

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-462

Administrative

Pease, Dorothy W

From: Hazarika, Maitreyee
Sent: Tuesday, January 20, 2004 9:20 AM
To: Johnson, John R; White Jr, Robert M
Cc: Pease, Dorothy W
Subject: RE: Alimta 120 Day Safety Update

There was an update submitted around May 2003. I did go through it while writing up my review.
MH

-----Original Message-----

From: Johnson, John R
Sent: Saturday, January 17, 2004 10:19 AM
To: Pease, Dorothy W
Cc: Hazarika, Maitreyee; White Jr, Robert M
Subject: Alimta 120 Day Safety Update

Has a 120 Day Safety Update been submitted? If so, has it been reviewed?

John

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-462	Efficacy Supplement Type SE-	Supplement Number
Drug: ALIMTA® (pemetrexed, LY231514)		Applicant: Eli Lilly & Company
RPM: Patty Garvey, R.Ph.	HFD-150	Phone # 301-594-5766
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		I
• Other (e.g., orphan, OTC)		Orphan designation
❖ User Fee Goal Dates		March 31, 2004
❖ Special programs (indicate all that apply)		<input type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input checked="" type="checkbox"/> Fast Track –Granted 6-10-02 <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
User Fee Information		
• User Fee		<input type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input checked="" type="checkbox"/> Orphan designation – Granted 8-28-01 <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that form FDA-3542a was submitted.		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	completed 2-12-04 in DFS
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	N/A
General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None (X) Press Release - FDA () Talk Paper () Dear Health Care Professional Letter (X) Other - e-mail burst
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	attached to letter
• Most recent applicant-proposed labeling	January 12, 2004 submission
• Original applicant-proposed labeling	September 29, 2003 submission
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	review of PI - 12-8-03 DPADP review of PI - 11/16/03 DSRCS review of PPI - 10/14/03 DMETS review of tradename - 10/3/03 and 6/10/02 DDMAC review of PI - 10/1/03
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	September 29, 2003 submission
• Reviews	Acceptable In CMC review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	none
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Included in package
❖ Memoranda and Telecons	Included in package
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	June 25, 1999 and March 1, 2000
• Pre-NDA meeting (indicate date)	January 30, 2002

• Pre-Approval Safety Conference (indicate date; approvals only)	November 13, 2003
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	in volume 3 of 3 Division Director 2-4-04 Medical Team Leader 1-24-04
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	CBER consult-9-23-03 vol 1)
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	in MOR 1-29-04 (vol. 3)
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	ODS – November 24, 2003
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	n/a
❖ Demographic Worksheet (NME approvals only)	see tab (vol. 1)
❖ Statistical review(s) (indicate date for each review)	December 10, 2003 (vol.2)
❖ Biopharmaceutical review(s) (indicate date for each review)	December 5, 2003 (vol. 2)
Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	December 17, 2003 (vol.1)
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	1-5-04 (vol. 2) 1-19-04 (vol.2)
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	pg. 88 of CMC review (vol. 2)
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	November 7, 2003
❖ Facilities inspection (provide EER report)	Date completed: December 8, 2003 (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed - (X) Requested () Not yet requested
Nonclinical Pharm/Tox Information	
Pharm/tox review(s); including referenced IND reviews (indicate date for each review)	Team Leader review 12-22-03 (vol. 2) December 19, 2003 (vol.2)
❖ Nonclinical inspection review summary	N/A

Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	N/A
❖ CAC/ECAC report	N/A

**APPEARS THIS WAY
ON ORIGINAL**

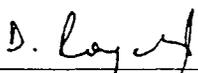
ITEM 13: PATENT INFORMATION

NDA 21-462
ALIMTA[®]
(pemetrexed)

The undersigned declares that the following patents cover the formulation, composition, and method of use of ALIMTA, as indicated. This product is the subject of this application for which approval is being sought:

Patent Number	Patent Expiry Date	Type of Patent (Drug Substance, Drug Product, or Method of Use)
5,344,932	September 6, 2011	Compound
5,217,974	March 29, 2011	Method of Use

The above patents are all owned by or exclusively licensed by Eli Lilly and Company, Indianapolis, IN.



Name of authorized official
Director, US Regulatory Affairs

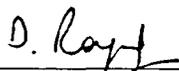
October 1, 2002

Date

ITEM 14: PATENT CERTIFICATION

NDA 21-462
ALIMTA[®]
(pemetrexed)

Eli Lilly and Company claims a five year period of exclusivity for the use of ALIMTA as provided by C.F.R. 314.108(b)(2). As evidenced by the absence in the Orange Book that ALIMTA has previously been approved by the FDA, to the best of Applicant's knowledge and belief, ALIMTA has not previously been approved under section 505(b) of the FDCA. Accordingly, Eli Lilly and Company submits ALIMTA as a new chemical entity entitled to a five year period of exclusivity as provided by FDCA 505(c)(3)(D)(ii) and 505(j)(4)(D)(ii)(21 U.S.C. 355(c)(3)(D)(ii) and 355(j)(4)(D)(ii)).



Name of authorized official
Director, US Regulatory Affairs

October 1, 2002

Date

EXCLUSIVITY SUMMARY for NDA # 21-462 SUPPL #

Trade Name ALIMTA Generic Name pemetrexed

Applicant Name Eli Lilly & Company HFD- 150

Approval Date 2-4-04

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES / X / NO / ___ /

b) Is it an effectiveness supplement? YES / ___ / NO / X /

If yes, what type(SE1, SE2, etc.)?

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 / X / 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 / X / 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 / X /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES / ___ / NO / X /

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES / ___ / NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 / X /

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 / X /

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 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S 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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 9:**

- (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:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

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 /___/

Investigation #3 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:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (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 /___/
Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (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"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

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 /___/ Explain _____ ! NO /___/ Explain _____
! !
! !
! !

Investigation #2 !
YES /___/ Explain _____ ! NO /___/ 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 / X /

If yes, explain: _____

Dotti Pease
Signature of Preparer
Title:

2-12-04
Date

Richard Pazdur, M.D.
Signature Division Director

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Richard Pazdur
2/12/04 09:23:20 AM

Pending APPROVAL
(on disk)
PM Signoff
DRAFT

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA #: 21-462 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 9-30-2003 Action Date: 3-31-2003

HFD -150 Trade and generic names/dosage form: ALIMTA® (pemetrexed)

Applicant: Eli Lilly & Company Therapeutic Class: 5010120 Cytotoxic
Antimetabolite

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Alimta in combination with cisplatin for the indication of malignant pleural mesothelioma

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: Orphan designation

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA

HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Application Information (Enter all identifying information for the submission pertaining to this summary)

NDA Number: **21-462**

Submission Type: **N/A (pilot)**

Serial Number: **N/A (pilot)**

Populations Included In Application (Please provide information for each category listed below from the primary safety database excluding PK studies)

CATEGORY	NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG	
Gender	Males	365	All Females	83	Females >50	60
Age	0-4 Mo.	0	>1 Mo.-2 Year	0	>2-12	0
	12-16	0	17-64	266	65	182
Race	White	410	Black	1	Asian	14
	Other	23(Hispanic)				

Gender-Based Analyses (Please provide information for each category listed below.)

Category	Was Analysis Performed?				
			If not checked, indicate why (e.g., Inadequate #s, Disease Absent)		
Efficacy	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	Inadequate #'s	Disease Absent	
Safety	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	Inadequate #'s	Disease Absent	

Was gender-based analysis included in labeling?	
YES	NO
	<input checked="" type="checkbox"/>
	<input checked="" type="checkbox"/>

Is a dosing modification based on gender recommended in the label? Yes No

If the analysis was completed, who performed the analysis Sponsor FDA

Age-Based Analyses (Please provide information for each category listed below.)

