

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 5,344,932

Patentee(s) : Edward C. Taylor      Attn: Mail Stop Patent Ext.

Assignee     : Trustees of Princeton University

Issue Date   : September 6, 1994

LETTER OF TRANSMITTAL OF APPLICATION  
FOR EXTENSION OF PATENT TERM

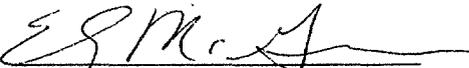
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450  
Sir:

Transmitted herewith for filing is an application for extension of term of U.S. Patent No. 5,344,932 and a duplicate thereof, certified as such.

Please charge the filing fee of \$1,120 to deposit account No. 05-0840 in the name of Eli Lilly and Company. An original and two copies of this paper are enclosed. The Commissioner is hereby authorized to charge any additional fees which may be required or credit any overpayment to account No. 05-0840.

The application transmitted herewith has been executed by the undersigned agent of the owner of record of the subject patent. Therefore, the present application is complete and entitled to a filing date of March 19, 2004, as indicated by the Certificate of Mailing by "Express Mail".

ELI LILLY AND COMPANY

By:   
Elizabeth A. McGraw  
Attorney for Applicant  
Registration No. 44,646  
Phone: 317-277-7443

Eli Lilly and Company  
Patent Division  
P.O. Box 6288  
Indianapolis, Indiana 46206-6288

March 17, 2004

2004E-0307

APP1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 5,344,932  
Patentee(s) : Edward C. Taylor  
Assignee : Trustees of Princeton University  
Attn : Mail Stop Patent Ext.  
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RECEIVED  
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REEXAM UNIT

REQUEST FOR EXTENSION OF  
PATENT TERM UNDER 35 U.S.C. 156

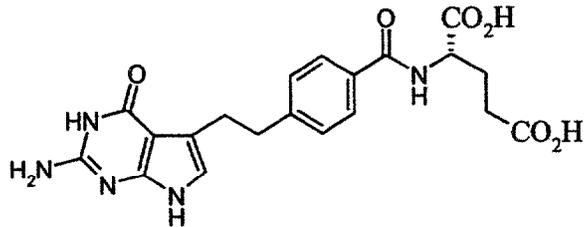
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. 156, Eli Lilly and Company, agent of the patent owner, by grant of an exclusive license to the patent, hereby requests an extension of the patent term of U.S. Patent No. 5,344,932 (hereinafter variously referred to either as "U.S. Patent No. 5,344,932" or "the '932 patent"). The following information is submitted in accordance with 35 U.S.C. 156(d) and 37 C.F.R. 1.710 et seq. and follows the numerical format set forth in 37 C.F.R. 1.740(a):

**(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:**

The approved product is pemetrexed, which has the chemical name, as assigned by Chemical Abstracts, L-Glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-. Pemetrexed has the following structure:



Pemetrexed is the active ingredient in the product Alimta<sup>®</sup> as can be seen from the Product Information sheet, e.g. lines 12-16, which is attached as Exhibit I.

Pemetrexed can exist in multiple tautomeric forms, see e.g. column 1, lines 48-55 of United States patent number 5,344,932. The aforereferenced nomenclature is in no way to be interpreted as limiting the protection of the drug product pemetrexed.

**(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:**

The regulatory review occurred under Section 505 of the Federal Food, Drug and Cosmetic Act (FFDCA), 21 U.S.C. 301 et seq. Section 505 provides for the submission and approval of new drug applications (NDAs) for human drug products meeting the definition of "new drug" under Section 201(p) of the Act.

**(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:**

Pemetrexed was approved by the Food and Drug Administration (FDA) for commercial marketing pursuant to Section 505 of the FFDCA on February 4, 2004.

**(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of**

when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient in the product Alimta<sup>®</sup> is pemetrexed. Pemetrexed had not previously been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act. Approval under the Federal Food, Drug and Cosmetic Act was received on February 4, 2004 for the use of pemetrexed in combination with cisplatin for the indication of malignant pleural mesothelioma under Section 505 of the FDCA.

**(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to §1.720(f) and an identification of the date of the last day on which the application could be submitted:**

The product was approved on February 4, 2004. The last day within the sixty day period permitted for submission of this application for extension of a patent is April 4, 2004. As this application is being hand-carried to the Office of Patent Legal Administration (Crystal Plaza 3, 3D09) on March 19, 2004, this application is timely filed within the permitted sixty day period.

**(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:**

The patent for which extension is being sought is:  
U.S. Patent No.: 5,344,932  
Inventor: Edward C. Taylor  
Issued: September 6, 1994  
Expires: September 6, 2011

**(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings:**

A complete copy of U.S. Patent No. 5,344,932 is attached hereto as Exhibit II.

**(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent:**

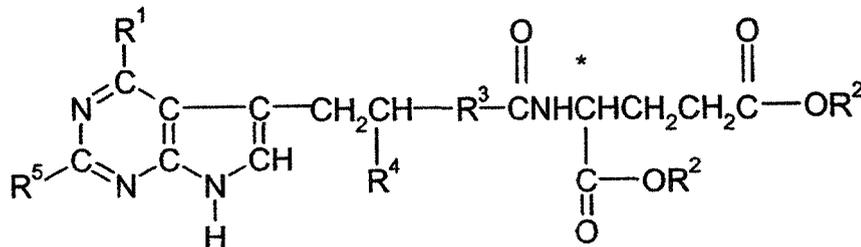
A copy of the receipt of maintenance fee payment is attached hereto as Exhibit III. No disclaimer, certificate of correction, or reexamination certificate has issued in connection with the '932 patent.

**(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on the approved product or a method of using or manufacturing the approved product:**

The '932 patent contains 7 claims. Claims 1 and 7 are independent claims; each one of remaining claims 2-6 depends directly from Claim 1. Claims 1, 2, 3 and 7 recite genus or species claims which read on the active ingredient contained in the approved product, pemetrexed.

For example, Claim 1 of the '932 patent recites a compound as follows:

Claim 1. A compound of the formula:



in which:

R<sup>1</sup> is -OH or -NH<sub>2</sub>;

R<sup>2</sup> is hydrogen or a pharmaceutically acceptable cation;  
R<sup>3</sup> is 1,4-phenylene unsubstituted or substituted with chloro, fluoro, methyl, methoxy, or trifluoromethyl;  
R<sup>4</sup> is hydrogen, or methyl;  
R<sup>5</sup> is amino; and  
the configuration about the carbon atom designated \* is S.

Specifically, pemetrexed is read upon when R<sup>1</sup> is -OH, R<sup>2</sup> is a pharmaceutically acceptable cation, R<sup>3</sup> is unsubstituted 1,4-phenylene, and R<sup>4</sup> is hydrogen. Thus, Claim 1, reads on pemetrexed. Claims 2, 3 and 7 each reads on the active ingredient contained in the approved product.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted, and the NDA or PLA number and the date on which the NDA was approved or the Product License issued;

(ii) For a patent claiming a new animal drug, the date a major health or environmental effects test on the drug was initiated and any available substantiation of that date, or the date an exemption under subsection (j) of Section 512 of the Federal Food, Drug, and Cosmetic Act became effective for such animal drug; the date on which a new animal drug application (NADA) was initially submitted and the NADA number; and the date on which the NADA was approved;

(iii) For a patent claiming a veterinary biological product, the date the authority to prepare an experimental biological product under the Virus-Serum-Toxin Act became effective; the date an application for a license was submitted under the Virus-Serum-Toxin Act; and the date the license issued;

(iv) For a patent claiming a food or color additive, the date a major health or environmental effects test on the additive was initiated and any available substantiation of that date; the date on which a petition for product approval under the Federal Food, Drug, and Cosmetic Act was initially submitted and the petition number; and the date on which the FDA published a *Federal Register* notice listing the additive for use;

(v) For a patent claiming a medical device, the effective date of the investigational device exemption (IDE) and the IDE number, if applicable, or the date on which the

applicant began the first clinical investigation involving the device, if no IDE was submitted, and any available substantiation of that date; the date on which the application for product approval or notice of completion of a product development protocol under section 515 of the Federal Food, Drug, and Cosmetic Act was initially submitted and the number of the application; and the date on which the application was approved or the protocol declared to be completed:

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On July 8, 1992 Eli Lilly and Company, the NDA owner of pemetrexed, submitted to the FDA a "Notice of Claimed Investigational Exemption for a New Drug" (IND) under Section 505(i) of the FDCA to permit the interstate shipment of LY231514 disodium (now known as pemetrexed) for the purpose of conducting clinical studies to support the approval of a subsequent NDA for pemetrexed. A copy of the letter transmitting the IND to the FDA is attached hereto as Exhibit IV. The FDA acknowledged receipt of the IND, and assigned the IND number 40,061. On August 24, 1992, during a . teleconference, Eli Lilly and Company was notified by the FDA that clinical investigation of compound LY231514 disodium may be initiated simultaneously upon submission of certain information. A confirmation letter was received from the FDA by Lilly on September 11, 1992, reiterating in writing the FDA position in the teleconference of August 24<sup>th</sup>. A copy of the letter is attached hereto as Exhibit VI. Lilly provided the FDA with information requested on September 10, 1992, and administered the first human dose of LY231514 disodium on September 29, 1992. Copies of these letters are attached hereto as Exhibits V and VI, respectively. As the clinical investigation of pemetrexed was allowed to be initiated simultaneously upon submission of the information requested, which information was submitted on September 10, 1992. Therefore, the beginning of the "regulatory review period" under 35 U.S.C. 156(g)(1) is September 10, 1992, the effective date of an exemption under Section 505(i).

