cc: Kacuba, Alice; Tanner, Linnea
Subject: RE: Comments to Folotyn Labels and Labeling
Importance: High

Dear Milinda:

In response to our brief recent phone conversation that included several of the FOLOTYN review team members, Allos has revised (actually unrevised) the total strength per total volume and (strength per volume) for the 40 mg/2 mL presentation's carton and vial labels. As agreed during the call, we have continued to include the volume, 2 mL, on these labels.

Therefore, I attach the full-scale artwork-only layouts for the 40 mg/2 mL FOLOTYN carton and vial label.

We will again appreciate the Agency's prompt feedback on these 2 labels so that we can formally submit all 4 revised labels in an NDA amendment this afternoon.

Thank you again for your prompt response to our previous email,

Todd

Todd Marshall
Director of Regulatory Affairs
Allos Therapeutics
303 817 1074 (Mobile)
720 540 5256 (Work)
303 412 9162 (Fax)
email: TMarshall@Allos.Com

From: Marshall, Todd
Sent: Wednesday, September 23, 2009 11:06 AM
To: 'Kacuba, Alice'; Tanner, Linnea
Cc: 'Milinda.Vialpando@fda.hhs.gov'
Subject: RE: Comments to Folotyn Labels and Labeling
Importance: High

Dear Alice:

We have revised our FOLOTYN cartons and vial labels for both presentation. We have fully complied with the 3 requests iterated below.

I attach the full-scale artwork-only layouts for the 2 FOLOTYN cartons and the 2 FOLOTYN vial labels.

WE WOULD GREATLY APPRECIATE THE AGENCY'S FEEDBACK ON THESE LABELS AS SOON AS IS POSSIBLE SO THAT WE CAN FORMALLY SUBMIT THE REVISED LABELS IN AN NDA AMENDMENT THIS AFTERNOON.

Thank you,

Todd

Todd Marshall
Director of Regulatory Affairs
Allos Therapeutics
303 817 1074 (Mobile)
720 540 5256 (Work)
303 412 9162 (Fax)
email: TMarshall@Allos.Com

From: Kacuba, Alice [<mailto:Alice.Kacuba@fda.hhs.gov>]
Sent: Tuesday, September 22, 2009 5:11 PM
To: Marshall, Todd; Tanner, Linnea
Cc: Vialpando, Milinda
Subject: RE: Comments to Folutyn Labels and Labeling

Hi,

I have discussed your email with the review team and we reiterate our requests:

1. Revise the current presentation of strength on the container label and carton label "20 mg/1 mL" to read "20 mg/mL".
2. Add to the principal display panel of each carton and container the total volume (i.e. "1 mL", "2 mL"). Present this information as a separate statement away from the total drug content and strength.
3. Revise the abbreviation 'IV' to state 'intravenous'. We note that the abbreviation 'IV' has been misinterpreted as 'IU' or the number '10'. As part of a national campaign to prevent the use of dangerous abbreviations in 2006, FDA agreed not to approve such abbreviations in labels and labeling.

We will need to attach mock ups to the action letter.

Thank you.

Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-1381
(f)301-796-9845
alice.kacuba@fda.hhs.gov

From: Marshall, Todd [<mailto:tmarshall@ALLOS.com>]
Sent: Tuesday, September 22, 2009 5:26 PM

To: Kacuba, Alice
Cc: Tanner, Linnea; Vialpando, Milinda
Subject: RE: Comments to Folutyn Labels and Labeling; URGENT!

Alice:

I located the attached label for a recently approved parenteral drug – it follows the current USP <1> for the 2 drug strengths. See labels on Pages 31 to 34.

From: Marshall, Todd
Sent: Tuesday, September 22, 2009 2:43 PM
To: 'Alice.Kacuba@fda.hhs.gov'
Cc: Tanner, Linnea; milinda.vialpando@fda.hhs.gov
Subject: RE: Comments to Folutyn Labels and Labeling; URGENT!
Importance: High

Dear Ms Kacuba:

Per our recent, short telephone conversation, I attach the current USP <1> Injections chapter. Please see the bolded text on Page 5 of 12 regarding inclusion of both strength per total volume and strength per mL enclosed by parentheses. We followed this USP in the development of our labels.

We have no objection to the Agency's proposed changes 1) and 2) but wish to remain in compliance with USP.

