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

<table>
<thead>
<tr>
<th>Previous Documents</th>
<th>Document Date</th>
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</thead>
<tbody>
<tr>
<td>IND 40,061</td>
<td>11-16-1993</td>
</tr>
<tr>
<td>NDA 21-462</td>
<td>12-31-2002</td>
</tr>
</tbody>
</table>

6. SUBMISSION(S) BEING REVIEWED:

<table>
<thead>
<tr>
<th>Submission(s) Reviewed</th>
<th>Document Date</th>
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<tbody>
<tr>
<td>Original</td>
<td>11-03-2003</td>
</tr>
<tr>
<td>Amendment</td>
<td>08-13-2004</td>
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7. NAME & ADDRESS OF APPLICANT:

<table>
<thead>
<tr>
<th>Name:</th>
<th>Eli Lilly and Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address:</td>
<td>Lilly Corporate Center</td>
</tr>
<tr>
<td></td>
<td>Indianapolis, IN 46285</td>
</tr>
</tbody>
</table>

| Representative:     | NA                     |
| Telephone:          | NA                     |

8. DRUG PRODUCT NAME/CODE/TYPE:

| a. Proprietary:     | Alimta                 |
| b. Nonproprietary Name/USAN: | Pemetrexed disodium |
| c. Code Name/#:     | LY231514.2Na.7H2O      |

<table>
<thead>
<tr>
<th>d. Chem. Type/Submission Priority</th>
<th>Chem. Type</th>
<th>Submission Priority</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>6</td>
<td>S</td>
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</table>

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY/INDICATION: Malignant pleural mesothelioma

11. DOSAGE FORM: for injection (lyophilized powder)
CHEMISTRY REVIEW

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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:

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

\[C_{20}H_{19}N_{5}O_{8}Na_{2} \cdot 7H_{2}O, \text{ MW = 597.49}\]

17. RELATED/SUPPORTING DOCUMENTS:

<table>
<thead>
<tr>
<th>A. DMFS:</th>
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<tbody>
<tr>
<td>DMF #</td>
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<tr>
<td>III</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>V</td>
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</table>

^1 Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF

Chengyi Liang, Ph.D.
Aug., 2004
CHEMISTRY REVIEW

NDA 21-677 Review #1, ALIMTA™ (pemetrexed disodium) for Injection, Page 4 of 7

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:

<table>
<thead>
<tr>
<th>Document</th>
<th>Application Number</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>IND</td>
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<td>LY231514</td>
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<tr>
<td>NDA</td>
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<td>LY231514</td>
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18. STATUS of NDA 21-462:

<table>
<thead>
<tr>
<th>Consults/CMC Related Reviews</th>
<th>Recommendation</th>
<th>Date</th>
<th>Reviewer</th>
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<tbody>
<tr>
<td>EBS</td>
<td>Acceptable</td>
<td>12-10-2003</td>
<td>OC</td>
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<tr>
<td>OPDRA</td>
<td>Acceptable</td>
<td>7-11-2003</td>
<td>Charlie Hoppes</td>
</tr>
<tr>
<td>Methods Validation</td>
<td>Pending</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA</td>
<td>Categorical exclusion is acceptable</td>
<td>11-20-2003</td>
<td>Chengyi Liang</td>
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<tr>
<td>Microbiology</td>
<td>Acceptable</td>
<td>10-29-2003</td>
<td>Paul Stinavage</td>
</tr>
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</table>

The Chemistry Review for NDA 21-677

Chengyi Liang, Ph.D.
Aug., 2004
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®, 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 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.

Chengyi Liang, Ph.D.
Aug., 2004
III. Administrative
A. Reviewer’s Signature

Chengyi Liang, Ph.D.,
Review Chemist

Nallaperumal Chidambaram, Ph.D.
Chemistry Team Leader
Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential
§ 552(b)(4) Draft Labeling
§ 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry—____
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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

Nallaperumal Chidambaram
8/13/04 04:08:20 PM
CHEMIST