Eli Lilly and Company submitted an NDA for pemetrexed, NDA 21-462, as a "rolling" submission as per the Fast Track Designation for Alimta granted by the FDA on June 10, 2002. The final stage, stage D, of the NDA submission was submitted on September 29, 2003. Copies of the letters transmitting all four stages (A through D) of the NDA are attached hereto as Exhibit VII. Stage D of the NDA submission was received by the FDA on September 30, 2003 as indicated by Exhibit VIII. Thus, for the purpose of the "regulatory review period" under 35 U.S.C. 156(g)(1), September 29, 2003, is the

date the new drug application for pemetrexed was initially submitted under Section 505.

The NDA described above was approved on February 4, 2004. Attached as Exhibit IX is a letter dated February 4, 2004, from the FDA to Eli Lilly and Company approving the NDA for pemetrexed. Thus, for the purpose of the "regulatory review period" under 35 U.S.C. 156(g)(1), February 4, 2004 is the date of approval of the NDA application for pemetrexed submitted on September 29, 2003.

**(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:**

During the applicable regulatory review period, Eli Lilly and Company was actively involved in obtaining NDA approval for pemetrexed. As discussed in Section (10) above, the IND for pemetrexed was submitted on July 8, 1992, the NDA was a rolling submission which was finally submitted on September 29, 2003, and the NDA was approved on February 4, 2004. Eli Lilly and Company was in close consultation with the FDA during the clinical studies conducted under the IND. Similarly, subsequent to the submission of the NDA, Eli Lilly and Company had numerous contacts and meetings with the FDA with respect to the NDA approval. The description of significant activities undertaken by Eli Lilly and Company with respect to pemetrexed during the applicable regulatory review period as set forth in Exhibit X attached hereto is illustrative of the activities undertaken.

**(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined:**

(a) Statement regarding eligibility of the '932 patent for extension under 35 U.S.C. 156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended from the original expiration date of the patent if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended, (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. 156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied in the present case:

(1) The term of U.S. Patent No. 5,344,932 expires on September 6, 2011. This application for patent term extension has, therefore, been submitted before the expiration of the patent term.

(2) The term of the '932 patent has never been extended.

(3) This application is being submitted by the NDA owner of pemetrexed who is also the agent of the owner of record of the '932 patent, as is evidenced in Exhibit XI. The applicant is the exclusive licensee of patent '932 by agreement executed between Eli Lilly & Co. and the Trustees of Princeton University on December 19, 1985. The Trustees of Princeton University are the owner of patent '932 by an Assignment recorded in the United States Patent and Trademark

Office on January 12, 1990, in Reel No. 5274, Frame No. 0016. This application is submitted in accordance with 35 U.S.C. 156(d) in that it is submitted by the agent of the patent owner in accordance with 37 CFR 1.730(c) within the sixty day period beginning on the date, February 4, 2004, the product received permission for marketing under the FDCA and contains the information required under 35 U.S.C. 156(d).

(4) As evidenced by the February 4, 2004, letter from the FDA (Exhibit IX), the product was subject to a regulatory review period under Section 505 of the FDCA before its commercial marketing or use.

(5) Finally, the permission for the commercial marketing of pemetrexed after regulatory review under Section 505 is the first permitted commercial marketing of pemetrexed. This is confirmed by the absence of any approved new drug application for pemetrexed prior to February 4, 2004.

(b) Statement as to length of extension claimed, including how the length of extension was determined:

The term of U.S. Patent No. 5,344,932 should be extended by 1784 days to July 25, 2016. This extension was determined as follows and as outlined in Supplemental Exhibit B(Exhibit XII).

As set forth in 35 U.S.C. 156(g)(1) and 37 C.F.R. 1.775(c), the regulatory review period equals the length of time on and between the effective date of the initial IND (September 10, 1992) and the initial submission of the NDA (September 29, 2003), a period of 4,037 days, plus the length of time between the initial submission of the NDA (September 29, 2003) to NDA approval (February 4, 2004), a period of 129 days. These two periods added together equal 4,166 days.

Pursuant to 35 U.S.C. 156(c) and 37 C.F.R. 1.775 (d)(1)(i), the term of the patent eligible for extension shall be extended by the time equal to the regulatory review period which occurs after the date the patent was issued. In this case, this is a period running from the date of patent issue, September 6, 1994, to the date of NDA approval, February 4, 2004, a period of 3,439 days.

As discussed in paragraph (11) above and as illustrated in Exhibit X, Eli Lilly and Company was continuously and diligently working toward securing NDA approval for pemetrexed. As Eli Lilly and Company acted with due diligence during the entire period of regulatory review, the 3,439 day period calculated above as the term of the patent eligible for extension should not be reduced for lack of diligence under 35 U.S.C. 156(c)(1) or 37 C.F.R. 1.775 (d)(1)(ii).

Pursuant to 35 U.S.C. 156(c)(2) and 37 C.F.R. 1.775 (d)(1)(iii), this 3,439 day period is to be reduced by one-half of the time from the effective date of the initial IND, September 29, 1992, or the date of patent issue, September 6, 1994, whichever is later, to the date of initial submission of the NDA, September 29, 2003, a period of 3,310 days. One half of this period is 1,655 days. The 3,310 day period is reduced by 1,655 days, leaving a revised regulatory period of 1,784 days.

Pursuant to 35 U.S.C. 156(c)(3), the term remaining on the '932 patent after the date of approval of pemetrexed, February 4, 2004, when added to the revised regulatory period may not exceed fourteen years. Fourteen years post approval expires on February 4, 2018. The term remaining on the patent added to the revised regulatory period is July 25, 2016, which does not exceed the fourteen year limit.

The period of patent term extension as calculated above is also subject to the provisions of 35 U.S.C. 156(g)(4) and 37 C.F.R. 1.775(d)(5-6). The patent to be extended issued after, and clinical evaluation of the approved product began, after the enactment of the statute, September 24, 1984. Since commercial marketing of the drug was approved after enactment of the statute, the five year maximum on extension as provided in 35 U.S.C. 156(g)(6)(B) and 37 C.F.R. 1.775(d)(6) is applicable. Thus, the term of the '932 patent is eligible for a 1,784 day extension until July 25, 2016.

**(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (See §1.765):**

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information that is material to the determination of entitlement to the extension sought herein.

**(14) The prescribed fee for receiving and acting upon the application for extension (See §1.20(j)):**

As indicated on the letter of transmittal submitted with this application, the Commissioner of Patents and Trademarks has been authorized to charge the filing fee of \$1,120.00, and any additional fees which may be required by this or any other related paper, or credit any overpayment, to Deposit Account No. 05-0840 in the name of Eli Lilly and Company.

**(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:**

Please address all correspondence to Elizabeth A. McGraw, Eli Lilly and Company, Patent Division/EAM, Lilly Corporate Center, Indianapolis, Indiana 46285. Please direct telephone calls to Elizabeth A. McGraw, 317-277-7443. Please direct facsimiles to 317-277-1917.

**(16) In accordance with 37 C.F.R. 1.740(b), submission of two additional copies of the present application. As requested by the Office of Legal Administration, two additional copies have been included, for a total of four copies:**

In addition to the present application for extension of the patent term of U.S. Patent No. 5,344,932, Applicant

also submits herewith three additional complete copies, for a total of four copies of the present application.

**(17) Signature Requirements: In accordance with 37 C.F.R. 1.730, submission of proof that the present application for extension of the term of U.S. Patent No. 5,344,932 is submitted on behalf of the patent owner by a registered practitioner who is authorized to act on behalf of the patent owner:**

Eli Lilly and Company, the current NDA holder and exclusive licensee of United States patent 5,344,932, is acting as agent for the Trustees of Princeton University, owner of United States patent 5,344,932 by assignment recorded on January 12, 1990, in Reel No. 5274, Frame No. 0016, for which an extension of the term is sought in the present application.