Thank you,

Todd

From: Kacuba, Alice [mailto:Alice.Kacuba@fda.hhs.gov]
Sent: Tuesday, September 22, 2009 1:32 PM
To: Tanner, Linnea
Cc: Vialpando, Milinda
Subject: FW: Folutyn Labels and Labeling
Importance: High

Hi,

One more request: Please revise labels as follows:

- 1 . Revise the current presentation of strength on the container label and carton labeling "20 mg/1 mL" to read "20 mg/mL".
2. Add to the principal display panel of each carton and container the total volume (i.e. "1 mL", "2 mL"). Present this information as a separate statement away from the total drug content and strength.
3. Revise the abbreviation 'IV' to state 'intravenous'. We note that the abbreviation 'IV' has been misinterpreted as 'IU' or the number '10'. As part of a national campaign to prevent the use of dangerous abbreviations in 2006, FDA agreed not to approve such abbreviations in labels and labeling.

We will need to attach mock ups to the action letter.

Thank you.

Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-1381
(f)301-796-9845
alice.kacuba@fda.hhs.gov

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you are hereby notified that any review, disclosure, copying, distribution, retention or taking of any action in reliance upon the contents of this email or any attachment, or any

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computer.

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

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/s/

MILINDA F VIALPANDO
09/24/2009

Kacuba, Alice

From: Kacuba, Alice
Sent: Tuesday, September 22, 2009 3:32 PM
To: 'Tanner, Linnea'
Cc: Vialpando, Milinda
Subject: FW: Folotyn Labels and Labeling
Importance: High
Follow Up Flag: Follow up
Due By: Tuesday, September 22, 2009 3:00 PM
Flag Status: Flagged
Tracking: **Recipient** **Read**
 'Tanner, Linnea'
 Vialpando, Milinda Read: 9/22/2009 4:25 PM

Hi,

One more request: Please revise labels as follows:

- 1, Revise the current presentation of strength on the container label and carton labeling "20 mg/1 mL" to read "20 mg/mL".
2. Add to the principal display panel of each carton and container the total volume (i.e. "1 mL", "2 mL"). Present this information as a separate statement away from the total drug content and strength.
3. Revise the abbreviation 'IV' to state 'intravenous'. We note that the abbreviation 'IV' has been misinterpreted as 'IU' or the number '10'. As part of a national campaign to prevent the use of dangerous abbreviations in 2006, FDA agreed not to approve such abbreviations in labels and labeling.

We will need to attach mock ups to the action letter.

Thank you.

Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-1381
(f)301-796-9845
alice.kacuba@fda.hhs.gov

9/22/2009

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22468

ORIG-1

ALLOS
THERAPEUTICS
INC

FOLOTYN

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/s/

ALICE KACUBA

09/22/2009

Kacuba, Alice

From: Kacuba, Alice
Sent: Tuesday, September 22, 2009 12:08 PM
To: 'Tanner, Linnea'
Cc: Vialpando, Milinda
Subject: RE: NDA 22-468; FOLOTYN; Confirm if there any FDA comments to the PI
Importance: High
Follow Up Flag: Follow up
Due By: Monday, September 21, 2009 12:00 AM
Flag Status: Flagged
Tracking:

Recipient	Read
'Tanner, Linnea'	
Vialpando, Milinda	Read: 9/22/2009 4:22 PM

Hi,

Getting there....

The team has rewored the PMC. Please review and send in written agreement to conduct this PMC.

Perform *in vitro* studies to determine if transporters are involved in the elimination of pralatrexate.

Description of study: This will be an *in vitro* study to determine whether pralatrexate is a substrate for the organic anion transporter (OAT) family, including but not limited to OAT1 and OAT3, and whether drugs that interfere with or compete for these transporters (e.g., acyclovir, probenecid, NSAIDS) have an effect on pralatrexate transport [Takeda M *et al.* Characterization of methotrexate transport and its drug interactions with human organic anion transporters. Journal of Pharmacological and Experimental Therapeutics (2002)].

Study Start Date: December 1, 2009
Study Completion Date: January 31, 2011
Final Report Submission Date: July 31, 2011

Thank you.

Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-1381
(f)301-796-9845

9/22/2009

alice.kacuba@fda.hhs.gov

From: Kacuba, Alice
Sent: Tuesday, September 22, 2009 11:52 AM
To: Kacuba, Alice; 'Tanner, Linnea'
Cc: Vialpando, Milinda
Subject: RE: NDA 22-468; FOLOTYN; Confirm if there any FDA comments to the PI
Importance: High

Hi,

You can send in "final agreed to labeling" if you agree to the revisions. We will need a WORD version to attach to action letter.

I am still working on labels.

From: Kacuba, Alice
Sent: Tuesday, September 22, 2009 11:44 AM
To: 'Tanner, Linnea'
Cc: Vialpando, Milinda
Subject: RE: NDA 22-468; FOLOTYN; Confirm if there any FDA comments to the PI
Importance: High

Hi,

Minor requests for revision. See attached. Also, team requests that you revise all table titles to Times New Roman font.

