CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-462

Chemistry Review(s)

NDA 21-462

ALIMTA™ (pemetrexed disodium) for Injection

Eli Lilly and Company

CMC Review 2

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

HFD-150/810

Table of Contents

Chemistry Review Data Sheet

1. **NDA #:** 21-462

2. **CHEM. REVIEW #:** 2

3. **REVIEW DATE:** Dec.31, 2003

4. **REVIEWER:** Chengyi Liang, Ph.D.

5. **PREVIOUS DOCUMENTS**

Previous Documents	Document Date
IND 40,061	

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

Submission(s) Reviewed	Documnnent Date
Original (DS)	12-31-2002
Original (DP)	09-30-2003
Amendment	09-30-2003
Amendment	11-06-2003
Amendment	12-11-2003
Amendment	12-16-2003
Amendment	12-29-2003

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

Name: Eli Lilly and Company

Address: Lilly Corporate Center
Indianapolis, IN 46285

Representative:

Telephone:

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

a. Proprietary: Alimta

b. Nonproprietary Name/USAN: Pemetrexed disodium

c. Code Name/#: LY231514.2Na.7H_2O

d. Chem. Type/Submission Priority

Chem. Type 1

Submission Priority P

9. **LEGAL BASIS FOR SUBMISSION:** Fulfilled PDUFA filing requirements

10. PHARMACOL. CATEGORY/INDICATION: Malignant pleural mesothelioma

11. DOSAGE FORM: for injection (lyophilized powder)

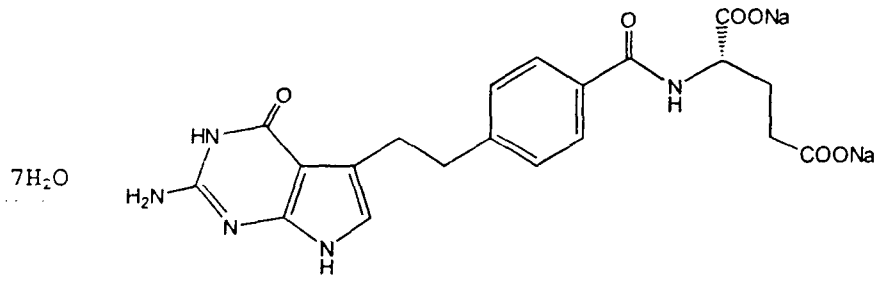
12. STRENGTHS/POTENCY: 500 mg/vial

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:



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

$C_{20}H_{19}N_5O_6Na_2.7H_2O$, MW = 597.49

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COM-PLETED	COM-MENTS
—	III	[redacted]	[redacted]	1	adequate	11-20-2003	None
—	III	[redacted]	[redacted]	1	adequate	9-2-2003	None
—	V	[redacted]	[redacted]			9-24-	None

			1	adequate	2001	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

B. Other Documents:

Document	Application Number	Description
IND	40,061	LY231514

18. STATUS:

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

Chengyi Liang, Ph.D.
Dec., 2003

The Chemistry Review for NDA 21-462

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended to be approved based on the submitted CMC information. The deficiencies related to the drug substance and drug product have been forwarded to the applicant during the fast-track, priority review cycle.

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®, 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 and its structure is well characterized by 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

Alimta for Injection is a single-use, sterile, lyophilized powder packaged in a glass vial, containing — of pemetrexed disodium equivalent to — mg of pemetrexed free acid including —overages as label claimed. Each 50 ml vial is reconstituted with 20 ml of commercially available 0.9% Sodium Chloride Injection without preservatives. The concentration of reconstituted drug product solution is 25 mg/ml of pemetrexed. The reconstituted pemetrexed solution must be further diluted to 100 mL with 0.9% Sodium Chloride Injection prior to intravenous infusion. The final

concentration of drug product solution to be administrated is 0.25 mg/ml.