This application is submitted on behalf of Eli Lilly and Company by Elizabeth A. McGraw, Registration No. 44,646, authorized as an agent thereof with full power to transact all business in the United States Patent and Trademark Office in connection therewith. This is evidenced by the Power of Attorney submitted concurrently with this application.

Respectfully submitted,



Elizabeth A. McGraw  
Attorney for Applicant  
Registration No. 44,646  
Phone: 317-277-7443

Eli Lilly and Company  
Patent Division  
P.O. Box 6288  
Indianapolis, Indiana 46206-6288

March 17, 2004

EXHIBITS

- I. PRODUCT INFORMATION SHEET
- II. U.S. PATENT NO. 5,344,932
- III. MAINTENANCE FEE STATEMENT
- IV. LETTER TRANSMITTING THE IND TO THE FDA
- V. ELI LILLY LETTER PROVIDING THE FDA WITH INFORMATION REQUESTED ON SEPTEMBER 10, 1992
- VI. CONFIRMATION LETTER RECEIVED FROM THE FDA BY ELI LILLY ON SEPTEMBER 11, 1992
- VII. LETTERS TRANSMITTING ALL FOUR STAGES (A THROUGH D) OF THE NDA
- VIII. LETTER CONFIRMING STAGE D OF THE NDA WAS RECEIVED BY THE FDA ON SEPTEMBER 30, 2003
- IX. NDA APPROVAL LETTER
- X. DESCRIPTION OF SIGNIFICANT ACTIVITIES UNDERTAKEN BY ELI LILLY AND COMPANY WITH RESPECT TO PEMETREXED DISODIUM DURING THE APPLICABLE REGULATORY REVIEW PERIOD
- XI. LETTER INDICATING THAT ELI LILLY IS THE AGENT OF THE OWNER OF RECORD OF THE '932 PATENT
- XII. SUPPLEMENTAL EXHIBIT B

PA 9301 FSAMP

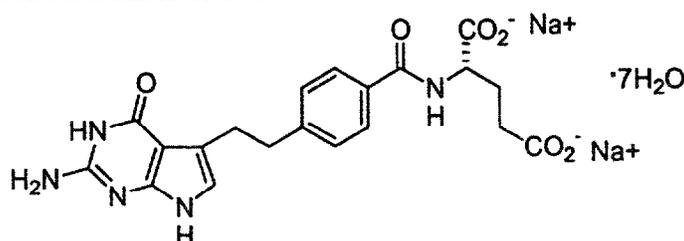
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## ALIMTA<sup>®</sup> pemetrexed for injection

5

### DESCRIPTION

6 ALIMTA<sup>®</sup>, pemetrexed for injection, is an antifolate antineoplastic agent that exerts its action  
7 by disrupting folate-dependent metabolic processes essential for cell replication. Pemetrexed  
8 disodium heptahydrate has the chemical name L-Glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-  
9 oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate. It is a white  
10 to almost-white solid with a molecular formula of C<sub>20</sub>H<sub>19</sub>N<sub>5</sub>Na<sub>2</sub>O<sub>6</sub>·7H<sub>2</sub>O and a molecular weight  
11 of 597.49. The structural formula is as follows:



12 ALIMTA is supplied as a sterile lyophilized powder for intravenous infusion available in  
13 single-dose vials. The product is a white to either light yellow or green-yellow lyophilized solid.  
14 Each 500-mg vial of ALIMTA contains pemetrexed disodium equivalent to 500 mg pemetrexed  
15 and 500 mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to  
16 adjust pH.

17

### CLINICAL PHARMACOLOGY

18

#### Pharmacodynamics

19 Pemetrexed is an antifolate containing the pyrrolopyrimidine-based nucleus that exerts its  
20 antineoplastic activity by disrupting folate-dependent metabolic processes essential for cell  
21 replication. In vitro studies have shown that pemetrexed inhibits thymidylate synthase (TS),  
22 dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT),  
23 all folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine  
24 nucleotides. Pemetrexed is transported into cells by both the reduced folate carrier and  
25 membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to  
26 polyglutamate forms by the enzyme folyl polyglutamate synthase. The polyglutamate forms are  
27 retained in cells and are inhibitors of TS and GARFT. Polyglutamation is a time- and  
28 concentration-dependent process that occurs in tumor cells and, to a lesser extent, in normal  
29 tissues. Polyglutamated metabolites have an increased intracellular half-life resulting in  
30 prolonged drug action in malignant cells.

31 Preclinical studies have shown that pemetrexed inhibits the in vitro growth of mesothelioma  
32 cell lines (MSTO-211H, NCI-H2052). Studies with the MSTO-211H mesothelioma cell line  
33 showed synergistic effects when pemetrexed was combined concurrently with cisplatin.

34 Absolute neutrophil counts (ANC) following single-agent administration of pemetrexed to  
35 patients not receiving folic acid and vitamin B<sub>12</sub> supplementation were characterized using  
36 population pharmacodynamic analyses. Severity of hematologic toxicity, as measured by the  
37 depth of the ANC nadir, is inversely proportional to the systemic exposure of ALIMTA. It was  
38 also observed that lower ANC nadirs occurred in patients with elevated baseline cystathionine or  
39 homocysteine concentrations. The levels of these substances can be reduced by folic acid and  
40 vitamin B<sub>12</sub> supplementation. There is no cumulative effect of pemetrexed exposure on ANC  
41 nadir over multiple treatment cycles.

42 Time to ANC nadir with pemetrexed systemic exposure (AUC), varied between 8 to 9.6 days  
43 over a range of exposures from 38.3 to 316.8  $\mu\text{g}\cdot\text{hr}/\text{mL}$ . Return to baseline ANC occurred 4.2 to  
44 7.5 days after the nadir over the same range of exposures.

#### 45 **Pharmacokinetics**

46 The pharmacokinetics of pemetrexed administered as a single agent in doses ranging from  
47 0.2 to 838  $\text{mg}/\text{m}^2$  infused over a 10-minute period have been evaluated in 426 cancer patients  
48 with a variety of solid tumors. Pemetrexed is not metabolized to an appreciable extent and is  
49 primarily eliminated in the urine, with 70% to 90% of the dose recovered unchanged within the  
50 first 24 hours following administration. The total systemic clearance of pemetrexed is  
51 91.8  $\text{mL}/\text{min}$  and the elimination half-life of pemetrexed is 3.5 hours in patients with normal  
52 renal function (creatinine clearance of 90  $\text{mL}/\text{min}$ ). The clearance decreases, and  
53 exposure (AUC) increases, as renal function decreases. Pemetrexed total systemic  
54 exposure (AUC) and maximum plasma concentration ( $C_{\text{max}}$ ) increase proportionally with dose.  
55 The pharmacokinetics of pemetrexed do not change over multiple treatment cycles. Pemetrexed  
56 has a steady-state volume of distribution of 16.1 liters. In vitro studies indicate that pemetrexed  
57 is approximately 81% bound to plasma proteins. Binding is not affected by degree of renal  
58 impairment.

#### 59 **Drug Interactions**

60 *Chemotherapeutic Agents* — Cisplatin does not affect the pharmacokinetics of pemetrexed and  
61 the pharmacokinetics of total platinum are unaltered by pemetrexed.

62 *Vitamins* — Coadministration of oral folic acid or intramuscular vitamin B<sub>12</sub> does not affect the  
63 pharmacokinetics of pemetrexed.

64 *Drugs Metabolized by Cytochrome P450 Enzymes* — Results from in vitro studies with human  
65 liver microsomes predict that pemetrexed would not cause clinically significant inhibition of  
66 metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2. No  
67 studies were conducted to determine the cytochrome P450 isozyme induction potential of  
68 pemetrexed, because ALIMTA used as recommended (once every 21 days) would not be  
69 expected to cause any significant enzyme induction.

70 *Aspirin* — Aspirin, administered in low to moderate doses (325 mg every 6 hours), does not  
71 affect the pharmacokinetics of pemetrexed. The effect of greater doses of aspirin on pemetrexed  
72 pharmacokinetics is unknown.

73 *Ibuprofen* — Daily ibuprofen doses of 400 mg qid reduce pemetrexed's clearance by about  
74 20% (and increase AUC by 20%) in patients with normal renal function. The effect of greater  
75 doses of ibuprofen on pemetrexed pharmacokinetics is unknown (*see Drug Interactions under*  
76 **PRECAUTIONS**).

#### 77 **Special Populations**

78 The pharmacokinetics of pemetrexed in special populations were examined in about  
79 400 patients in controlled and single arm studies.

80 *Geriatric* — No effect of age on the pharmacokinetics of pemetrexed was observed over a  
81 range of 26 to 80 years.

82 *Pediatric* — Pediatric patients were not included in clinical trials.