Category	Was Analysis Performed?				
			If not checked, indicate why (e.g., Inadequate #s, Disease Absent)		
Efficacy	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	Inadequate #'s	Disease Absent	
Safety	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	Inadequate #'s	Disease Absent	

Was age-based analysis included in labeling?	
YES	NO
	<input checked="" type="checkbox"/>
	<input checked="" type="checkbox"/>

Is a dosing modification based on age recommended in the label? Yes No

If the analysis was completed, who performed the analysis Sponsor FDA

Race-Based Analyses (Please provide information for each category listed below.)

Category	Was Analysis Performed?				
			If not checked, indicate why (e.g., Inadequate #s, Disease Absent)		
Efficacy	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Inadequate #'s	Disease Absent	
Safety	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Inadequate #'s	Disease Absent	

Was race-based analysis included in labeling?	
YES	NO
	<input checked="" type="checkbox"/>
	<input checked="" type="checkbox"/>

Is a dosing modification based on race recommended in the label? Yes No

If the analysis was completed, who performed the analysis Sponsor FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

Comment:

**APPEARS THIS WAY
ON ORIGINAL**

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ON ORIGINAL**

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

/s/

John Johnson
1/8/04 01:27:58 PM

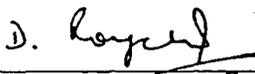
Debarment Certification

NDA Application No.: 21-462

Drug Name: Alimta (pemetrexed)

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Debasish F. Roychowdhury, M.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: 
Debasish F. Roychowdhury, M.D.

Title: Director, U.S. Regulatory Affairs

Date: September 30, 2002

62 pages redacted from this section of
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 14, 2003

TO: Richard Pazdur, M.D., Director
Division of Oncologic Drug Products
HFD-150

VIA: Patty Garvey, Regulatory Health Project Manager
Division of Oncologic Drug Products
HFD-150

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Alimta (pemetrexed for injection), NDA 21-462

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Alimta (pemetrexed for injection), NDA 21-462. We have simplified the wording, made it consistent with the PI, and removed other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications, not to provide detailed information about the condition), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. These revisions are based on draft labeling submitted by the sponsor on September 29, 2003. Patient information should always be consistent with the prescribing information. All future changes to the PI should also be reflected in the PPI

Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division. Please let us know if you have any questions.

INFORMATION FOR PATIENTS AND CAREGIVERS

3 pages redacted from this section of
the approval package consisted of draft labeling

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this page is the manifestation of the electronic signature.

/s/

Jeanine Best
10/14/03 11:24:05 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
10/14/03 04:52:02 PM
DRUG SAFETY OFFICE REVIEWER

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: July 11, 2003

DUE DATE: October 10, 2003

ODS CONSULT #: 01-0063-1

TO: Richard Pazdur, M.D.
Director, Division of Oncology Drug Products
HFD-150

THROUGH: Patricia Garvey
Project Manager, Division of Oncology Drug Products
HFD-150

PRODUCT NAME:

Alimta (Pemetrexed Disodium for Injection)
500 mg/Vial

NDA SPONSOR: Eli Lilly and Company

NDA#: 21-462

SAFETY EVALUATOR: Charlie Hoppes, R.Ph., M.P.H.

SUMMARY: In response to a consult from the Division of Oncology Drug Products, (HFD-150), the Division of Medication Errors and Technical Support (DMETS) conducted a re-review of the proposed proprietary name "Alimta" to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS has no objection to the use of the proprietary name Alimta. ODS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.
2. DMETS recommends implementation of the labeling revisions as outlined in Section III of this review.
3. DDMAC finds the proposed name, Alimta, acceptable from a promotional perspective.

/S/

/S/

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Jerry Phillips, R.Ph.
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Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Rm. Parklawn Room 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 25, 2003
NDA# 21-462
NAME OF DRUG: Alimta (Pemetrexed Disodium for Injection) 500 mg/Vial
NDA HOLDER: Eli Lilly and Company

I. INTRODUCTION:

This consult is written in response to a request from the Division of Oncology Drug Products (HFD-150)

for a re-review of the proposed proprietary name Alimta. DMETS previously reviewed Alimta in a review dated May 17, 2002, and had no objections to the use of the proprietary name (ODS consult #01-0063). Container labels, carton and professional package insert labeling were reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

Alimta (Pemetrexed Disodium) is a folate antagonist proposed for the treatment of malignant pleural mesothelioma in combination with cisplatin. The recommended dose is 500 mg/m² over 10 minutes once every 21 days followed approximately 30 minutes later by a 2 hour infusion of 75 mg/m² cisplatin. Dose may be adjusted based on individual tolerance to adverse effects. The product is reconstituted by adding 20 mL of 0.9% sodium chloride injection to a solution containing 25 mg/mL pemetrexed. The reconstituted solution is further diluted for IV infusion. The product will be available in a 500 mg vial of lyophilized pemetrexed for injection.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to "Alimta" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use

¹ MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 00-03, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/maintrademarks.htm>.

database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Alimta. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. Since the completion of the initial review of the proprietary name Alimta (ODS consult 01-0063), the Expert Panel identified three proprietary names that were thought to have the potential for confusion with Alimta. These products are listed in Table 1 (below), along with the dosage forms available and usual dosage.

2. DDMAC did not have concerns with the name Alimta in regard to promotional claims.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Alimta	Premetrexed Disodium for Injection 500 mg/Vial	500 mg/m ² over 10 minutes once every 21 days	
Alinia	Nitazoxanide for Oral Suspension 100 mg/5 mL	Take one or two teaspoonfuls every 12 hours for 3 days.	LA
Climara	Estradiol Transdermal System 0.025 mg/day, 0.05 mg/day, 0.075 mg/day, 0.1 mg/day	Apply a new patch once weekly.	LA
AlitraQ	Protein, Fat, Carbohydrates for Oral/Nasogastric Suspension 76 g per packet	Take one (or more) packets orally at meals times for supplemental or sole- source nutrition.	LA/SA
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike)			

B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

DMETS' Phonetic Orthographic Computer Analysis (POCA) database was unavailable to search at the time of this review.

C. SAFETY EVALUATOR RISK ASSESSMENT

Since the completion of our initial review of the proprietary name Alimta, conducted on May 17, 2002 (ODS consult 01-0063), DMETS has identified three additional proprietary names, which may be confused with Alimta: Alinia, Climara, and AlitraQ.

1. Alimta and Alinia may look similar when written (see writing sample on page 4). Alinia (Nitazoxanide for Oral Suspension) is indicated for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in pediatric patients 1 through 11 years of age.

⁵Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

The recommended dosage is for, ages 12-47 months: 5 mL (100 mg nitazoxanide) every 12 hours for 3 days, and 10 mL (200 mg nitazoxanide) every 12 hours for 3 days for ages 4-11 years. Alinia for Oral Suspension is a pink-colored powder formulation that, when reconstituted as directed, contains 100 mg nitazoxanide/5 mL. The reconstituted suspension has a strawberry flavor and is available in a 60 mL bottle. Alimta and Alinia are names with the same number of letters and shape. The name pair shares 4 of 6 total letters.

Alimta
Alinia

The “mt” in Alimta may also look like the “ni” in Alinia if the number of “humps” in the “m” and “n” are undefined and if the cross stroke of the “t” looks like the dot over the “i”.

Alinia
Alimta

Despite look-alike and sound-alike similarities, Alimta and Alinia have differences which may distinguish the products as indicated in the table below.

	Alimta	Alinia
Route of Administration	Intravenous infusion only.	Oral.
Packaging	Vial with special handling precautions.	60 mL bottle with distinctive looking/smelling suspension.
Dosing Interval	Administered over 10 minutes every 21 days.	Taken twice daily.
Administration Setting	Administered by health care practitioner.	Parent/guardian administered.

