

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-677**

**CHEMISTRY REVIEW(S)**

**NDA 21-677**

**ALIMTA™ (pemetrexed disodium) for Injection**

**Eli Lilly and Company**

**Chengyi Liang, Ph.D.  
Division of Oncological Drug Products**

**HFD-150/810**

## Chemistry Review Data Sheet

1. NDA #: 21-677
2. CHEM. REVIEW #: 1
3. REVIEW DATE: Aug. 13, 2004
4. REVIEWER: Chengyi Liang, Ph.D.

**5. PREVIOUS DOCUMENTS**

<u>Previous Documents</u>	<u>Document Date</u>
IND 40,061	11-16-1993
NDA 21-462	12-31-2002

**6. SUBMISSION(S) BEING REVIEWED:**

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	11-03-2003
Amendment	08-13-2004

**7. NAME & ADDRESS OF APPLICANT:**

<b>Name:</b>	Eli Lilly and Company
<b>Address:</b>	Lilly Corporate Center Indianapolis, IN 46285

<b>Representative:</b>	NA
<b>Telephone:</b>	NA

**8. DRUG PRODUCT NAME/CODE/TYPE:**

a. Proprietary:	Alimta
b. Nonproprietary Name/USAN:	Pemetrexed disodium
c. Code Name/#:	LY231514.2Na.7H <sub>2</sub> O
d. Chem. Type/Submission Priority	
Chem. Type	6
Submission Priority	S

**9. LEGAL BASIS FOR SUBMISSION:** N/A

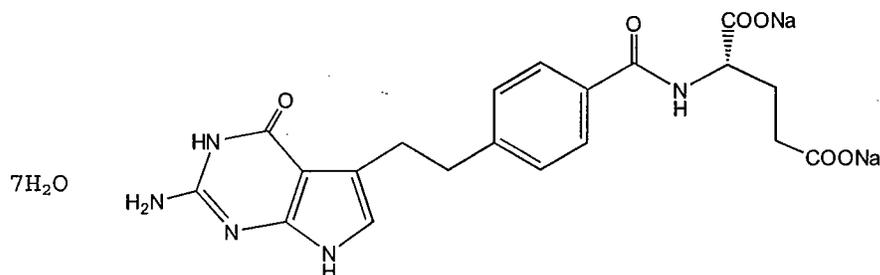
**10. PHARMACOL. CATEGORY/INDICATION:** Malignant pleural mesothelioma

**11. DOSAGE FORM:** for injection (lyophilized powder)

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12. STRENGTHS/POTENCY: 500 mg/vial
13. ROUTE OF ADMINISTRATION: IV
14. Rx/OTC DISPENSED:   x   Rx        OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)  
No
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR  
FORMULA, MOLECULAR WEIGHT:



N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid disodium salt

C<sub>20</sub>H<sub>19</sub>N<sub>5</sub>O<sub>6</sub>Na<sub>2</sub>·7H<sub>2</sub>O, MW = 597.49

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	III			1	adequate	11-20-2003	None
	III			1	adequate	9-2-2003	None
	V			1	adequate	9-24-2001	None

<sup>1</sup> Action codes for DMF Table:

1 - DMF Reviewed.

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

2 - Type 1 DMF

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- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

**B. Other Documents:**

Document	Application Number	Description
IND	40,061	LY231514
NDA	21-462	LY231514

**18. STATUS of NDA 21-462:**

Consults/CMC Related Reviews	Recommendation	Date	Reviewer
EES	Acceptable	12-10-2003	OC
OPDRA	Acceptable	7-11-2003	Charlie Hoppes
Methods Validation	Pending		
EA	Categorical exclusion is acceptable	11-20-2003	Chengyi Liang
Microbiology	Acceptable	10-29-2003	Paul Stinavage

## The Chemistry Review for NDA 21-677

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval as the applicant has cross-referenced entire CMC section to recently approved NDA 21-462.

#### B. Recommendation on Phase 4 (post marketing) Commitments, Agreements and/or Risk Management Steps, if Approvable

There are no phase 4 commitments.

### II. Summary of Chemistry Assessments

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

ALIMTA<sup>®</sup>, Pemetrexed for Injection, is a novel antifolate antineoplastic agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication. The drug substance, containing one chiral center, is synthesized in ~~two~~ steps and its structure is well characterized by x-ray and 2D NMR. ALIMTA drug product is supplied as a sterile lyophilized powder for intravenous infusion available in single-dose vials. Each 50 ml vial of ALIMTA contains pemetrexed disodium equivalent to 500 mg pemetrexed free acid and 500 mg of mannitol. Sodium hydroxide and, if necessary, hydrochloric acid are added to adjust pH. DP will be manufactured by Eli Lilly's French facility.

The drug substance, drug product, and the reconstituted drug product solution have good stability characteristics under various test conditions. The proposed 24 months shelf life of drug product is acceptable based on primary and supportive stability data.

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

The applicant proposes to use this drug product to treat the patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) previously treated with chemotherapy.

Alimta for Injection is a single-use, sterile, lyophilized powder packaged in a glass vial, containing

#### C. Basis for Approvability Recommendation

The information provided is adequate to support the approval of this NDA from a CMC perspective.



## CHEMISTRY REVIEW



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### III. Administrative

#### A. Reviewer's Signature

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Chengyi Liang, Ph.D.,  
Review Chemist

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Nallaperumal Chidambaram, Ph.D.  
Chemistry Team Leader

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Chengyi Liang, Ph.D.  
Aug., 2004

1 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-

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/s/

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Chengyi Liang  
8/13/04 03:26:35 PM  
CHEMIST

Nallaperumal Chidambaram  
8/13/04 04:08:28 PM  
CHEMIST