83 *Gender* — The pharmacokinetics of pemetrexed were not different in male and female  
84 patients.

85 *Race* — The pharmacokinetics of pemetrexed were similar in Caucasians and patients of  
86 African descent. Insufficient data are available to compare pharmacokinetics for other ethnic  
87 groups.

88 *Hepatic Insufficiency* — There was no effect of elevated AST (SGOT), ALT (SGPT), or total  
 89 bilirubin on the pharmacokinetics of pemetrexed. However, studies of hepatically impaired  
 90 patients have not been conducted (*see PRECAUTIONS*).

91 *Renal Insufficiency* — Pharmacokinetic analyses of pemetrexed included 127 patients with  
 92 reduced renal function. Plasma clearance of pemetrexed in the presence of cisplatin decreases as  
 93 renal function decreases, with increase in systemic exposure. Patients with creatinine clearances  
 94 of 45, 50, and 80 mL/min had 65%, 54%, and 13% increases, respectively in pemetrexed total  
 95 systemic exposure (AUC) compared to patients with creatinine clearance of 100 mL/min (*see*  
 96 **WARNINGS and DOSAGE AND ADMINISTRATION**).

### 97 **CLINICAL STUDIES**

98 *Malignant Pleural Mesothelioma* — The safety and efficacy of ALIMTA have been evaluated  
 99 in chemo-naïve patients with malignant pleural mesothelioma (MPM) in combination with  
 100 cisplatin.

101 **Randomized Trial:** A multi-center, randomized, single-blind study in 448 chemo-naïve patients  
 102 with MPM compared survival in patients treated with ALIMTA in combination with cisplatin to  
 103 survival in patients receiving cisplatin alone. ALIMTA was administered intravenously over  
 104 10 minutes at a dose of 500 mg/m<sup>2</sup> and cisplatin was administered intravenously over 2 hours at  
 105 a dose of 75 mg/m<sup>2</sup> beginning approximately 30 minutes after the end of administration of  
 106 ALIMTA. Both drugs were given on Day 1 of each 21-day cycle. After 112 patients were  
 107 treated, white cell and GI toxicity led to a change in protocol whereby all patients were given  
 108 folic acid and vitamin B<sub>12</sub> supplementation.

109 The primary analysis of this study was performed on the population of all patients randomly  
 110 assigned to treatment who received study drug (randomized and treated). An analysis was also  
 111 performed on patients who received folic acid and vitamin B<sub>12</sub> supplementation during the entire  
 112 course of study therapy (fully supplemented), as supplementation is recommended (*see*  
 113 **DOSAGE AND ADMINISTRATION**). Results in all patients and those fully supplemented  
 114 were similar. Patient demographics are shown in Table 1.  
 115

**Table 1: Summary of Patient Characteristics**

Patient characteristic	Randomized and Treated Patients		Fully Supplemented Patients	
	ALIMTA/cis (N=226)	Cisplatin (N=222)	ALIMTA/cis (N=168)	Cisplatin (N=163)
<b>Age (yrs)</b>				
Median (range)	61 (29-85)	60 (19-84)	60 (29-85)	60 (19-82)
<b>Gender (%)</b>				
Male	184 (81.4)	181 (81.5)	136 (81.0)	134 (82.2)
Female	42 (18.6)	41 (18.5)	32 (19.0)	29 (17.8)
<b>Origin (%)</b>				
Caucasian	204 (90.3)	206 (92.8)	150 (89.3)	153 (93.9)
Hispanic	11 (4.9)	12 (5.4)	10 (6.0)	7 (4.3)
Asian	10 (4.4)	4 (1.9)	7 (4.2)	3 (1.8)
African descent	1 (0.4)	0	1 (0.6)	0
<b>Stage at Entry (%)</b>				
I	16 (7.1)	14 (6.3)	15 (8.9)	12 (7.4)
II	35 (15.6)	33 (15.0)	27 (16.2)	27 (16.8)
III	73 (32.4)	68 (30.6)	51 (30.5)	49 (30.4)

IV	101 (44.9)	105 (47.2)	74 (44.3)	73 (45.3)
Unspecified	1 (0.4)	2 (0.9)	1 (0.6)	2 (1.2)
<b>Diagnosis/Histology<sup>a</sup> (%)</b>				
Epithelial	154 (68.1)	152 (68.5)	117 (69.6)	113 (69.3)
Mixed	37 (16.4)	36 (16.2)	25 (14.9)	25 (15.3)
Sarcomatoid	18 (8.0)	25 (11.3)	14 (8.3)	17 (10.4)
Other	17 (7.5)	9 (4.1)	12 (7.1)	8 (4.9)
<b>Baseline KPS<sup>b</sup> (%)</b>				
70-80	109 (48.2)	97 (43.7)	83 (49.4)	69 (42.3)
90-100	117 (51.8)	125 (56.3)	85 (50.6)	94 (57.7)

<sup>a</sup> Only 67% of the patients had the histologic diagnosis of malignant mesothelioma confirmed by independent review.

<sup>b</sup> Karnofsky Performance Scale.

Table 2 summarizes the survival results for all randomized and treated patients regardless of vitamin supplementation status and those patients receiving vitamin supplementation from the time of enrollment in the trial.

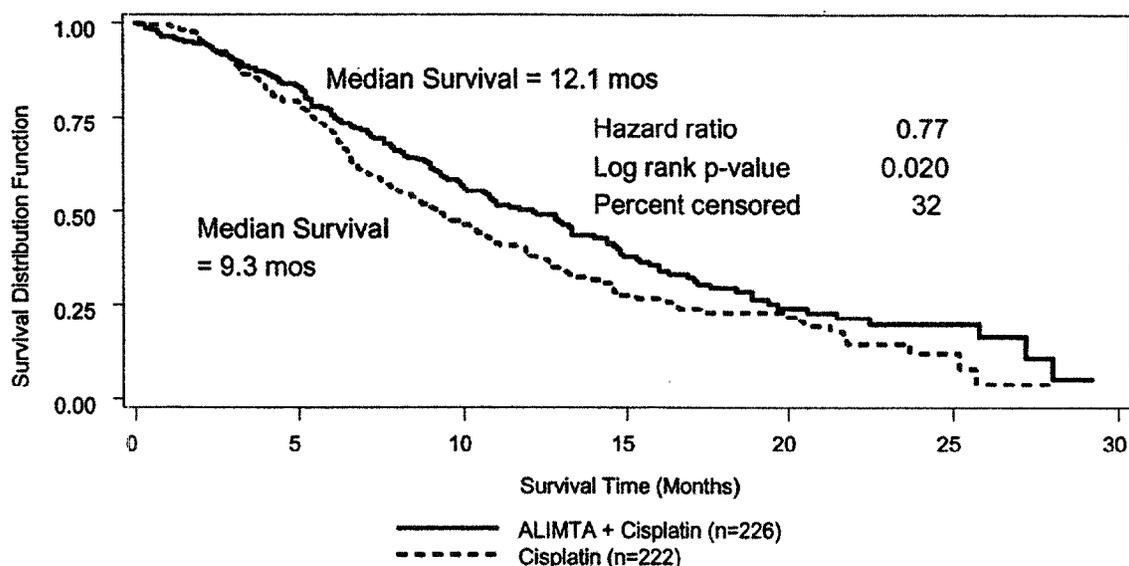
**Table 2: Efficacy of ALIMTA plus Cisplatin vs. Cisplatin in Malignant Pleural Mesothelioma**

Efficacy Parameter	Randomized and Treated Patients		Fully Supplemented Patients	
	ALIMTA/cis (N=226)	Cisplatin (N=222)	ALIMTA/cis (N=168)	Cisplatin (N=163)
Median overall survival (95% CI)	12.1 mos (10.0-14.4)	9.3 mos (7.8-10.7)	13.3 mos (11.4-14.9)	10.0 mos (8.4-11.9)
Hazard ratio	0.77		0.75	
Log rank p-value*	0.020		0.051	

\* p-value refers to comparison between arms.

Similar results were seen in the analysis of patients (N=303) with confirmed histologic diagnosis of malignant pleural mesothelioma. Exploratory demographic analyses showed no apparent differences in patients over or under 65. There were too few non-white patients to assess possible ethnic differences. The effect in women (median survival 15.7 months with the combination vs. 7.5 months on cisplatin alone), however, was larger than the effect in males (median survival 11 vs. 9.4 respectively). As with any exploratory analysis, it is not clear whether this difference is real or is a chance finding.