In addition to the differences listed above, the administration of Alimta is often closely associated with administration of cisplatin. This association could serve to prevent confusion with Alinia whenever cisplatin and Alimta are ordered together. An order for cisplatin/Alimta is therapeutically logical compared to an order for cisplatin/Alinia. The dose of Alimta will also vary depending on the surface area of the body whereas Alinia dosing calculations are based on weight. Although it is possible for the names to be confused, the risk of dispensing the wrong medication should be low based on these product differences.

- Alimta and Climara may look similar when written (see writing sample on page 5). Climara (Estradiol Transdermal System) is indicated for the treatment of moderate to severe vasomotor symptoms associated with the menopause, treatment of vulvar and vaginal atrophy, treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure, and for prevention of postmenopausal osteoporosis (loss of bone mass). The recommended dosage is one transdermal system applied to the skin once every week.

Systems are available in four different sizes delivering daily doses of 0.025 mg, 0.05 mg, 0.075 mg, and 0.1 mg. Alimta and Climara owe look-alike properties to the shared letters, “lim” in the middle of the name, the terminal “a”, and the similarities in word length. The “A” in Alimta and “C” in “Climara” may also look similar when scripted. The “t” in Alimta may serve as a distinguishing feature for this name pair.

Alimta

Climara

Despite look-alike and sound-alike similarities, Alimta and Climara have differences which may distinguish the products as indicated in the table below.

	Alimta	Climara
Route of Administration	Intravenous infusion only.	Transdermal.
Packaging	Vial with special handling precautions.	Cartons containing specific patient information and four individually pouched systems.
Strengths	500 mg vial strength with specific “mg” dosing based on body surface area.	As daily dose: 0.025 mg, 0.05 mg, 0.075 mg, and 0.1 mg, or patch size: 6.5 cm ² , 12.5 cm ² , 18.75 cm ² , 25 cm ² , respectively.
Dosing Interval	Administered over 10 minutes every 21 days.	Apply a new patch once every week.
Dosage Form	Powder for Injection	Transdermal System.
Administration Setting	Administered by health care practitioner.	Patient Administered.

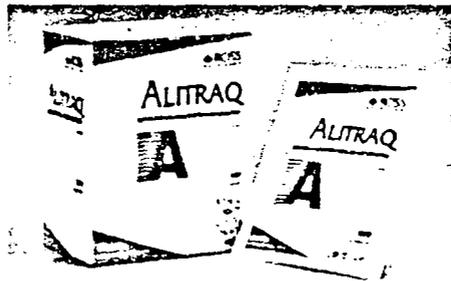
In addition to the differences listed above, the administration of Alimta is often closely associated with administration of cisplatin. This association could serve to prevent confusion with Climara whenever cisplatin and Alimta are ordered together. An order for cisplatin/Alimta is therapeutically logical compared to an order for cisplatin/Climara. Although it is possible for the names to be confused, the risk of dispensing the wrong medication should be low based on these product differences.

- Alimta and AlitraQ may look similar when written (see writing sample on page 6) and sound similar when spoken. AlitraQ is a nutritional supplement containing protein, fat, and carbohydrates, designed for metabolically stressed patients with impaired gastrointestinal function. Dosing is based on the patients’ nutritional requirements and is provided by reconstituting a 76 gram packet of powder with water and administering orally or via a nasogastric tube. On the web site for this product, the name appears as, “AlitraQ®”, ending with an upper case “Q”. By capitalizing the letter “Q”, it is possible that this letter may be misinterpreted as a modifier or a separate entity, thus increasing the potential for confusion with regard to the name. Post-marketing experience has shown modifiers being omitted. In the event that the “Q” is inadvertently omitted during the scripting of AlitraQ or left off a verbal order, the resulting script has the potential of looking like Alimta. Look-alike

properties are foremost the result of the shared first three letters, "Ali". Overall, Alimta and Alitra share the letters "A", "I", "i", "t", and "a".

Alitra Alimta

The name pair may also sound similar if the "Q" is inadvertently omitted. Each name has three syllables and shares five of six letters as discussed above. The names will sound especially similar if Alitra is pronounced with a short "i" sound. Although Alimta and AlitraQ may look and sound similar, the "Q" may serve to differentiate the name pair orthographically and phonetically. Carton labeling and container labels for AlitraQ are labeled with all capital letters and without a space between "Alitra" and the "Q" (see image below).



In addition, AlitraQ may actually be pronounced "alley track", as it would for a contraction of the words, "alimentary" and "track". This pronunciation of AlitraQ sounds quite different than Alimta. Despite look-alike and sound-alike similarities, Alimta and AlitraQ have differences which may distinguish the products as indicated in the table below.

	Alimta	AlitraQ
Route of Administration	Intravenous infusion only.	Oral or nasogastric.
Packaging	Vial with special handling precautions.	Powder packet.
Product strength/ Product dosing	500 mg vial strength with specific "mg" dosing based on body surface area.	No specific packet strength; dosing based on nutritional needs specified in terms of number of packets
Dosing Interval	Administered over 10 minutes every 21 days.	Administered multiple times daily at "meal time".

In addition to the differences listed above, the administration of Alimta is often closely associated with administration of cisplatin. This association could serve to prevent confusion with AlitraQ whenever cisplatin and Alimta are ordered together. An order for cisplatin/Alimta is therapeutically logical compared to an order for cisplatin/AlitraQ. Although it is possible for the names to be confused, the risk of dispensing the wrong medication should be low based on these product differences and lack of convincing look-alike, sound-alike similarities.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES:

In reviewing the draft container labels, carton, and insert labeling for Alimta, DMETS has focused on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user errors.

A. CARTON LABELING (500 mg Single-Use Vial)

1. Increase the prominence of the route of administration on the principal display panel by bolding or some other means.
2. Repeat the statement, "Caution: Cytotoxic Agent" on the principal display panel.

B. PACKAGE INSERT LABELING (HOW SUPPLIED)

Revise the first sentence of this section as follows,

IV. RECOMMENDATIONS:

- A. DMETS has no objection to the use of the proprietary name Alimta. ODS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.
- B. DMETS recommends implementation of the labeling revisions as outlined in Section III of this review.
- C. DDMAC finds the proprietary name, Alimta, acceptable from a promotional perspective.

/s/

Charlie Hoppes, R.Ph., M.P.H.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

/s/

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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this page is the manifestation of the electronic signature.

/s/

Charles Hoppes
10/3/03 12:51:51 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
10/3/03 02:19:47 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/3/03 03:54:28 PM
DRUG SAFETY OFFICE REVIEWER

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-420)

DATE RECEIVED: 2/16/01

DUE DATE: 06/10/02

ODS CONSULT #: 01-0063

TO:

Richard Pazdur, M.D.
Director, Division of Oncology Drug Products
HFD-150

THROUGH:

Debra Vause
Project Manager
HFD-150

PRODUCT NAME: Alimta® (Pemetrexed Disodium for Injection)
500 mg/vial

IND: 40,061

IND SPONSOR: Eli Lilly and Co.

SAFETY EVALUATOR: David Diwa, Pharm.D.

SUMMARY: In response to a consult from the Division of Oncology Drug Products (HFD-150), the Division of Medication Errors and Technical Support (DMETS) has performed a review of the proposed proprietary name *Alimta* to determine the potential for confusion with approved proprietary and established names as well as pending drug names.

DMETS RECOMMENDATION: DMETS has no objection to the use of the proposed name *Alimta*. In addition, we recommend implementation of labeling revisions contained in section III of this review to minimize potential errors with the use of this product. This name and its associated labels and labeling must be re-evaluated upon submission of the NDA, and approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names, and established names from the signature date of this document.

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Carol Holquist, R.Ph
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**Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 05/17/02
IND: 40,061
NAME OF DRUG: Alimta (Pemetrexed Disodium for Injection) 500 mg/vial
IND HOLDER: Eli Lilly and Co

I. INTRODUCTION:

This consult is written in response to a February 7, 2001 request from the Division of Oncology Drug Products (HFD-150) for an assessment of the proposed proprietary name, Alimta. The sponsor also submitted an independent analysis of the proprietary name conducted by Medical Error Recognition and Revision Strategies, Inc. (Med-ERRS) for review and comment.