Serious Adverse Events

Forty-four percent of patients (n = 49) experienced a serious adverse event while on study or within 30 days after their last dose of FOLOTYN. The most common serious adverse events (> 3%), regardless of causality, were pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea and thrombocytopenia. One death from cardiopulmonary arrest in a patient with mucositis and febrile neutropenia was reported in this trial. Deaths from mucositis, febrile neutropenia, sepsis, and pancytopenia occurred in 1.2% of patients treated on all FOLOTYN trials at doses ranging from 30 to 325 mg/m².

Thank you.

Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-1381

9/22/2009

(f)301-796-9845
alice.kacuba@fda.hhs.gov

From: Tanner, Linnea [mailto:ltanner@ALLOS.com]
Sent: Tuesday, September 22, 2009 11:01 AM
To: Kacuba, Alice
Cc: Vialpando, Milinda
Subject: NDA 22-468; FOLOTYN; Confirm if there any FDA comments to the PI

Alice,

Would you confirm whether there will be any additional FDA recommendations to the PI? We are now in the process of coordinating submissions to DDMAC and would like to send a final agreed PI, if possible.

Regards,
Linnea

Linnea Tanner, M.S., RAC
Senior Director, Regulatory Affairs
Allos Therapeutics, Inc.
11080 CirclePoint Road
Westminster, CO 80020
Telephone: 720-540-5340
Fax: 303.412.9160
e-mail: ltanner@ALLOS.com

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9/22/2009

Application
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Submitter Name

Product Name

NDA-22468

ORIG-1

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INC

FOLOTYN

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/s/

ALICE KACUBA

09/22/2009

Kacuba, Alice

From: Kacuba, Alice
Sent: Tuesday, September 22, 2009 11:44 AM
To: 'Tanner, Linnea'
Cc: Vialpando, Milinda
Subject: RE: NDA 22-468; FOLOTYN; Confirm if there any FDA comments to the PI
Importance: High
Follow Up Flag: Follow up
Due By: Monday, September 21, 2009 12:00 AM
Flag Status: Flagged
Attachments: 9-22-09-int-meeting-Allos Redlines_21Sep2009_9-18-09-mtg-Allos Redlines_Labeling Meeting # 5 Folotyn package insert 09 21 09.doc

Tracking:

Recipient	Read
'Tanner, Linnea'	
Vialpando, Milinda	Read: 9/22/2009 11:55 AM

Hi,

Minor requests for revision. See attached. Also, team requests that you revise all table titles to Times New Roman font.

Serious Adverse Events

Forty-four percent of patients (n = 49) experienced a serious adverse event while on study or within 30 days after their last dose of FOLOTYN. The most common serious adverse events (> 3%), regardless of causality, were pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea and thrombocytopenia. One death from cardiopulmonary arrest in a patient with mucositis and febrile neutropenia was reported in this trial. Deaths from mucositis, febrile neutropenia, sepsis, and pancytopenia occurred in 1.2% of patients treated on all FOLOTYN trials at doses ranging from 30 to 325 mg/m².

Thank you.

Alice
 Alice Kacuba, RN, MSN, RAC
 Chief, Project Management Staff
 Division of Drug Oncology Products
 Office of Oncology Drug Products
 OND/CDER/FDA
 301-796-1381
 (f)301-796-9845
 alice.kacuba@fda.hhs.gov

9/22/2009

From: Tanner, Linnea [mailto:ltanner@ALLOS.com]
Sent: Tuesday, September 22, 2009 11:01 AM
To: Kacuba, Alice
Cc: Vialpando, Milinda
Subject: NDA 22-468; FOLOTYN; Confirm if there any FDA comments to the PI

Alice,

Would you confirm whether there will be any additional FDA recommendations to the PI? We are now in the process of coordinating submissions to DDMAC and would like to send a final agreed PI, if possible.

Regards,
Linnea

Linnea Tanner, M.S., RAC
Senior Director, Regulatory Affairs
Allos Therapeutics, Inc.
11080 CirclePoint Road
Westminster, CO 80020
Telephone: 720-540-5340
Fax: 303.412.9160
e-mail: ltanner@ALLOS.com

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9/22/2009

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NDA-22468

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/s/

ALICE KACUBA
09/22/2009

Kacuba, Alice

From: Kacuba, Alice
Sent: Thursday, September 17, 2009 3:44 PM
To: 'Tanner, Linnea'
Cc: Vialpando, Milinda
Subject: NDA 22-468; FOLOTYN; Labeling request
Importance: High
Follow Up Flag: Follow up
Due By: Thursday, September 17, 2009 1:30 AM
Flag Status: Flagged

Hi,

One more thing: In package insert, please change "adverse events" to "adverse reactions" through out package insert.

Thank you.

Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-1381
(f)301-796-9845
alice.kacuba@fda.hhs.gov

9/17/2009

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

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/s/

ALICE KACUBA
09/17/2009

From: Vialpando, Milinda
To: "Tanner, Linnea";
cc: Kacuba, Alice;
Subject: NDA 22-
468, FDA Proposed changes to the Folutyn Label - your responses due by COB today, 9/17/09
Date: Thursday, September 17, 2009 11:40:09 AM
Attachments: Labeling Meeting # 3 Folutyn package insert 09 17 09.doc

Linnea,

See the attached labeling and provide your responses by COB today, 9/17/09. We are aware of the short notice but will need your responses soon. Please note the tracked changes in the Highlights, Sections 1 - 3, 5 - 8, 10 - 14, and 16. Go ahead and accept the changes in the document if you agree (in an effort to manage the changes in the label).

Also, since the patient information section cannot be reviewed before the action date we request that you resubmit this information as an amendment after the action date. Please contact me if you have any questions.

Kind Regards,

Milinda F. Vialpando
*Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products, FDA
10903 New Hampshire Avenue
Building 22, Room 2133
Silver Spring, MD 20993
Tel: 301-796-1444
Fax: 301-796-9845
Milinda.Vialpando@fda.hhs.gov*

Application
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FOLOTYN

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/s/

MILINDA F VIALPANDO
09/17/2009

Kacuba, Alice

From: Kacuba, Alice
Sent: Wednesday, September 16, 2009 2:41 PM
To: 'Tanner, Linnea'
Cc: Vialpando, Milinda
Subject: RE: NDA 22-468; FOLOTYN; Request Feedback on Proposed Printed Format of PI and Patient Information
Importance: High
Attachments: 9-16-09-Request-for-PMC&dates-for-PMR.doc

Tracking:

Recipient	Read
'Tanner, Linnea'	
Vialpando, Milinda	Read: 9/16/2009 2:41 PM

Hi,

In preparation for our tcon on Friday, please find attached. We will need you to fill in the "description" and "milestone dates" for PMRs.

For the PMC, fill in "description" and "milestone dates" along with a commitment to conduct. The PMRs will be mandatory so no need to provide written agreement to those.

I attempted to copy what dates I could from your recent submission, but check them closely.

Dates must be Month, day, year--in the format I provided.

You may want to wait until after our tcon Friday to return the information so as to have any of your questions clarified. If you change any wording, please use track changes. Our safety team is also reviewing so we may have additional revisions. If so, I will send along ASAP.

Any questions, I need to leave at 3:30 today but may be on line later this evening and will be in my office Thursday AM.

Thank you.

Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-1381
(f)301-796-9845
alice.kacuba@fda.hhs.gov

9/17/2009

Your response should include the proposed schedule for conducting the study/clinical trial, including all major milestones for the study/clinical trial, e.g., submission to the FDA of the finalized protocol, completion of the study/clinical trial, and submission of the final report. Dates must include month, day, year as indicated below.

Provide a description of the study and fill in milestones for Postmarketing Requirements.

Postmarketing Requirements Under 21 CFR 31.510 (Subpart H)

1. A randomized trial of maintenance treatment with pralatrexate in previously untreated patients with PTCL who have demonstrated a response to CHOP or a CHOP-like regimen.

Description of trial/study:

Final Protocol Submission: By: December __, 2009
Trial/Study Completion: By: ____, 2010
Final Report Submission: By: ____, 2017

2. A randomized controlled trial of single agent pralatrexate vs. an appropriate control in patients with relapsed or refractory PTCL.

Description of trial/study:

Final Protocol Submission: By: _____
Trial/Study Completion: By: _____
Final Report Submission: By: _____

Postmarketing Requirements Under 505(O):

3. A clinical trial in patients with renal impairment to include patients with severe renal impairment, and

Description of trial/study:

Final Protocol Submission: By: January __, 2010
Trial Completion: By: June __, 2010
Final Report Submission: By: January __, 2013

4. Completion of the planned mass balance trial, and contingent on FDA review of the mass balance results, a trial in patients with hepatic impairment.

Description of trial/study:

Final Protocol Submission: By: October 29, 2008
Trial Completion: By: May 18, 2009
Final Report Submission: By: December __, 2010

Postmarketing Commitment:

Please submit a written agreement to conduct the following postmarketing commitment, with milestones.