133



**Figure 1: Kaplan-Meier Estimates of Survival Time for ALIMTA plus Cisplatin and Cisplatin Alone in all Randomized and Treated Patients.**

134

135 Objective tumor response for malignant pleural mesothelioma is difficult to measure and  
 136 response criteria are not universally agreed upon. However, based upon prospectively defined  
 137 criteria, the objective tumor response rate for ALIMTA plus cisplatin was greater than the  
 138 objective tumor response rate for cisplatin alone. There was also improvement in lung function  
 139 (forced vital capacity) in the ALIMTA plus cisplatin arm compared to the control arm.

140 Patients who received full supplementation with folic acid and vitamin B<sub>12</sub> during study  
 141 therapy received a median of 6 and 4 cycles in the ALIMTA/cisplatin (N=168) and  
 142 cisplatin (N=163) arms, respectively. Patients who never received folic acid and vitamin B<sub>12</sub>  
 143 during study therapy received a median of 2 cycles in both treatment arms (N=32 and N=38 for  
 144 the ALIMTA/cisplatin and cisplatin arm, respectively). Patients receiving ALIMTA in the fully  
 145 supplemented group received a relative dose intensity of 93% of the protocol specified ALIMTA  
 146 dose intensity; patients treated with cisplatin in the same group received 94% of the projected  
 147 dose intensity. Patients treated with cisplatin alone had a dose intensity of 96%.

148

### INDICATIONS AND USAGE

149 ALIMTA in combination with cisplatin is indicated for the treatment of patients with  
 150 malignant pleural mesothelioma whose disease is unresectable or who are otherwise not  
 151 candidates for curative surgery.

152

### CONTRAINDICATIONS

153 ALIMTA is contraindicated in patients who have a history of severe hypersensitivity reaction  
 154 to pemetrexed or to any other ingredient used in the formulation.

155

### WARNINGS

#### Decreased Renal Function

156 ALIMTA is primarily eliminated unchanged by renal excretion. No dosage adjustment is  
 157 needed in patients with creatinine clearance  $\geq 45$  mL/min. Insufficient numbers of patients have  
 158 been studied with creatinine clearance  $< 45$  mL/min to give a dose recommendation. Therefore,  
 159 ALIMTA should not be administered to patients whose creatinine clearance is  $< 45$  mL/min (*see*  
 160 *Dose Reduction Recommendations under DOSAGE AND ADMINISTRATION*).  
 161

162 One patient with severe renal impairment (creatinine clearance 19 mL/min) who did not  
163 receive folic acid and vitamin B<sub>12</sub> died of drug-related toxicity following administration of  
164 ALIMTA alone.

### 165 **Bone Marrow Suppression**

166 ALIMTA can suppress bone marrow function, manifested by neutropenia, thrombocytopenia,  
167 and anemia (*see ADVERSE REACTIONS*); myelosuppression is usually the dose-limiting  
168 toxicity. Dose reductions for subsequent cycles are based on nadir ANC, platelet count, and  
169 maximum nonhematologic toxicity seen in the previous cycle (*see Dose Reduction*  
170 *Recommendations under DOSAGE AND ADMINISTRATION*).

### 171 **Need for Folate and Vitamin B<sub>12</sub> Supplementation**

172 Patients treated with ALIMTA must be instructed to take folic acid and vitamin B<sub>12</sub> as a  
173 prophylactic measure to reduce treatment-related hematologic and GI toxicity (*see DOSAGE*  
174 *AND ADMINISTRATION*). In clinical studies, less overall toxicity and reductions in  
175 Grade 3/4 hematologic and nonhematologic toxicities such as neutropenia, febrile neutropenia,  
176 and infection with Grade 3/4 neutropenia were reported when pretreatment with folic acid and  
177 vitamin B<sub>12</sub> was administered.

### 178 **Pregnancy Category D**

179 ALIMTA may cause fetal harm when administered to a pregnant woman. Pemetrexed was  
180 fetotoxic and teratogenic in mice at i.v. doses of 0.2 mg/kg (0.6 mg/m<sup>2</sup>) or 5 mg/kg (15 mg/m<sup>2</sup>)  
181 when given on gestation days 6 through 15. Pemetrexed caused fetal malformations (incomplete  
182 ossification of talus and skull bone) at 0.2 mg/kg (about 1/833 the recommended i.v. human dose  
183 on a mg/m<sup>2</sup> basis), and cleft palate at 5 mg/kg (about 1/33 the recommended i.v. human dose on  
184 a mg/m<sup>2</sup> basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced  
185 litter sizes. There are no studies of ALIMTA in pregnant women. Patients should be advised to  
186 avoid becoming pregnant. If ALIMTA is used during pregnancy, or if the patient becomes  
187 pregnant while taking ALIMTA, the patient should be apprised of the potential hazard to the  
188 fetus.

## 189 **PRECAUTIONS**

### 190 **General**

191 ALIMTA should be administered under the supervision of a qualified physician experienced in  
192 the use of antineoplastic agents. Appropriate management of complications is possible only  
193 when adequate diagnostic and treatment facilities are readily available. Treatment-related  
194 adverse events of ALIMTA seen in clinical trials have been reversible. Skin rash has been  
195 reported more frequently in patients not pretreated with a corticosteroid in clinical trials.  
196 Pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of  
197 cutaneous reaction (*see DOSAGE AND ADMINISTRATION*).

198 The effect of third space fluid, such as pleural effusion and ascites, on ALIMTA is unknown.  
199 In patients with clinically significant third space fluid, consideration should be given to draining  
200 the effusion prior to ALIMTA administration.

### 201 **Laboratory Tests**

202 Complete blood cell counts, including platelet counts and periodic chemistry tests, should be  
203 performed on all patients receiving ALIMTA. Patients should be monitored for nadir and  
204 recovery, which were tested in the clinical study before each dose and on days 8 and 15 of each  
205 cycle. Patients should not begin a new cycle of treatment unless the ANC is  $\geq 1500$  cells/mm<sup>3</sup>,  
206 the platelet count is  $\geq 100,000$  cells/mm<sup>3</sup>, and creatinine clearance is  $\geq 45$  mL/min.

**207 Drug Interactions**

208 ALIMTA is primarily eliminated unchanged renally as a result of glomerular filtration and  
209 tubular secretion. Concomitant administration of nephrotoxic drugs could result in delayed  
210 clearance of ALIMTA. Concomitant administration of substances that are also tubularly secreted  
211 (e.g., probenecid) could potentially result in delayed clearance of ALIMTA.

212 Although ibuprofen (400 mg qid) can be administered with ALIMTA in patients with normal  
213 renal function (creatinine clearance  $\geq 80$  mL/min), caution should be used when administering  
214 ibuprofen concurrently with ALIMTA to patients with mild to moderate renal insufficiency  
215 (creatinine clearance from 45 to 79 mL/min). Patients with mild to moderate renal insufficiency  
216 should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the  
217 day of, and 2 days following administration of ALIMTA.

218 In the absence of data regarding potential interaction between ALIMTA and NSAIDs with  
219 longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days  
220 before, the day of, and 2 days following ALIMTA administration. If concomitant administration  
221 of an NSAID is necessary, patients should be monitored closely for toxicity, especially  
222 myelosuppression, renal, and gastrointestinal toxicity.

**223 Drug/Laboratory Test Interactions**

224 None known.

**225 Carcinogenesis, Mutagenesis, Impairment of Fertility**

226 No carcinogenicity studies have been conducted with pemetrexed. Pemetrexed was clastogenic  
227 in the in vivo micronucleus assay in mouse bone marrow but was not mutagenic in multiple  
228 in vitro tests (Ames assay, CHO cell assay). Pemetrexed administered at i.v. doses of  
229 0.1 mg/kg/day or greater to male mice (about 1/1666 the recommended human dose on a mg/m<sup>2</sup>  
230 basis) resulted in reduced fertility, hypospermia, and testicular atrophy.

**231 Pregnancy**

232 Pregnancy Category D (*see* WARNINGS).

**233 Nursing Mothers**

234 It is not known whether ALIMTA or its metabolites are excreted in human milk. Because  
235 many drugs are excreted in human milk, and because of the potential for serious adverse  
236 reactions in nursing infants from ALIMTA, it is recommended that nursing be discontinued if the  
237 mother is treated with ALIMTA.

**238 Pediatric Use**

239 The safety and effectiveness of ALIMTA in pediatric patients have not been established.

**240 Geriatric Use**

241 Dose adjustments based on age other than those recommended for all patients have not been  
242 necessary (*see* Special Populations under CLINICAL PHARMACOLOGY and DOSAGE  
243 AND ADMINISTRATION).

**244 Gender**

245 Dose adjustments based on gender other than those recommended for all patients have not been  
246 necessary (*see* Special Populations under CLINICAL PHARMACOLOGY and DOSAGE  
247 AND ADMINISTRATION).