PRODUCT INFORMATION

Alimta (Pemetrexed Disodium) is a folate antagonist proposed for the treatment of malignant pleural mesothelioma in combination with cisplatin. Originally, Eli Lilly intended to market a 200 mg and 1 g liquid formulation. However, according to the Division, the sponsor intends to market a 500 mg lyophilized powder for injection. The recommended dose is 500 mg/m² over 10 minutes once every 21 days followed approximately 30 minutes later by a 2 hour infusion of 75 mg/m² cisplatin. Dose may be adjusted based on individual tolerance to adverse effects. The product is reconstituted by adding 20 mL of 0.9% sodium chloride injection to a solution containing 25 mg/mL pemetrexed. The reconstituted solution is further diluted for IV infusion.

II. RISK ASSESSMENT:

The DMETS medication error staff conducted a search of several standard published drug product reference texts^{1,2,3} as well as several FDA databases⁴ and SAEGIS™ Pharma-In-Use database⁵ for existing drug names which sound-alike or look-alike to Alimta to a degree where potential confusion between drug names could occur under usual clinical practice settings.

¹ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ Drug Information Handbook 1999-2000, Lacy CF, Armstrong LL, Goldman MP, Lance LL (eds) Lexi-Comp Inc, Hudson

⁴ New Drug Approvals 98-01, and the electronic online version of the FDA Orange Book.

⁵ Data provided by T&T's SAEGIS™ online service available at www.thomson-thomson.com

A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁶. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written inpatient prescription studies and one verbal prescription study, involving health care practitioners within the FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the proposed name *Alimta*.

A. EXPERT PANEL DISCUSSION

An expert panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name *Alimta*. Potential concerns regarding drug marketing and promotion relating to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical experience, other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The panel believed that *Alimta* posed a potential risk of look-alike and sound-alike confusion with *Alfenta*. Additionally, from an independent review *Elimite* was identified as having sound-alike and look-alike similarity to the proposed name as well. Product summaries are provided in Table 1 below, along with the dosage forms and usual dosage.

DDMAC did not have any concerns with the name regarding promotional claims.

TABLE 1

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Alimta	Premetrexed Disodium for Injection 500 mg/vial	500 mg/m ² over 10 minutes once every 21 days	
Alfenta	Alfentanil HCl Injection 500 mcg/mL; 2,5,10 and 20 mL ampules	8-40 mcg/kg for surgical procedures lasting up to 30 minutes	SA/ LA
Elimite	Permethrin 5% Cream 60 g/tube	Apply to skin from head to soles of feet and remove after 8-14 hours	SA/ LA

*Frequently used, not all-inclusive **LA (look-alike), SA (sound-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

A study was conducted within the FDA to determine the degree of confusion due to similarities in visual appearance of handwritten prescriptions or verbal pronunciation of the drug name *Alimta* and other U.S. drug names. The studies employed a total of 85 health care professionals (nurses, pharmacists, and physicians). The exercise was conducted in an attempt to simulate the prescription ordering process. DMETS staff members wrote two inpatient prescriptions, each consisting of a combination of marketed, unapproved drug products, and prescriptions for *Alimta* (see page 4). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one DMETS staff member recorded a verbal prescription that was then delivered to a group of study participants via telephone voicemail. Each study participant was then requested to provide an interpretation of the prescription via email.

⁶ WWW location <http://www.uspto.gov/tmdb/index.html>.

INPATIENT PRESCRIPTION I

INPATIENT PRESCRIPTION II

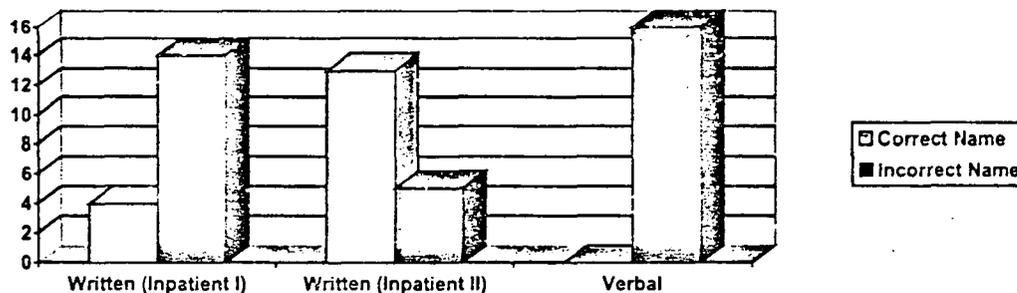
Alimta 600mg IV over 10 minutes followed in 30 min with cisplatin 90mg IV over 2 hrs	Alimta 600mg IV over 10 minutes followed in 30 min with cisplatin 90mg IV over 2 hrs
--	--

VERBAL PRESCRIPTION
 Alimta 600 mg IV over 10 minutes followed in 30 minutes with cisplatin 90 mcg IV over 2 hours.

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Alimta" response	Other response
Written: Inpatient I	30	19 (63%)	4 (21%)	15 (79%)
Written: Inpatient II	28	18 (64%)	13 (72%)	5 (28%)
Verbal:	27	16 (59%)	0 (0%)	16 (100%)
Total:	85	53 (62%)	17 (32%)	36 (68%)



Sixty-eight percent of all study participants incorrectly interpreted the proposed product name Alimta. Written and verbal scores of the incorrect responses are summarized above. Incorrect responses were misspelled phonetic variations of the proposed drug name. We recorded the highest number of incorrect responses in the verbal study (16 of 16). In the first written prescription study, 15 out of 19 participants incorrectly interpreted the prescription order. Out of 18 participants, 5 misinterpreted the proposed name in the second written prescription study. The difference between the two written inpatient prescription studies is most likely due to penmanship. Overall none of the responses overlapped with currently marketed products. Spelling variations from the written and verbal prescription studies are summarized in Table II on page 5.

Table II

Incorrectly Interpreted	
Written Inpatient I	Ainata
	Alinta (13)
	Alinto
Written Inpatient II	Alimata
	Alimsta (2)
	Alinosta
	Almenta
Verbal	Alecta
	Alenta
	Alipta (2)
	Elipta(6)
	Ellipta(3)
	Elypta
	Olympha (2)

C. SAFETY EVALUATOR RISK ASSESSMENT

The expert panel identified Alfenta as potentially problematic in terms of look-alike and/or sound-alike similarity with the proposed name Alimta. From an independent review, Elimite was identified as having sound-alike and look-alike similarity with the proposed name.

Alfenta (alfentanil) is an opioid analgesic with a rapid onset of action that is used for the primary induction of anesthesia in general surgery when endotracheal or mechanical ventilation is required. It is also used as an analgesic adjunct for the maintenance of anesthesia. The usual dose for induction of anesthesia in surgery lasting 30 to 60 minutes is 20 to 50 mcg/kg, followed by 5 to 15 mcg/kg every 5 to 20 minutes. The names *Alfenta* and *Alimta* both start with the letters "Al" and end with "ta". When poorly scripted, the letters "fen" in *Alfenta* and "lim" in *Alimta* may be difficult to distinguish. *Alfenta* is available in 500 mcg/mL glass ampules of 2, 5, 10 and 20 mL while *Alimta* will be available in 500 mg/vial. The strength expression 500 mcg/mL and 500 mg/vial bear similarities that may be confused when selecting these products. Although there are name and some strength expression similarities between the two products, they vary in dosage and dosing interval. While *Alimta* will be administered every 21 days, *Alfenta* is only administered over a short period of time in the induction of anesthesia during surgery. *Alimta* will be dosed in milligrams per body surface area (mg/m^2), whereas *Alfenta* is dosed in micrograms per body weight (mcg/kg). Moreover, *Alfenta* is a schedule II controlled substance that is mostly restricted to surgical units. Based on information currently available, the likelihood of name confusion between *Alfenta* and *Alimta* appears to be minimal.