1. Perform *in vitro* studies to determine if transporters are involved in the elimination of pralatrexate.

Description of trial/study:

Final Protocol Submission: By: November __, 2009
Study Completion: By: _____
Final Report Submission: By: July __, 2011

Application
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Product Name

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/s/

ALICE KACUBA
09/17/2009

Kacuba, Alice

From: Kacuba, Alice
Sent: Tuesday, September 15, 2009 5:32 PM
To: 'Tanner, Linnea'
Cc: Vialpando, Milinda
Subject: RE: NDA 22-468; FOLOTYN; FDA Comments PI
Importance: High
Follow Up Flag: Follow up
Due By: Tuesday, September 15, 2009 6:00 PM
Flag Status: Flagged

Hi,

1. You asked about when we'd get you labeling (package insert) edits. It will be late Friday or early Monday.

2. In addition, if we should approve this under accelerated approval, you will need to submit any advertising that you plan to use in the 1st 120 days of approval to DDMAC PRIOR to approval. Keep in mind that I can not tell you what the action is so these requests should not be interrupted as an approval action based on this email.

Immediately submit all promotional materials (both promotional labeling and advertisements) to be used within the first 120 days after approval. Send one copy to this division and two copies of the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

3. Submit final labels as discussed in the September 3, 2009 tcon, if not already submitted.

CMC carton and container label changes:

1. The graphic in its current location and size detracts from the proprietary and established name. Decrease the size and relocate the graphic away from the proprietary name on the principal display panel. The proprietary and established name should be the most prominent information on the label and labeling (see CFR 201.15(a)(6)).
2. Further increase the prominence of the nonproprietary name relative to the proprietary name.
3. As requested by FDA on August 27, 2009, revise the "Contents" on carton labeling to the following:

(For the 40 mg/2 mL size): "Each vial contains 40 mg of pralatrexate in 2 mL of sterile solution. Also contains....."

(For the 20 mg/1 mL size): "Each vial contains 20 mg of pralatrexate in 1 mL of sterile solution."

9/15/2009

Also contains.....”

4. The NDC Product Code (the area next to the Product Type) in SPL Drug Listing Data Element (DLDE) should contain the first two segments of the NDC and thus both the 20 mg/1 mL and 40 mg/2 mL configurations should have the same NDC Product Code. It is noted that you have included the complete NDC (i.e., three segments) in this section of the DLDE. Please revise.

I will be sending PMCs in AM.
Thank you.

Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-1381
(f)301-796-9845
alice.kacuba@fda.hhs.gov

From: Tanner, Linnea [mailto:ltanner@ALLOS.com]
Sent: Tuesday, September 15, 2009 10:25 AM
To: Kacuba, Alice
Cc: Vialpando, Milinda
Subject: FW: NDA 22-468; FOLOTYN; FDA Comments PI

Dear Alice,

In follow-up to our telephone conversation regarding the status of receiving FDA comments to the PI for NDA 22-468 (FOLOTYN), below is my contact information.

Telephone: 720-540-5340
Fax: 303.412.9160
e-mail: ltanner@ALLOS.com

Regards,
Linnea

Linnea Tanner, M.S., RAC
Senior Director, Regulatory Affairs
Allos Therapeutics, Inc.
11080 CirclePoint Road
Westminster, CO 80020

9/15/2009

Telephone: 720-540-5340
Fax: 303.412.9160
e-mail: ltanner@ALLOS.com

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9/15/2009

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/s/

ALICE KACUBA
09/15/2009

From: Vialpando, Milinda
To: "Tanner, Linnea";
Subject: 9/3/09 Telecon Minutes for NDA 22-468, Folutyn
Date: Thursday, September 10, 2009 2:32:35 PM
Attachments: Praletrexate SPONTelecon 09 03 09.pdf

Linnea,

See the attached telecon minutes from our discussion on 9/3/09.

Regards,

Milinda F. Vialpando
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products, FDA
10903 New Hampshire Avenue
Building 22, Room 2133
Silver Spring, MD 20993
Tel: 301-796-1444
Fax: 301-796-9845
Milinda.Vialpando@fda.hhs.gov

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Product Name

NDA-22468

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/s/

MILINDA F VIALPANDO

09/17/2009

From: Vialpando, Milinda
To: "Tanner, Linnea";
Subject: 9/9/09 Telecon Minutes for NDA 22-468, Folutyn
Date: Thursday, September 10, 2009 3:29:30 PM
Attachments: SPONTelecon 09 09 09 v3.pdf

Linnea,

See the attached 9/9/09 telecon minutes for Folutyn.

Regards,

Milinda F. Vialpando

Regulatory Health Project Manager

Division of Drug Oncology Products

Office of Oncology Drug Products, FDA

10903 New Hampshire Avenue

Building 22, Room 2133

Silver Spring, MD 20993

Tel: 301-796-1444

Fax: 301-796-9845

Milinda.Vialpando@fda.hhs.gov

Application
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Product Name

NDA-22468

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INC

FOLOTYN

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/s/

MILINDA F VIALPANDO

09/17/2009

From: Vialpando, Milinda
To: "Tanner, Linnea";
Subject: RE: Convenient Time to Have Teleconference -- PI?
Date: Wednesday, September 09, 2009 3:44:51 PM

Linnea,

FDA is working to finalize the telecon minutes and working on the package insert. I will provide feedback as soon as I receive it.