**248 Patients with Hepatic Impairment**

249 Patients with bilirubin  $>1.5$  times the upper limit of normal were excluded from clinical trials  
250 of ALIMTA. Patients with transaminase  $>3.0$  times the upper limit of normal were routinely  
251 excluded from clinical trials if they had no evidence of hepatic metastases. Patients with

252 transaminase from 3 to 5 times the upper limit of normal were included in the clinical trial of  
253 ALIMTA if they had hepatic metastases.

254 Dose adjustments based on hepatic impairment experienced during treatment with ALIMTA  
255 are provided in Table 6 (*see Special Populations under CLINICAL PHARMACOLOGY and*  
256 **DOSAGE AND ADMINISTRATION**).

#### 257 **Patients with Renal Impairment**

258 ALIMTA is known to be primarily excreted by the kidney. Decreased renal function will result  
259 in reduced clearance and greater exposure (AUC) to ALIMTA compared with patients with  
260 normal renal function. Cisplatin coadministration with ALIMTA has not been studied in patients  
261 with moderate renal impairment (*see Special Populations under CLINICAL*  
262 **PHARMACOLOGY**).

#### 263 **ADVERSE REACTIONS**

264 In Table 3 adverse events occurring in at least 5% of patients are shown along with important  
265 effects (renal failure, infection) occurring at lower rates. Adverse events equally or more  
266 common in the cisplatin group are not included. The adverse effects more common in the  
267 ALIMTA group were primarily hematologic effects, fever and infection, stomatitis/pharyngitis,  
268 and rash/desquamation.

**Table 3: Adverse Events\* in Fully Supplemented Patients Receiving  
ALIMTA plus Cisplatin in MPM  
CTC Grades (% incidence)**

	All Reported Adverse Events Regardless of Causality					
	ALIMTA/cis (N=168)			Cisplatin (N=163)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
<b>Laboratory</b>						
<b>Hematologic</b>						
Neutropenia	58	19	5	16	3	1
Leukopenia	55	14	2	20	1	0
Anemia	33	5	1	14	0	0
Thrombocytopenia	27	4	1	10	0	0
<b>Renal</b>						
Creatinine elevation	16	1	0	12	1	0
Renal failure	2	0	1	1	0	0
<b>Clinical</b>						
<b>Constitutional Symptoms</b>						
Fatigue	80	17	0	74	12	1
Fever	17	0	0	9	0	0
Other constitutional symptoms	11	2	1	8	1	1
<b>Cardiovascular General</b>						
Thrombosis/embolism	7	4	2	4	3	1
<b>Gastrointestinal</b>						
Nausea	84	11	1	79	6	0
Vomiting	58	10	1	52	4	1
Constipation	44	2	1	39	1	0
Anorexia	35	2	0	25	1	0
Stomatitis/pharyngitis	28	2	1	9	0	0
Diarrhea without colostomy	26	4	0	16	1	0
Dehydration	7	3	1	1	1	0
Dysphagia/esophagitis/ odynophagia	6	1	0	6	0	0
<b>Pulmonary</b>						
Dyspnea	66	10	1	62	5	2
<b>Pain</b>						
Chest pain	40	8	1	30	5	1
<b>Neurology</b>						
Neuropathy/sensory	17	0	0	15	1	0

Mood alteration/ depression	14	1	0	9	1	0
<b>Infection/Febrile Neutropenia</b>						
Infection without neutropenia	11	1	1	4	0	0
Infection with Grade 3 or Grade 4 neutropenia	6	1	0	4	0	0
Infection/febrile neutropenia-other	3	1	0	2	0	0
Febrile neutropenia	1	1	0	1	0	0
<b>Immune</b>						
Allergic reaction/ hypersensitivity	2	0	0	1	0	0
<b>Dermatology/Skin</b>						
Rash/desquamation	22	1	0	9	0	0

\* Refer to NCI CTC Version 2.0.

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271  
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277

Table 4 compares the incidence (percentage of patients) of CTC Grade 3/4 toxicities in patients who received vitamin supplementation with daily folic acid and vitamin B<sub>12</sub> from the time of enrollment in the study (fully supplemented) with the incidence in patients who never received vitamin supplementation (never supplemented) during the study in the ALIMTA plus cisplatin arm.

**Table 4: Selected Grade 3/4 Adverse Events Comparing Fully Supplemented versus Never Supplemented Patients in the ALIMTA plus Cisplatin arm (% incidence)**

Adverse Event Regardless of Causality <sup>a</sup> (%)	Fully Supplemented Patients (N=168)	Never Supplemented Patients (N=32)
Neutropenia	24	38
Thrombocytopenia	5	9
Nausea	12	31
Vomiting	11	34
Anorexia	2	9
Diarrhea without colostomy	4	9
Dehydration	4	9
Fever	0	6
Febrile neutropenia	1	9
Infection with Grade 3/4 neutropenia	1	6
Fatigue	17	25

<sup>a</sup> Refer to NCI CTC criteria for lab and non-laboratory values for each grade of toxicity (Version 2.0).

278  
279  
280  
281  
282

The following adverse events were greater in the fully supplemented group compared to the never supplemented group: hypertension (11%, 3%), chest pain (8%, 6%), and thrombosis/embolism (6%, 3%).

283 For fully supplemented patients treated with ALIMTA plus cisplatin, the incidence of CTC  
 284 Grade 3/4 fatigue, leukopenia, neutropenia, and thrombocytopenia were greater in patients  
 285 65 years or older as compared to patients younger than 65. No relevant effect for ALIMTA  
 286 safety due to gender or race was identified, except an increased incidence of rash in men (24%)  
 287 compared to women (16%).

## 288 OVERDOSAGE

289 There have been few cases of ALIMTA overdose. Reported toxicities included neutropenia,  
 290 anemia, thrombocytopenia, mucositis, and rash. Anticipated complications of overdose include  
 291 bone marrow suppression as manifested by neutropenia, thrombocytopenia, and anemia. In  
 292 addition, infection with or without fever, diarrhea, and mucositis may be seen. If an overdose  
 293 occurs, general supportive measures should be instituted as deemed necessary by the treating  
 294 physician.

295 In clinical trials, leucovorin was permitted for CTC Grade 4 leukopenia lasting  $\geq 3$  days,  
 296 CTC Grade 4 neutropenia lasting  $\geq 3$  days, and immediately for CTC Grade 4 thrombocytopenia,  
 297 bleeding associated with Grade 3 thrombocytopenia, or Grade 3 or 4 mucositis. The following  
 298 intravenous doses and schedules of leucovorin were recommended for intravenous use:  
 299  $100 \text{ mg/m}^2$ , intravenously once, followed by leucovorin,  $50 \text{ mg/m}^2$ , intravenously every 6 hours  
 300 for 8 days.

301 The ability of ALIMTA to be dialyzed is unknown.

## 302 DOSAGE AND ADMINISTRATION

### 303 ALIMTA is for Intravenous Infusion Only

#### 304 Combination Use With Cisplatin

305 *Malignant Pleural Mesothelioma* — The recommended dose of ALIMTA is  $500 \text{ mg/m}^2$   
 306 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. The  
 307 recommended dose of cisplatin is  $75 \text{ mg/m}^2$  infused over 2 hours beginning approximately  
 308 30 minutes after the end of ALIMTA administration. Patients should receive hydration consistent  
 309 with local practice prior to and/or after receiving cisplatin. See cisplatin package insert for more  
 310 information.

#### 311 Premedication Regimen

312 *Corticosteroid* — Skin rash has been reported more frequently in patients not pretreated with a  
 313 corticosteroid. Pretreatment with dexamethasone (or equivalent) reduces the incidence and  
 314 severity of cutaneous reaction. In clinical trials, dexamethasone 4 mg was given by mouth  
 315 twice daily the day before, the day of, and the day after ALIMTA administration.

316 *Vitamin Supplementation* — To reduce toxicity, patients treated with ALIMTA must be  
 317 instructed to take a low-dose oral folic acid preparation or multivitamin with folic acid on a daily  
 318 basis. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the  
 319 first dose of ALIMTA; and dosing should continue during the full course of therapy and for  
 320 21 days after the last dose of ALIMTA. Patients must also receive one (1) intramuscular  
 321 injection of vitamin B<sub>12</sub> during the week preceding the first dose of ALIMTA and every 3 cycles  
 322 thereafter. Subsequent vitamin B<sub>12</sub> injections may be given the same day as ALIMTA. In clinical  
 323 trials, the dose of folic acid studied ranged from 350 to 1000  $\mu\text{g}$ , and the dose of vitamin B<sub>12</sub> was  
 324 1000  $\mu\text{g}$ . The most commonly used dose of oral folic acid in clinical trials was 400  $\mu\text{g}$  (*see*  
 325 **WARNINGS**).