Elimite 5% (permethrin) is used as a scabicide. It is usually applied topically and removed by washing after 8-14 hours. The letters "Elim" in *Elimite* and "Alim" in *Alimta* are similar in sound and script. In addition, *Elimite* ends with the letters "ite" and *Alimta* with "ta". The interpretation of the two names can be problematic in that a poorly scripted "e" look like an "a". Although the two names bear some look-alike and sound-alike similarities, *Elimite* is available as a topical cream while *Alimta* will be available as a lyophilized powder for injection. The recommended dose of *Alimta* is $500 \text{ mg}/\text{m}^2$ administered over 10 minutes once every 21 days. *Elimite* is topically applied and repeated only as necessary. *Alimta* and *Elimite* will not be stored in close proximity with one another. The risk of selecting the wrong product in storage is therefore minimal. In addition, the container packaging of the two products is different. *Elimite* is in 60 g tubes while *Alimta* will be in 5 mL vials. The dosage form, route of administration, potential pharmacy shelf storage arrangement,

and packaging of *Alimta* make it unlikely that it will be confused with *Elimite*.

- D. STUDY SUBMITTED BY APPLICANT – Confidential and proprietary and should be noted for FOI purposes

C

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In reviewing the draft container labels, carton, and insert labeling for *Alimta*, DMETS has focused on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user errors.

A. CONTAINER LABEL

1. Express the strength as 500 mg/vial.
2. Increase the prominence of the statement "Discard unused portion."
3. Increase the prominence of the statement "Reconstituted solution must be further diluted before IV infusion".
4. Revise the reconstitution statement to read: _____

5. Relocate the statement "Rx only" to the lower portion of the label in order to give more prominence to the caution and "IV infusion only" statements.

B. CARTON LABELING

See comments A1 through A5.

C. PACKAGE INSERT LABELING

1. OVERDOSAGE

In the interest of minimizing the risk of harm from this product, *describe overdose management procedures including specific and/or supportive measures* to treat overdoses.

2. DOSAGE AND ADMINISTRATION

Although the container label refers to dilution instructions in the accompanying literature, none has been provided in the package insert. Provide dilution instructions.

3. HOW SUPPLIED

Provide a description of how this product will be packaged and made available for use.

**APPEARS THIS WAY
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IV. RECOMMENDATIONS:

- A. DMETS has no objection to the use of the proposed proprietary drug name Alimta.
- B. We recommend implementation of the labeling revisions contained in section III of this review to minimize potential errors with the use of this product.

We would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact the project manager, Sammie Beam, R.Ph. at 301-827-3242.



David Diwa, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety

Concur:



Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety

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/s/

David Diwa
6/6/02 07:50:11 AM
PHARMACIST

Alina Mahmud
6/6/02 10:33:30 AM
PHARMACIST

Carol Holquist
6/7/02 03:45:17 PM
PHARMACIST

Jerry Phillips
6/10/02 03:47:23 PM
DIRECTOR

Redacted 7

pages of trade

secret and/or

confidential

commercial

information

22 pages redacted from this section of
the approval package consisted of draft labeling

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION



OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF DRUG SAFETY
Memorandum

Office of Drug Safety (ODS) Memo to the file

November 21, 2003

NDA 21-462

Drug: Alimta (pemetrexed)

Issue: RMP submitted February 21, 2003

PID# D030621

This document was reviewed by ODS and represents a compilation of comments put forward by the Division of Drug Risk Evaluation (DDRE), Division of Medication Errors and Technical Support (DMETS) and the Division of Surveillance, Research and Communication Support (DSRCS). The members of the ODS review team are listed at the end of the document.

Summary

Overall, the Alimta RMP, as submitted February 21, 2003, does not appear to differ substantially from a typical new product launch and routine postmarketing safety surveillance. There are minor differences in postmarketing surveillance which may be appropriate for the nature and severity of the perceived risk. However, they are insufficient to be designated a RMP. We commend Lilly for their concern and attention to risk mitigation and encourage them to take the steps they have outlined in their proposal; however, the FDA views this effort as enhanced labeling.

Recommendations

ODS recommends that the sponsor evaluate their answers to items numbered 1, 2, and 3 before proceeding with the formulation of a RMP. If the sponsor feels that a RMP is warranted, then ODS offers additional recommendations to enhance the goal of the RMP.

1. Does the sponsor consider a lack of premedication a product risk that merits more than conventional product labeling for risk management?
 - Other antineoplastic agents require premedications. An example is Taxotere, which requires premedication for hypersensitivity reactions.
2. How will the Patient Package Insert (PPI) be distributed and to whom?
 - There is no explanation of how literature for patients will be distributed except that they "may" receive literature from HCP or find it on www.Alimta.com. If the sponsor decides to utilize a PPI, ODS needs to see a concrete plan for literature distribution that maximizes patient access.
 - The PPI should be the primary communication tool for patients.

3.

[

]

Materials below which are used in the launch of the product need to be reviewed by DDMAC.

-
-

Patient Information

-

[

]

-

[

]

Post Marketing Surveillance

The RMP may differ from usual postmarketing safety surveillance in the intensified follow-up of reports that do not specify the use of vitamin supplementation and of reports that include one of the five targeted surveillance terms. Prescriber training in proper Alimta use, that is, use of concomitant vitamins, will be part of the follow-up process. This enhanced follow-up is an interesting tool with potential value in promoting proper drug use. We are interested in observing the outcome of this activity. The five targeted surveillance terms are grade 4 neutropenia lasting at least 5 days, grade 4 thrombocytopenia, grade 3 or 4 diarrhea, grade 3 or 4 mucositis, and toxic death. We request that reports of these adverse events be submitted as 15-day reports.

Labeling

- Under the product label, The RMP states that lack of information regarding use in patients with hepatic failure is in the *Warnings* section of the Prescribing Information. This information

actually appears in the *Precautions* section and FDA agrees that the *Precautions* section is the appropriate section for it.

- DSRCS and DMETS agree with the inclusion of a comprehensive *Information for Patients* subsection under the PRECAUTIONS section of the Prescribing Information (PI). Refer to 21 CFR 201.56, 21 (General requirements on content and format of labeling for human prescription drugs), CFR 201.57 (Specific requirements of labeling for human prescription drugs), and specifically 21 CFR 201.57(3)(v)(f)(2) (*Information for Patients*). The purpose of the *Information for Patients* subsection of the PI is to provide counseling information on the safe and effective use of the product for healthcare providers to provide to patients. The Patient Package Insert is not/was not intended to replace this subsection of the PI. Also, patients may not always obtain or read the PPI.
- The recommended, optimal reading comprehension level for all patient materials is the 6th to 8th grade reading level in order to reach a broad population of patients, including those with lower literacy.

References

Davis, D. A., Thomson, M. A., Oxman, A. D., & Haynes, R. B. (1992). Evidence for the effectiveness of CME. A review of 50 randomized controlled trials. JAMA, 268, 1111-1117.

/S/

Mark Avigan, M.D., Acting Director
Division of Drug Risk Evaluation, HFD-430
Office of Drug Safety

/S/

Toni Piazza-Hepp, R.Ph., Acting Director
Division of Surveillance, Research, and Communication Support, HFD-410
Office of Drug Safety

/S/

Jerry Phillips, R.Ph., Acting Director
Division of Medication Errors and Technical Support, HFD-420
Office of Drug Safety

ODS Review Team

Kathleen Phelan, R.Ph., Safety Evaluator, DDRE
Susan Lu, R.Ph., Team Leader, DDRE
Leslie Wheelock, M.S., R.N., Associate Director for Communications DSRCS
Jeanine Best, M.S.N., R.N., P.N.P., Patient Product Information Specialist, DSRCS
Carol Holquist, R.Ph., Deputy Director DMETS
Denise Toyer, R.Ph., PharmD, Team Leader DMETS
Alima Mahmud, R.Ph., Team Leader DMETS
Mary Dempsey, Project Management Officer, ODS-IO

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/s/

Mary Dempsey
11/21/03 01:16:11 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
11/21/03 03:33:30 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
11/24/03 07:36:54 AM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
11/24/03 07:57:17 AM
DRUG SAFETY OFFICE REVIEWER

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DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

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Fax: (301) 594-0498

Phone: 317-276-5052

Phone: (301) 594-5766

Pages (including cover): 17

Date: December 19, 2003

Re: NDA 21-462 Alimta

Urgent For Review Please Comment Please Reply Please Recycle

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● **Comments:**

John,

Please refer to your NDA 21-462 Alimta mesothelioma indication submission dated December 15, 2003.