C. Basis for Approvability Recommendation

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

III. Administrative

A. Reviewer's Signature

/S/

Chengyi Liang, Ph.D.,
Review Chemist

/S/

Richard Lostritto, Ph.D.
Chemistry Team Leader

B. Endorsement Block
Chemist Name/Date: Chengyi Liang, Ph.D.
Chemistry Team Leader Name/Date: Richard Lostritto, Ph.D.
Project Manager Name/Date: Patricia Garvey

C. CC Block
CC:

Orig. NDA 21-462
HFD-150 Division File
HFD-150/CLiang
HFD-150/RLostritto
HFD-150/PGarvey

Chemistry Assessment

The deficiencies related to the Alimta drug substance and drug product have been addressed satisfactorily by the applicant and the commitments are also provided to solve the remaining issues.

Chengyi Liang, Ph.D.
Dec., 2003

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/s/

Chengyi Liang
1/16/04 10:17:14 AM
CHEMIST

Richard Lostritto
1/19/04 12:31:03 PM
CHEMIST

NDA 21-462

ALIMTA™ (pemetrexed disodium) for Injection

Eli Lilly and Company

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

HFD-150/810

Table of Contents

Chemistry Review Data Sheet

1. **NDA #:** 21-462

2. **CHEM. REVIEW #:** 1

3. **REVIEW DATE:** Nov. 2, 2003

4. **REVIEWER:** Chengyi Liang, Ph.D.

5. **PREVIOUS DOCUMENTS**

Previous Documents	Document Date
IND 40,061	

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

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Original (DS)	12-31-2002
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7. **NAME & ADDRESS OF APPLICANT:**

Name:	Eli Lilly and Company
Address:	Lilly Corporate Center Indianapolis, IN 46285
Representative:	NA
Telephone:	NA

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

a. Proprietary:	Alimta
b. Nonproprietary Name/USAN:	Pemetrexed disodium
c. Code Name/#:	LY231514.2Na.7H_2O
d. Chem. Type/Submission Priority	
Chem. Type	1
Submission Priority	P (fast track, rolling)

9. **LEGAL BASIS FOR SUBMISSION:** Fulfilled PDUFA filing requirements

10. PHARMACOL. CATEGORY/INDICATION: Malignant pleural mesothelioma

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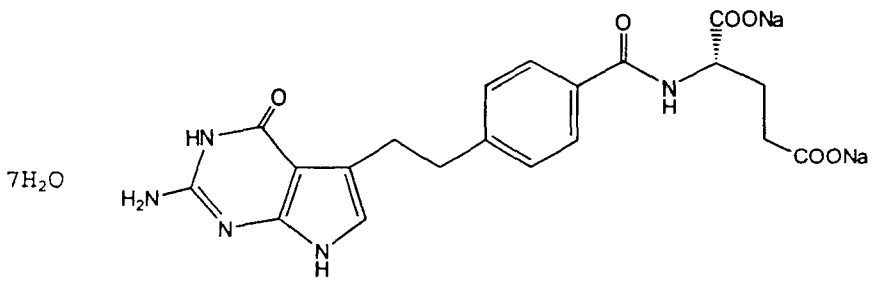

N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid disodium salt

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Chengyi Liang, Ph.D.
Dec., 2003

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Chengyi Liang, Ph.D.
Dec., 2003

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The drug substance, containing one chiral center, is and its structure is well characterized

The drug substance, drug product, and the reconstituted drug product solution exhibit good stability under various test conditions. The proposed shelf life for the drug productP is 24 months.

B. Description of How The Drug Product Is Intended To Be Used

Pemetrexed is an antifolate containing the structurally novel pyrrolopyrimidine-based nucleus that exerts its antineoplastic activity by disrupting crucial folate-dependent metabolic processes that are essential for cell replication and then causes mediates cell death by inhibiting DNA synthesis. The applicant proposes

C. Basis for Approvability Recommendation

The information provided is adequate to support the approval of

this NDA from a CMC perspective.

III. Administrative

A. Reviewer's Signature

/S/

Chengyi Liang, Ph.D.,
Review Chemist

/S/

Richard Lostritto, Ph.D.
Chemistry Team Leader

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HFD-150/CLiang
HFD-150/RLostritto
HFD-150/PGarvey

Chemistry Assessment

INTRODUCTION

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/s/

Chengyi Liang
12/31/03 02:40:02 PM
CHEMIST

Richard Lostritto
1/5/04 11:29:06 AM
CHEMIST