#### 326 Laboratory Monitoring and Dose Reduction Recommendations

327 *Monitoring* — Complete blood cell counts, including platelet counts, should be performed on  
 328 all patients receiving ALIMTA. Patients should be monitored for nadir and recovery, which were  
 329 tested in the clinical study before each dose and on days 8 and 15 of each cycle. Patients should  
 330 not begin a new cycle of treatment unless the ANC is  $\geq 1500 \text{ cells/mm}^3$ , the platelet count is

331  $\geq 100,000$  cells/mm<sup>3</sup>, and creatinine clearance is  $\geq 45$  mL/min. Periodic chemistry tests should be  
 332 performed to evaluate renal and hepatic function.

333 *Dose Reduction Recommendations* — Dose adjustments at the start of a subsequent cycle  
 334 should be based on nadir hematologic counts or maximum nonhematologic toxicity from the  
 335 preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery.  
 336 Upon recovery, patients should be retreated using the guidelines in Tables 5-7.

337

**Table 5: Dose Reduction for ALIMTA and Cisplatin - Hematologic Toxicities**

Nadir ANC $< 500/\text{mm}^3$ and nadir platelets $\geq 50,000/\text{mm}^3$ .	75% of previous dose (both drugs).
Nadir platelets $< 50,000/\text{mm}^3$ regardless of nadir ANC.	50% of previous dose (both drugs).

338

339 If patients develop nonhematologic toxicities (excluding neurotoxicity)  $\geq$  Grade 3 (except  
 340 Grade 3 transaminase elevations), ALIMTA should be withheld until resolution to less than or  
 341 equal to the patient's pre-therapy value. Treatment should be resumed according to guidelines in  
 342 Table 6.

343

**Table 6: Dose Reduction - Nonhematologic Toxicities<sup>a,b</sup>**

	Dose of ALIMTA (mg/m <sup>2</sup> )	Dose of Cisplatin (mg/m <sup>2</sup> )
Any Grade 3 <sup>c</sup> or 4 toxicities except mucositis	75% of previous dose	75% of previous dose
Any diarrhea requiring hospitalization	75% of previous dose	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose

344 <sup>a</sup> NCI Common Toxicity Criteria (CTC).

345 <sup>b</sup> Excluding neurotoxicity.

346 <sup>c</sup> Except Grade 3 transaminase elevation.

347

348 In the event of neurotoxicity, the recommended dose adjustments for ALIMTA and cisplatin  
 349 are described in Table 7. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is  
 350 experienced.

351

**Table 7: Dose Reduction for ALIMTA and Cisplatin - Neurotoxicity**

CTC Grade	Dose of ALIMTA (mg/m <sup>2</sup> )	Dose of Cisplatin (mg/m <sup>2</sup> )
0-1	100% of previous dose	100% of previous dose
2	100% of previous dose	50% of previous dose

352

353 ALIMTA therapy should be discontinued if a patient experiences any hematologic or  
 354 nonhematologic Grade 3 or 4 toxicity after 2 dose reductions (except Grade 3 transaminase  
 355 elevations) or immediately if Grade 3 or 4 neurotoxicity is observed.

356 *Elderly Patients* — No dose reductions other than those recommended for all patients are  
 357 necessary for patients  $\geq 65$  years of age.

358 *Children* — ALIMTA is not recommended for use in children, as safety and efficacy have not  
 359 been established in children.

360 *Renally Impaired Patients* — In clinical studies, patients with creatinine clearance  $\geq 45$  mL/min  
 361 required no dose adjustments other than those recommended for all patients. Insufficient  
 362 numbers of patients with creatinine clearance below 45 mL/min have been treated to make

363 dosage recommendations for this group of patients. Therefore, ALIMTA should not be  
 364 administered to patients whose creatinine clearance is <45 mL/min using the standard Cockcroft  
 365 and Gault formula (below) or GFR measured by Tc99m-DPTA serum clearance method:  
 366

$$\text{Males: } \frac{[140 - \text{Age in years}] \times \text{Actual Body Weight (kg)}}{72 \times \text{Serum Creatinine (mg/dL)}} = \text{mL/min}$$

Females: Estimated creatinine clearance for males  $\times$  0.85

367  
 368 Caution should be exercised when administering ALIMTA concurrently with NSAIDs to  
 369 patients whose creatinine clearance is <80 mL/min (*see Drug Interactions under*  
 370 **PRECAUTIONS**).

371 *Hepatically Impaired Patients* — ALIMTA is not extensively metabolized by the liver. Dose  
 372 adjustments based on hepatic impairment experienced during treatment with ALIMTA are  
 373 provided in Table 6 (*see Patients with Hepatic Impairment under PRECAUTIONS*).

### 374 **Preparation and Administration Precautions**

375 As with other potentially toxic anticancer agents, care should be exercised in the handling and  
 376 preparation of infusion solutions of ALIMTA. The use of gloves is recommended. If a solution  
 377 of ALIMTA contacts the skin, wash the skin immediately and thoroughly with soap and water. If  
 378 ALIMTA contacts the mucous membranes, flush thoroughly with water. Several published  
 379 guidelines for handling and disposal of anticancer agents are available.<sup>1-8</sup> There is no general  
 380 agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

381 ALIMTA is not a vesicant. There is no specific antidote for extravasation of ALIMTA. To  
 382 date, there have been few reported cases of ALIMTA extravasation, which were not assessed as  
 383 serious by the investigator. ALIMTA extravasation should be managed with local standard  
 384 practice for extravasation as with other non-vesicants.

### 385 **Preparation for Intravenous Infusion Administration**

- 386 1. Use aseptic technique during the reconstitution and further dilution of ALIMTA for  
 387 intravenous infusion administration.
- 388 2. Calculate the dose and the number of ALIMTA vials needed. Each vial contains 500 mg  
 389 of ALIMTA. The vial contains an excess of ALIMTA to facilitate delivery of label  
 390 amount.
- 391 3. Reconstitute 500-mg vials with 20 mL of 0.9% Sodium Chloride Injection (preservative  
 392 free) to give a solution containing 25 mg/mL ALIMTA. Gently swirl each vial until the  
 393 powder is completely dissolved. The resulting solution is clear and ranges in color from  
 394 colorless to yellow or green-yellow without adversely affecting product quality. The pH  
 395 of the reconstituted ALIMTA solution is between 6.6 and 7.8. **FURTHER DILUTION IS**  
 396 **REQUIRED.**
- 397 4. Parenteral drug products should be inspected visually for particulate matter and  
 398 discoloration prior to administration. If particulate matter is observed, do not administer.
- 399 5. The appropriate volume of reconstituted ALIMTA solution should be further diluted to  
 400 100 mL with 0.9% Sodium Chloride Injection (preservative free) and administered as an  
 401 intravenous infusion over 10 minutes.
- 402 6. Chemical and physical stability of reconstituted and infusion solutions of ALIMTA were  
 403 demonstrated for up to 24 hours following initial reconstitution, when stored at  
 404 refrigerated or ambient room temperature [see USP Controlled Room Temperature] and  
 405 lighting. When prepared as directed, reconstitution and infusion solutions of ALIMTA  
 406 contain no antimicrobial preservatives. Discard any unused portion.

407 Reconstitution and further dilution prior to intravenous infusion is only recommended with  
 408 0.9% Sodium Chloride Injection (preservative free). ALIMTA is physically incompatible with

409 diluents containing calcium, including Lactated Ringer's Injection, USP and Ringer's  
 410 Injection, USP and therefore these should not be used. Coadministration of ALIMTA with other  
 411 drugs and diluents has not been studied, and therefore is not recommended.

#### 412 HOW SUPPLIED

413 ALIMTA<sup>®</sup>, pemetrexed for injection is available in sterile single-use vials containing 500 mg  
 414 pemetrexed.

415 NDC 0002-7623-01 (VL7623): single-use vial with flip-off cap individually packaged in a  
 416 carton.

#### 417 Storage

418 ALIMTA, pemetrexed for injection, should be stored at 25°C (77°F); excursions permitted to  
 419 15-30°C (59-86°F) [see USP Controlled Room Temperature].

420 Chemical and physical stability of reconstituted and infusion solutions of ALIMTA were  
 421 demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated,  
 422 2-8°C (36-46°F), or at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP  
 423 Controlled Room Temperature]. When prepared as directed, reconstituted and infusion solutions  
 424 of ALIMTA contain no antimicrobial preservatives. Discard unused portion.