Attached is the FDA proposed package insert (PI) in response to your proposed PI dated December 15, 2003. We have agreed with your changes except for the sentence regarding _____
Your proposal is unacceptable.

We also acknowledge your agreement with the FDA patient package insert emailed/faxed to you on December 10, 2003.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

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/s/

Patricia Garvey
12/19/03 02:15:49 PM
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Pages (including cover): 2

Date: December 17, 2003

Re: NDA 21-462 Alimta

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● **Comments:**

John,

Please refer to your NDA 21-462 Alimta submission dated February 21, 2003 regarding your Risk Management Plan. The following recommendations are for your consideration.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

RISK MANAGEMENT PLAN: RECOMMENDATIONS

Overall, your Alimta (mesothelioma) Risk Management Plan (RMP) does not appear to differ substantially from a typical new product launch and routine postmarketing safety surveillance. There are minor differences in postmarketing surveillance which may be appropriate for the nature and severity of the perceived risk. However, they are insufficient to be designated a RMP. We commend you for your concern and attention to risk mitigation and encourage you to take steps you have outlined in your proposal, however, the FDA views this effort as enhanced labeling.

The Office of Drug Safety (ODS) recommends that you evaluate your answers to items number 1, 2, and 3 before proceeding with the formulation of a RMP. If you feel that a RMP is warranted, then ODS offers additional recommendations to enhance the goal of the RMP.

1. Do you consider a lack of premedication a product risk that merits more than conventional product labeling for risk management?
 - Other antineoplastic agents require premedications. An example is Taxotere, which requires premedication for hypersensitivity reactions.
2. How will the Patient Package Insert (PPI) be distributed and to whom?
 - There is no explanation of how literature for patients will be distributed except that they "may" receive literature from Healthcare Professional (HCP) or find it on [www. Alimta.com](http://www.Alimta.com). If you decide to utilize a PPI, ODS needs to see a concrete plan for literature distribution that maximizes patient access.
 - The PPI should be the primary communication tool for patients.
 - The recommended, optimal reading comprehension level for all patient materials is the 6th to 8th grade reading level in order to reach a broad population of patients, including those with lower literacy.

3.

J

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Patricia Garvey
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Date: December 12, 2003

Re: NDA 21-462 Alimta

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◆ **Comments:**

John,

Please refer to your NDA 21-462 Alimta submission dated September 22, 2003. Please address the following request from the clinical reviewer.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

CLINICAL: INFORMATION REQUEST

With regard to the response by Lilly on 9/22/2003 to FDA query dated 9/2/2003, the information provided on independent pathology review took into account whether the diagnosis of mesothelioma was confirmed or not. The response did not take into account the histological subtype of mesothelioma, i.e., epithelial, sarcomatoid, and mixed and whether these subtypes were confirmed. For the patients that Lilly reported on 9/22/2003 as "Independent review confirmed pathology of malignant mesothelioma", please provide in table form (as well as, in an EXCEL spreadsheet): patient numbers, original pathology-mesothelioma subtype at the site, the independent review pathology-mesothelioma subtype, supplement status, stage, gender, and treatment arm. Also, provide the charter of the independent centralized pathology review and what responsibilities were charged to the independent review.

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Date: December 11, 2003

Re: NDA 21-462 Alimta

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John,

Please disregard the facsimile cover letter dated December 10, 2003 regarding the labeling comments. This facsimile will supercede the December 10, 2003 facsimile. Comment #6 for the Package Insert should now read:

"The Division does not agree with this statement. _____

[The word _____ was mistakenly written after _____
fax]

_____ in the December 10, 2003

Please refer to your NDA 21-462 Alimta submission dated December 5, 2003. Attached are FDA's comments to the package insert changes and patient package insert.

Please keep in mind that the immediate office has not reviewed the PI and PPI, therefore the PI and PPI are not final with the FDA.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager

Division of Oncology Drug Products
PATIENT PACKAGE INSERT: COMMENTS

1. Line 37: FDA deleted _____ and added "not receiving folic acid and Vitamin B12 supplementation".
2. Renal Insufficiency: Lilly's proposal is acceptable.
3. Objective tumor response: Lilly's proposal is acceptable however FDA made a minor change. FDA deleted _____ and replaced with "more".
4. _____ section: Lilly's proposal is not acceptable for the following reasons.

Although changes in some of the in the components of the LCSS are statistically significant, none of the changes are clearly clinically significant. Therefore, the FDA does not believe this information should be included in the label.

Although changes in pulmonary function evaluations are statistically significant, the changes are within the variability range for these tests (i.e., FVC) allowed by the American Thoracic Society and thus, the changes are not clinically significant. Also, over 20% of the patients did not contribute data to the pulmonary function evaluations; in a single-blinded study, this may suggest bias in testing and reporting. Therefore, the FDA does not believe this information should be included in the label.

5. Laboratory Tests section: FDA's revisions based on protocol.
6. Lilly's new proposed paragraph after Table 7: Lilly proposed paragraph is not acceptable. The Division does not agree with this statement.
7. Laboratory Monitoring and Dose Reduction Recommendations section: FDA's revisions based on protocol.

PATIENT PACKAGE INSERT:

FDA has decided not to make any additional revision.

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Patricia Garvey
12/11/03 12:23:28 PM
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Date: December 9, 2003

Re: NDA 21-462 Alimta

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● **Comments:**

John,

Please refer to your NDA 21-462 Alimta submission dated December 1, 2003. The following requests are from the clinical biopharmaceutics reviewer.

1. Please submit the NONMEM control streams used for the ISS_integrated_renal.xpt datafile
2. Please submit the output files for this (these) runs

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

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/s/

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Date: December 5, 2003

Re: NDA 21-462 Alimta

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● **Comments:**

John,

Please refer to your NDA 21-462 Alimta. The following are chemistry deficiencies regarding the drug product for Alimta. Please address these deficiencies as soon as possible.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

CHEMISTRY, MANUFACTURING AND CONTROLS: DRUG PRODUCT DEFICIENCIES

1. _____ seems superior to method _____ for Assay testing. Method _____ separates _____ impurities whereas the method proposed for Assay _____ detects only _____ impurities. This raises concern that some impurities may overlap with the DS peak or with other impurity peaks when using the proposed _____ method _____. If so, Assay testing might result in over estimated values. Please address this discrepancy with data.
2. The Total Impurities in the drug product is proposed as NMT ____%. However, the actual test data for Total Impurities from several stability lots is less than ____%. The proposed limit for total impurities is too broad to be reflective of the data. It is also unclear if the proposed level of total impurities has been appropriately qualified. The limit for Total Impurities in drug product should be tightened to better reflect actual manufacturing capability as well as be within qualified values.
3. To a substantial extent, your proposed 24 month drug product shelf life is based on supportive stability data. To support this risk management based decision, please agree to provide updated post approval stability test data from the three primary stability test lots for drug product, as general correspondence, every three months (or as indicated by your stability protocol) out to 24 months and include a summary in the appropriate Annual Report(s).