Kind Regards,

Milinda F. Vialpando
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products, FDA
10903 New Hampshire Avenue
Building 22, Room 2133
Silver Spring, MD 20993
Tel: 301-796-1444
Fax: 301-796-9845
Milinda.Vialpando@fda.hhs.gov

From: Tanner, Linnea [mailto:ltanner@ALLOS.com]
Sent: Wednesday, September 09, 2009 2:59 PM
To: Vialpando, Milinda
Subject: Convenient Time to Have Teleconference -- PI?

Milinda,

When would it be convenient to have a teleconference with you to discuss the next steps and timing in PI negotiations?

Regards,
Linnea

Linnea Tanner, M.S., RAC
Senior Director, Regulatory Affairs
Allos Therapeutics, Inc.

11080 CirclePoint Road
Westminster, CO 80020
Telephone: 720-540-5340
Fax: 303.412.9160
e-mail: ltanner@ALLOS.com

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

MILINDA F VIALPANDO
09/17/2009

From: Vialpando, Milinda
To: "Tanner, Linnea";
Subject: RE: NDA 22-468; FOLOTYN: Request Teleconference with Gene Williams, Ph.D., Clinical Pharm. and Bioph., DDPO
Date: Tuesday, September 08, 2009 5:39:03 PM

Linnea,

I have tentatively scheduled a telecon on Wednesday, September 9, 2009 1:00 - 1:30 pm, EST, with our clinical pharmacology group. Please send me the call information.

Thank You,

Milinda F. Vialpando
*Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products, FDA
10903 New Hampshire Avenue
Building 22, Room 2133
Silver Spring, MD 20993
Tel: 301-796-1444
Fax: 301-796-9845
Milinda.Vialpando@fda.hhs.gov*

From: Tanner, Linnea [mailto:ltanner@ALLOS.com]
Sent: Tuesday, September 08, 2009 11:59 AM
To: Vialpando, Milinda
Subject: NDA 22-468; FOLOTYN: Request Teleconference with Gene Williams, Ph.D., Clinical Pharm. and Bioph., DDPO
Importance: High

Milinda,

In follow-up to our teleconference held on Thursday, Sept. 3 regarding post-marketing commitments, I request a teleconference today or tomorrow, if possible, with Gene Williams, Ph.D., Clinical Pharmacology, so that Allos can receive additional clarification regarding needed vitro studies to evaluate the impact of transporter systems in the clearance of pralatrexate. The Allos participants in this teleconference will be the following:

Bert Pronk, Ph.D., Sr. Director, Pre-Clinical
Linnea Tanner, Sr. Director, Regulatory Affairs

I appreciate your assistance in arranging this teleconference so that we can provide our agreement to post-marketing commitments to the FDA as soon as possible.

Regards,
Linnea

Linnea Tanner, M.S., RAC
Senior Director, Regulatory Affairs
Allos Therapeutics, Inc.
11080 CirclePoint Road
Westminster, CO 80020
Telephone: 720-540-5340
Fax: 303.412.9160
e-mail: ltanner@ALLOS.com

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Application
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Submitter Name

Product Name

NDA-22468

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MILINDA F VIALPANDO
09/17/2009

From: Vialpando, Milinda
To: "Tanner, Linnea":
Subject: RE: NDA 22-468; FOLOTYN: FDA Comments to PI
Date: Tuesday, September 08, 2009 2:08:45 PM

Linnea,

You should have some feedback regarding the PI later today or tomorrow.

Milinda

From: Tanner, Linnea [mailto:ltanner@ALLOS.com]
Sent: Tuesday, September 08, 2009 2:06 PM
To: Vialpando, Milinda
Subject: RE: NDA 22-468; FOLOTYN: FDA Comments to PI

Milinda,

Thank you for your feedback regarding the request for the teleconference and meeting minutes. Do you anticipate that we will receive FDA comments to the PI today?

Regards,
Linnea

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MILINDA F VIALPANDO
09/17/2009

From: Vialpando, Milinda
To: "Tanner, Linnea";
Subject: RE: NDA 22-468; FOLOTYN: Request Teleconference with Gene Williams, Ph.D., Clinical Pharm. and Bioph., DDPO
Date: Tuesday, September 08, 2009 1:13:38 PM

Linnea,

Your request for a teleconference has been forwarded and the telecon minutes from 9/4/09 are still being finalized. I will send you the minutes later today, if possible.