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Date: December 5, 2003

Re: NDA 21-462 Alimta

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● **Comments:**

John,

Please refer to your NDA 21-462 Alimta. Please address the following request from the clinical reviewer.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

CLINICAL

1. Based on your 12/4/2003 response, please provide the Financial Disclosure forms (Form 3455) (and any disclosure) that Lilly has on file for _____ and _____ who were previously identified as having missing information.
2. Based on your 12/4/2003 response, please provide the Financial Disclosure forms (Form 3455) (and any disclosure) that Lilly has on file for the 12 investigators who previously did not comply with financial disclosure.
3. For study JMCH, please provide the Financial Disclosure forms (Form 3455) (and any disclosure) that Lilly has on file for the following investigators: Mattson, Gatzemeier, Kaukel, Manegold, Vogelzang, Denham, Ruffie, Boyer, and Emri.

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/s/

Patricia Garvey
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DIVISION OF ONCOLOGY DRUG PRODUCTS

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Pages (including cover): 2

Date: December 2, 2003

Re: NDA 21-462 Alimta

Urgent

For Review

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● **Comments:**

John,

Please refer to your NDA 21-462 Alimta. The following are chemistry deficiencies regarding the drug substance for Alimta. We will send you the drug product deficiencies by the end of this week. Please address these deficiencies as soon as possible.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

CHEMISTRY, MANUFACTURING AND CONTROLS: DRUG SUBSTANCE DEFICIENCIES

1. Please add the tests of optical rotation and _____ for _____ as part of in-process control.
2. Please add the tests for optical rotation and melting point into the specifications of the drug substance and reference standard.
3. []
4. Please provide quantification of the total impurity peaks seen below _____ (e.g., page 214) so as to a more appropriate quantitative determination of the relative amount of total impurities in the drug substance.
5. Please provide the names of _____ or provide appropriate Drug Master File (DMF) reference(s) with corresponding Letter(s) of Authorization. Also, the applicant needs to describe in detail how these _____ are included in the primary packaging material.
6. Due to the availability of 24 months primary stability data at present, the retest period of bulk drug substance can be granted to 24 months. This retest period can also be extended to the proposed _____ months only after the updated primary stability test data are provided in an annual report.

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Patricia Garvey
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Phone: 317-276-5052

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Pages (including cover): 2

Date: December 1, 2003

Re: NDA 21-462 Alimta

Urgent

For Review

Please Comment

Please Reply

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● **Comments:**

John,

Please refer to your NDA 21-462 Alimta. The following comments are from the biopharmaceutics reviewer regarding the proposed renal insufficiency labeling for Alimta.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS: COMMENTS

With regard to the proposed renal insufficiency labeling for Alimta, the use of a continuous function to relate drug exposure to renal function is acceptable. However, the following issue needs to be addressed

We disagree with referencing the change in Alimta exposure for a given degree of renal function, with 80 ml/min (the lower limit of normal). This is somewhat misleading because the average normal (\geq 80 ml/min) renal function in JMCH was 107 ml/min and in the combined ISS renal database it was 112 ml/min. As approximately 100 ml/min is a truer estimate of normal renal function in these patients, referencing changes to 80 ml/min provides an underestimate of the increases in AUC that are likely to be experienced.

Therefore, the labeling should read

Renal Insufficiency — Pharmacokinetic analyses of — ALIMTA included 127 patients

C

J

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/s/

Patricia Garvey
12/1/03 04:30:26 PM
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DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: John Worzalla – Eli Lilly and Company

From: Patty Garvey, R.Ph.

Fax: 317-276-1652

Fax: (301) 594-0498

Phone: 317-276-5052

Phone: (301) 594-5766

Pages (including cover): 2

Date: November 25, 2003

Re: NDA 21-462 Alimta

Urgent

For Review

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• **Comments:**

John,

Please refer to your NDA 21-462 Alimta. Please address the following request from the clinical and biopharmaceutical reviewer.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

CLINICAL

Financial Disclosure documentation for study JMCH, provided 3/2003, appeared incomplete.

1. There were four investigators who were indicated as "disclosure provided". Lilly has provided disclosure from one of these investigators. Please provide the disclosure for the other three investigators.
2. Please provide the financial disclosure for the seven U.S. investigators who were identified as having missing information.
3. It is noted that 47 investigators did not comply with financial disclosure (i.e., this was the group indicated as "disclosure not obtained; due diligence performed"). Please identify the patients these investigators entered and/or enrolled.
4. Please provide the financial disclosure for the two investigators whose information was not available at the time of the submission.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS

Please submit the NONMEM control streams, output files and table files. There should also be a report somewhere that describes this analysis (the reasoning used, methods, validation, etc) similar to the report for the linear (slope and intercept model)

Combined Population Pharmacokinetic Analyses of Studies:

JMAC, JMAD, JMAG, JMAH, JMAI, JMAJ, JMAK, JMAM, JMAL and JMBR

or

Population Pharmacokinetic Analyses of Study H3E-MC-JMCh:

A Single-blind Randomized Phase 3 Trial of MTA plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma

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Center for Drug Evaluation and Research, HFD-150

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Pages (including cover): 1

Date: November 14, 2003

Re: NDA 21-462 Alimta

Urgent

For Review

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● **Comments:**

John,

Please refer to your NDA 21-462 Alimta. Please address the following request from the clinical reviewer:

For the following cases, although the response evaluation by the readers may have been scored as PR for best overall response, the independent reader or readers' numbers do not calculate to PR: #111-1351, #201-2192, #216-2164, #501-5001. Please clarify.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

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Patricia Garvey
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Center for Drug Evaluation and Research, HFD-150

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5600 Fishers Lane, Rockville, MD 20857



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Pages (including cover): 1

Date: November 13, 2003

Re: NDA 21-462 Alimta

Urgent

For Review

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• **Comments:**

John,

Please refer to your NDA 21-462 Alimta submission dated November 14, 2003, received via email November 12, 2003. This submission was in response to the renal insufficiency changes in the Alimta labeling sent via email to you on November 4, 2003. Please address the following issues from the biopharmaceutics reviewer.

Lilly quoted data and modeling used to generate figure 10.1 from the ISS (in the edr on 3/24/03). The biopharmaceutics reviewer has not been able to locate any of the modeling or analysis that was used to generate this figure in any of the submissions in the EDR.

Please to indicate exactly where in the NDA this information is located if it was submitted. If it is not in the NDA, you will need to submit this information (methods, data, modeling strategy, validation etc).

Please also explain how an analysis of studies JMAW (N=47), JMCH (N=70 on alimta), and the 10 phase 2 studies (n=209), yielded only 127 patients at the conclusion.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

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/s/

Patricia Garvey

11/18/03 01:11:59 PM

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Center for Drug Evaluation and Research, HFD-150

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Pages (including cover): 2

Date: November 10, 2003

Re: NDA 21-462 Alimta

Urgent For Review Please Comment Please Reply Please Recycle

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• **Comments:**

John,

Please refer to your email dated November 7, 2003 regarding clarification on FDA biopharmaceutics Alimta labeling changes. The following is a response from the biopharmaceutics reviewer regarding the rationale for the labeling change.

In addition, please refer to your submission dated November 4, 2003. The medical officer has completed the review of your proposed adverse event tables 6b, 7b, and 8b. The tables are acceptable therefore please incorporate these tables in your response to the FDA proposed labeling changes.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS: RESPONSE

Re: Alimta labeling of Renal insufficiency: 130% vs. —

FDA has replaced the value of — with 130% based on the results of the renal impairment study JMAW (n=47). Using the data provided by Lilly on dose, C_{max}, AUC, and creatinine clearance (CL_{cr}-Cockcroft-Gault) for the patients in this study, the results were stratified according to the FDA Guidance on Renal Impairment. As a result, the following Table was generated:

TABLE 1. ALIMTA C_{max} and AUC in patients with Renal Impairment (FDA Analysis)

Renal Function	N	C _{max} (dose-normalized)	AUC (dose-normalized)	% change
Normal > 80 ml/min	21	0.130 ± 0.044	0.193 ± 0.039	NA
Mild 50-80 ml/min	20	0.122 ± 0.054	0.274 ± 0.068	42.0 ↑
Moderate 30-50 ml/min	6	0.136 ± 0.083	0.448 ± 0.151	132 ↑
Severe <30 ml/min	1*	0.088	1.182	512 ↑

*Patient died from drug-related toxicity

As can be seen from the patient group with moderate renal impairment, AUC (dose normalized) increased by more than 2-fold compared to patients with normal renal function.

We disagree with predictions of the AUC in moderate renal impairment (or severe renal impairment) based on the population model that was developed for Alimta. This model was based on data from patients who are predominantly characterized with normal renal function. There were few if any patients with CL_{cr} less than 50 ml/min. The relationship between Alimta clearance and CL_{cr} is confounded by the physiologically implausible values observed over 140 ml/min. This produced a shallow relationship that is likely not representative of actual physiology.

Evidently, the slope/intercept equation will not adequately predict AUC at lower CL_{cr}. The expression for CL that was derived is

$$CL = 43 + 47.2(CL_{cr}/92.6)$$

Even patients who have complete renal failure (CL_{cr}=0 ml/min) will still have a systemic clearance according to this expression.

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Patricia Garvey

11/14/03 03:19:28 PM

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DIVISION OF ONCOLOGY DRUG PRODUCTS

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From: Patty Garvey, R.Ph.

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Fax: (301) 594-0498

Phone: 317-276-5052

Phone: (301) 594-5766

Pages (including cover): 1

Date: November 6, 2003

Re: NDA 21-462 Alimta

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

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● **Comments:**

John,

Please refer to NDA 21-462 Alimta. The following is a question from the medical officer.

For patient: #512-5117, please provide the CT scan report for baseline and first follow-up evaluation.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

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/s/

Patricia Garvey
11/6/03 12:34:46 PM
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Pages (including cover): 2

Date: October 31, 2003

Re: NDA 21-462 Alimta

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• **Comments:**

John,

Please refer to NDA 21-462 Alimta. Please response to the following question from the medical officer.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

CLINICAL:

In your response dated 9/12/2003 to FDA query dated 9/19/2003, you indicated that there were two alimta patients--#136-1631 and #720-7200--who did not receive cisplatin at baseline and/or at any time during the study. However, in Appendix 16.1.10 of the JMCH study report, it appears that patient #136-1631 did not receive cisplatin at baseline and in cycles 2 & 3. Further examination of this appendix suggested that there were several patients who did not receive cisplatin at baseline and/or at some time during the study. Below is a list of patients. Please clarify:

INVESTIGATOR #	PATIENT #
107	1072
107	1073
107	1074
109	1092
124	1201
130	1261
131	1272
131	1277
142	1475
510	5100
802	8020
804	8040
130	1266
131	1044
136	1631
140	1450
251	2550
510	5103
554	5516
805	8070
104	1046
119	1146
130	1191
131	1278
136	1633
142	1476
214	2146
510	5101
720	7200

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5600 Fishers Lane, Rockville, MD 20857



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Pages (including cover): 1

Date: October 10, 2003

Re: NDA 21-462 Alimta

Urgent

For Review

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● **Comments:**

John,

Please refer to NDA 21-462 Alimta. The following is a request from the medical officer.

For the JMCH study please submit for each patient the best tumor response (confirmed after at least 4 weeks for responders) as reported by the Study Investigator, External Reviewer #1, External Reviewer #2 and, if there is disagreement between Reviewer #1 and #2, the Adjudicating Reviewer.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

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/s/

Patricia Garvey
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Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857



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Pages (including cover): 2

Date: September 30, 2003.

Re: NDA 21-462 Alimta

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• **Comments:**

John,

Please address the following questions from biopharmaceutics reviewer.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS

1. In the renal impairment study JMAW (EDR Oct 2002 file submission), the DEFINE.PDF for JMAWc.xpt defines GFR as glucose fasting rate. Is this correct, or is this actually glomerular filtration rate?
2. We cannot find many of the tables that these data were derived from (no hyperlink;). What are the units for the serum creatinine column defined as CR?
3. Many (if not all) of the patients had several CR and CGCL values listed during a single visit (typically the first visit). Is this a typo, and if so, can you confirm that the starting values for CR and CGCL were used?
4. Where can the AEs for these patients be found?

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Patricia Garvey
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Center for Drug Evaluation and Research, HFD-150
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Pages (including cover): 1

Date: September 12, 2003

Re: NDA 21-462 Alimta

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● **Comments:**

John,

Please provide the following request from the medical officer.

From the alimta/cisplatin arm in the JMCH study, please provide the following patient numbers for patients:

- a. who did not receive cisplatin at baseline and/or at any time during the study
- b. who received alimta alone at baseline and/or at any time during the study
- c. who received carboplatin at baseline and/or at any time during the study
- d. who did not receive alimta and received only cisplatin at any time during the study

This query does not pertain to post study treatment.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

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Patricia Garvey
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Pages (including cover): 2

Date: September 8, 2003

Re: NDA 21-462 Alimta

Urgent

For Review

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● **Comments:**

John,

Please provide the following request from the medical officer and pharmacology/toxicology reviewer.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

CLINICAL

Study JMCH:

1. Please submit the median nadir ANC and median duration of neutropenia for the study.
2. Please submit the details for each patient, if any, who was transfused due to bleeding and the site of bleeding.
3. Please submit the median time to start of nausea after chemotherapy and the median duration of the nausea for the study.
4. In Section 12.3.1.1, of the NDA, please submit the patient numbers for the two deaths mentioned in the second paragraph.

Labeling:

1. In the 'Adverse Reactions' section of the package insert, please change the narrative and the Adverse Events tables to encompass all adverse events noted irrespective of whether they were probably or possibly related to the drugs. This is standard Oncology Division Policy for labeling of results of randomized trials.
2. Please amend the package insert by adding information on the effect of age, gender and race on both efficacy and safety. If there is no effect, this should be stated. The statement regarding efficacy should be in the Clinical Studies section. The statement regarding safety should be in the Adverse Reactions section. We note that you did report some gender and age effects regarding safety in this NDA.
3. The FDA informed you at the time you presented this NDA orally that the FDA finds a strong gender effect on survival with most of the Alimta benefit in women and much less in men. Have you found any explanation for this gender effect? Please indicate how you propose to address it in the Clinical Studies section of the package insert.

PHARMACOLOGY/TOXICOLOGY

Only an inhibition study was submitted in ADME Report 11, volume 1.7. Please tell us whether or not you have done a study to see if ALIMTA induced any CYP 450 enzymes? If you have, please submit the data ASAP.

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/s/

Patricia Garvey
9/9/03 10:00:44 AM
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Facsimile sent to sponsor on September 8, 2003

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Pages (including cover): 1

Date: September 2, 2003

Re: NDA 21-462 Alimta

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● **Comments:**

John,

Please address the following question from the medical officer.

The protocol indicated that patients were to be entered and randomized based on local pathology. Independent centralized pathology review was to be carried out on all patients if feasible. However, the ENTRY PROCEDURES AND CRITERIA FOR ENROLLMENT form (p. 1179) indicated that independent centralized pathology review was to be carried out on all patients. Please indicate the location of the independent centralized pathology reviews as stipulated in the protocol and the entry procedures and criteria for enrollment form. Identify the discrepant cases between the independent reviewer and the investigator and how this was adjudicated.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

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/s/

Patricia Garvey
9/2/03 01:46:12 PM
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Pages (including cover): 2

Date: August ²²14, 2003

Re: NDA 21-462 Alimta

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● **Comments:**

John,

Please provide the following request from the clinical pharmacology & biopharmaceutics reviewer. We would appreciate if you could provide us the information as soon as possible or no later than August 29, 2003.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products