Milinda

From: Tanner, Linnea [mailto:ltanner@ALLOS.com]
Sent: Tuesday, September 08, 2009 11:59 AM
To: Vialpando, Milinda
Subject: NDA 22-468; FOLOTYN: Request Teleconference with Gene Williams, Ph.D., Clinical Pharm. and Bioph., DDPO
Importance: High

Milinda,

In follow-up to our teleconference held on Thursday, Sept. 3 regarding post-marketing commitments, I request a teleconference today or tomorrow, if possible, with Gene Williams, Ph.D., Clinical Pharmacology, so that Allos can receive additional clarification regarding needed vitro studies to evaluate the impact of transporter systems in the clearance of pralatrexate. The Allos participants in this teleconference will be the following:

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Linnea Tanner, Sr. Director, Regulatory Affairs

I appreciate your assistance in arranging this teleconference so that we can provide our agreement to post-marketing commitments to the FDA as soon as possible.

Regards,
Linnea

Linnea Tanner, M.S., RAC
Senior Director, Regulatory Affairs
Allos Therapeutics, Inc.
11080 CirclePoint Road
Westminster, CO 80020
Telephone: 720-540-5340
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MILINDA F VIALPANDO
09/17/2009

From: Vialpando, Milinda
To: "Tanner, Linnea";
Subject: RE: Final List of Allos Participants
Date: Thursday, September 03, 2009 10:48:49 AM

The agenda will include PMCs, carton and container label changes from CMC (see below), and the information request from Micro.

1. Remove the graphic design from the carton labeling.
2. Further increase the prominence of the nonproprietary name relative to the proprietary name.
3. As requested by FDA on August 27, 2009, revise the "Contents" on carton labeling to the following:

(For the 40 mg/2 mL size): "Each vial contains 40 mg of pralatrexate in 2 mL of sterile solution. Also contains....."

(For the 20 mg/1 mL size): "Each vial contains 20 mg of pralatrexate in 1 mL of sterile solution. Also contains....."

4. The NDC Product Code (the area next to the Product Type) in SPL Drug Listing Data Element (DLDE) should contain the first two segments of the NDC and thus both the 20 mg/1 mL and 40 mg/2 mL configurations should have the same NDC Product Code. It is noted that you have included the complete NDC (i.e., three segments) in this section of the DLDE. Please revise.

From: Tanner, Linnea [mailto:ltanner@ALLOS.com]
Sent: Thursday, September 03, 2009 10:27 AM
To: Vialpando, Milinda
Subject: Final List of Allos Participants

Milinda,

Below is the final list of Allos participants:

Pablo Cagnoni, M.D., Chief Medical Officer
Adam Boyd, Associate Director, Biostatistics
Todd Marshall, Director, Regulatory Affairs (CMC)
Linnea Tanner, Sr. Director, Regulatory Affairs

Is there any final word on the final agenda?

Regards,
Linnea

Linnea Tanner, M.S., RAC
Senior Director, Regulatory Affairs
Allos Therapeutics, Inc.
11080 CirclePoint Road
Westminster, CO 80020
Telephone: 720-540-5340
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MILINDA F VIALPANDO
09/17/2009

From: Vialpando, Milinda
To: "Tanner, Linnea";
cc: Cagnoni, Pablo;
Subject: RE: Call-in Number FDA Teleconference at 11 EST
Date: Thursday, September 03, 2009 9:14:54 AM

Linnea,

Thanks for sending the call information and I will provide an agenda when available. However, a few of the agenda items will include some additional changes to the carton and container label from CMC (see below) and the information request from micro.

1. Remove the graphic design from the carton labeling.
2. Further increase the prominence of the nonproprietary name relative to the proprietary name.
3. As requested by FDA on August 27, 2009, revise the "Contents" on carton labeling to the following:

(For the 40 mg/2 mL size): "Each vial contains 40 mg of pralatrexate in 2 mL of sterile solution. Also contains....."

(For the 20 mg/1 mL size): "Each vial contains 20 mg of pralatrexate in 1 mL of sterile solution. Also contains....."

4. The NDC Product Code (the area next to the Product Type) in SPL Drug Listing Data Element (DLDE) should contain the first two segments of the NDC and thus both the 20 mg/1 mL and 40 mg/2 mL configurations should have the same NDC Product Code. It is noted that you have included the complete NDC (i.e., three segments) in this section of the DLDE. Please revise.

I have invited the Review Team and will send you a list of the participants after the telecon.

Milinda F. Vialpando
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products, FDA
10903 New Hampshire Avenue
Building 22, Room 2133
Silver Spring, MD 20993
Tel: 301-796-1444
Fax: 301-796-9845
Milinda.Vialpando@fda.hhs.gov

From: Tanner, Linnea [mailto:ltanner@ALLOS.com]
Sent: Thursday, September 03, 2009 9:05 AM
To: Vialpando, Milinda
Cc: Cagnoni, Pablo
Subject: Call-in Number FDA Teleconference at 11 EST

Milinda,

Below is the call-in number for the FDA teleconference scheduled at 11 EST:

Dial-in: 1-888-447-7153

Participant Code: 952546 (FDA, Other Allos participants)

Host Code (L. Tanner): 9525464

As soon as you receive final confirmation of the agenda and participants, please forward this to Dr. Pablo Cagnoni (cc: on this e-mail) and me.

I will try to reach Todd Marshall so that he can participate regarding remaining carton and vial issues, and so that he can provide a status of providing a response to the microbiologist.

I will provide you a final list of Allos participants after I confirm.

Regards,
Linnea

Linnea Tanner, M.S., RAC
Senior Director, Regulatory Affairs
Allos Therapeutics, Inc.
11080 CirclePoint Road
Westminster, CO 80020
Telephone: 720-540-5340
Fax: 303.412.9160
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MILINDA F VIALPANDO
09/17/2009

From: Vialpando, Milinda
To: "Tanner, Linnea";
Subject: CMC request for NDA 22-468, Folutyn, Due September 1, 2009
Date: Thursday, August 27, 2009 11:06:23 AM

Linnea,

See the following CMC request for NDA 22-468, Folutyn, and respond by Tuesday, September 1, 2009. Please confirm receipt of this message.

1. The following comments pertain to the immediate container label and carton labeling:

(a) Remove the large "20 mg" and "40 mg" presentations from the upper corner of the labels, because they are confusing as to whether they represent the total quantity or strength. Besides, they appear much more prominent than the drug name. The drug name should appear most prominent. The total quantity (e.g., 40 mg/2 mL) and content per mL (20 mg/mL) are currently displayed properly on your labels (immediately underneath the nonproprietary name of the drug) and thus additional presentations of quantity or strength should be removed.

(b) The graphic design next to the drug name appears to cause confusion with the drug name. Remove the graphic design to comply with 21CFR 201.15(a)(6).

(c) Increase the prominence of the nonproprietary name to at least half that of the proprietary name. Please note that prominence includes a combination of font shape, size, font color, and overall visual appeal.

(d) It is noted that the drug name is displayed vertically on the front panel of the carton. Align the drug name horizontally as the remaining panels.

(e) The expiration date and lot number should appear on the immediate container and carton to comply with 21CFR 201.17.

(f) Display “Rx only” statement prominently on the immediate container and the main panel of carton.

(g) Add “Do not dilute” statement on the immediate container. (This statement is already on the carton labeling.)

2. Revise the “Contents” on carton labeling to the following:

(For the 40 mg/2 mL size): “Each vial contains 40 mg of pralatrexate in 2 mL of sterile solution. Also contains.....”

(For the 20 mg/1 mL size): “Each vial contains 20 mg of pralatrexate in 1 mL of sterile solution. Also contains.....”

3. The following comments pertain to SPL Drug Listing Data Element (DLDE) for both the 20 mg/1 mL and 40 mg/2 mL configurations:

(a) Provide Drug NDC Product Code (in “Product Information” section).

(b) Revise the “Packaging” section to include multi-level packaging information and NDC number. The following is an example for the 1 mL/ vial size:

Packaging

NDC	Package Description	Multilevel Packaging
-----	---------------------	----------------------

(b) (4)

Thank You,

Milinda F. Vialpando

Regulatory Health Project Manager

Division of Drug Oncology Products

Office of Oncology Drug Products, FDA

10903 New Hampshire Avenue

Building 22, Room 2133

Silver Spring, MD 20993

Tel: 301-796-1444

Fax: 301-796-9845

Milinda.Vialpando@fda.hhs.gov

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/s/

MILINDA F VIALPANDO

08/27/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-468

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Allos Therapeutics, Inc.
11080 CirclePoint Road, Suite 200
Westminister, Colorado 80020

ATTENTION: Linnea Tanner, MS., R.A.C.
Senior Director, Regulatory Affairs

Dear Ms. Tanner:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Pralatrexate Injection, 20 mg/mL and 40 mg/2 mL.

We also refer to your May 27, 2009, correspondence, received May 27, 2009, requesting review of your proposed proprietary name, Folutyn. We have completed our review of the proposed proprietary name, Folutyn, and have concluded that it is acceptable.

The proposed proprietary name, Folutyn, 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 you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Melinda Vialpando at (301) 796-1444.

Sincerely,

{See appended electronic signature page}

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

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22468	----- ORIG 1	-----	----- FOLOTYN

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CAROL A HOLQUIST
08/12/2009