425 ALIMTA is not light sensitive.

426

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 428 Recommendations for Practice. Pittsburgh, PA: Oncology Nursing Society; 1999:32-41.
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447

448 Literature issued February 5, 2004

449

**Manufactured by Lilly France S.A.S.  
 F-67640 Fegersheim, France  
 for Eli Lilly and Company  
 Indianapolis, IN 46285, USA**

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**www.ALIMTA.com**

454 PA 9301 FSAMP

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456  
457**INFORMATION FOR PATIENTS AND CAREGIVERS**458  
459**ALIMTA<sup>®</sup> (uh-LIM-tuh)  
(pemetrexed for injection)**

460 Read the Patient Information that comes with ALIMTA before you start treatment and each time  
461 you get treated with ALIMTA. There may be new information. This leaflet does not take the  
462 place of talking to your doctor about your medical condition or treatment. Talk to your doctor if  
463 you have any questions about ALIMTA.

**464 What is ALIMTA?**

465 ALIMTA is a treatment for a type of cancer called malignant pleural mesothelioma. This cancer  
466 affects the inside lining of the chest cavity. ALIMTA is given with cisplatin, another anti-cancer  
467 medicine (chemotherapy). **To lower your chances of side effects of ALIMTA, you must also**  
468 **take folic acid and vitamin B<sub>12</sub> prior to and during your treatment with ALIMTA.** Your  
469 doctor will prescribe a medicine called a “corticosteroid” to take for 3 days during your  
470 treatment with ALIMTA. Corticosteroid medicines lower your chances of getting skin reactions  
471 with ALIMTA.

472 ALIMTA has not been studied in children.

**473 What should I tell my doctor before taking ALIMTA?**

474 Tell your doctor about all of your medical conditions, including if you:

- 475 • **are pregnant or planning to become pregnant.** ALIMTA may harm your unborn baby.
- 476 • **are breastfeeding.** It is not known if ALIMTA passes into breast milk. You should stop  
477 breastfeeding once you start treatment with ALIMTA.
- 478 • **are taking other medicines,** including prescription and nonprescription medicines,  
479 vitamins, and herbal supplements. ALIMTA and other medicines may affect each other  
480 causing serious side effects. Especially, tell your doctor if you are taking medicines  
481 called “nonsteroidal anti-inflammatory drugs” (NSAIDs) for pain or swelling. There are  
482 many NSAID medicines. If you are not sure, ask your doctor or pharmacist if any of your  
483 medicines are NSAIDs.

**484 How is ALIMTA given?**

- 485 • ALIMTA is slowly infused (injected) into a vein. The injection or infusion will last about  
486 10 minutes. You will usually receive ALIMTA once every 21 days (3 weeks).
- 487 • Cisplatin is infused in your vein for about 2 hours starting about 30 minutes after your  
488 treatment with ALIMTA.
- 489 • Your doctor will prescribe a medicine called a “corticosteroid” to take for 3 days during  
490 your treatment with ALIMTA. Corticosteroid medicines lower your chances for getting  
491 skin reactions with ALIMTA.
- 492 • **It is very important to take folic acid and vitamin B<sub>12</sub> during your treatment with**  
493 **ALIMTA to lower your chances of harmful side effects.** You must start taking  
494 350-1000 micrograms of folic acid every day for at least 5 days out of the 7 days before

495 your first dose of ALIMTA. You must keep taking folic acid every day during the time  
 496 you are getting treatment with ALIMTA, and for 21 days after your last treatment. You  
 497 can get folic acid vitamins over-the-counter. Folic acid is also found in many  
 498 multivitamin pills. Ask your doctor or pharmacist for help if you are not sure how to  
 499 choose a folic acid product. Your doctor will give you vitamin B<sub>12</sub> injections while you  
 500 are getting treatment with ALIMTA. You will get your first vitamin B<sub>12</sub> injection during  
 501 the week before your first dose of ALIMTA, and then about every 9 weeks during  
 502 treatment.

- 503 • You will have regular blood tests before and during your treatment with ALIMTA. Your  
 504 doctor may adjust your dose of ALIMTA or delay treatment based on the results of your  
 505 blood tests and on your general condition.

### 506 **What should I avoid while taking ALIMTA?**

- 507 • **Women who can become pregnant should not become pregnant during treatment**  
 508 **with ALIMTA.** ALIMTA may harm the unborn baby.
- 509 • **Ask your doctor before taking medicines called NSAIDs.** There are many NSAID  
 510 medicines. If you are not sure, ask your doctor or pharmacist if any of your medicines are  
 511 NSAIDs.

### 512 **What are the possible side effects of ALIMTA?**

513 Most patients taking ALIMTA will have side effects. Sometimes it is not always possible to tell  
 514 whether ALIMTA, another medicine, or the cancer itself is causing these side effects. **Call your**  
 515 **doctor right away if you have a fever, chills, diarrhea, or mouth sores.** These symptoms  
 516 could mean you have an infection.

517 The most common side effects of ALIMTA when taken with cisplatin are:

- 518 • **Stomach upset, including nausea, vomiting, and diarrhea.** You can obtain medicines  
 519 to help control some of these symptoms. Call your doctor if you get any of these  
 520 symptoms.
- 521 • **Low blood cell counts:**
  - 522 • **Low red blood cells.** Low red blood cells may make you feel tired, get tired  
 523 easily, appear pale, and become short of breath.
  - 524 • **Low white blood cells.** Low white blood cells may give you a greater chance for  
 525 infection. If you have a fever (temperature above 100.4°F) or other signs of  
 526 infection, call your doctor right away.
  - 527 • **Low platelets.** Low platelets give you a greater chance for bleeding. Your doctor  
 528 will do blood tests to check your blood counts before and during treatment with  
 529 ALIMTA.
- 530 • **Tiredness.** You may feel tired or weak for a few days after your ALIMTA treatments. If  
 531 you have severe weakness or tiredness, call your doctor.
- 532 • **Mouth, throat, or lip sores (stomatitis, pharyngitis).** You may get redness or sores in  
 533 your mouth, throat, or on your lips. These symptoms may happen a few days after  
 534 ALIMTA treatment. Talk with your doctor about proper mouth and throat care.
- 535 • **Loss of appetite.** You may lose your appetite and lose weight during your treatment.  
 536 Talk to your doctor if this is a problem for you.

537 • **Rash.** You may get a rash or itching during treatment. These usually appear between  
538 treatments with ALIMTA and usually go away before the next treatment. Call your  
539 doctor if you get a severe rash or itching.

540 Talk with your doctor, nurse or pharmacist about any side effect that bothers you or that doesn't  
541 go away.

542 These are not all the side effects of ALIMTA. For more information, ask your doctor, nurse or  
543 pharmacist.

#### 544 **General information about ALIMTA**

545 Medicines are sometimes prescribed for conditions other than those listed in patient information  
546 leaflets. ALIMTA was prescribed for your medical condition.

547 This leaflet summarizes the most important information about ALIMTA. If you would like more  
548 information, talk with your doctor. You can ask your doctor or pharmacist for information about  
549 ALIMTA that is written for health professionals. You can also call 1-800-LILLY-RX  
550 (1-800-545-5979) or visit [www.ALIMTA.com](http://www.ALIMTA.com).

551 Literature issued February 5, 2004

552 **Manufactured by Lilly France S.A.S.**  
553 **F-67640 Fegersheim, France**  
554 **for Eli Lilly and Company**  
555 **Indianapolis, IN 46285, USA**

556 **[www.ALIMTA.com](http://www.ALIMTA.com)**

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US005344932A

**United States Patent** [19][11] **Patent Number:** **5,344,932****Taylor**[45] **Date of Patent:** **Sep. 6, 1994**[54] **N-(PYRROLO(2,3-D)PYRIMIDIN-3-YLACYL)-GLUTAMIC ACID DERIVATIVES**[75] **Inventor:** **Edward C. Taylor, Princeton, N.J.**[73] **Assignee:** **Trustees of Princeton University,  
Princeton, N.J.**[21] **Appl. No.:** **674,541**[22] **Filed:** **Mar. 22, 1991****Related U.S. Application Data**[63] **Continuation of Ser. No. 448,742, Dec. 11, 1989, abandoned, and Ser. No. 479,655, Feb. 8, 1990, abandoned.**[51] **Int. Cl.<sup>5</sup> .....** **C07D 487/04; A61K 31/505**[52] **U.S. Cl. ....** **544/280**[58] **Field of Search .....** **544/280; 514/258**[56] **References Cited****U.S. PATENT DOCUMENTS**

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4,996,206	2/1991	Taylor et al. ....	514/258
4,997,838	3/1991	Akimoto et al. ....	514/258

**FOREIGN PATENT DOCUMENTS**

334636 9/1989 European Pat. Off. .

*Primary Examiner*—Emily Bernhard  
*Attorney, Agent, or Firm*—Mathews, Woodbridge & Collins

[57] **ABSTRACT**

N-(Acyl)glutamic acid derivatives in which the acyl group is substituted with 4-hydroxypyrrolo[2,3-d]-pyrimidin-3-yl group are antineoplastic agents. A typical embodiment is N-[4-(2-{4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl}ethyl)benzoyl]-L-glutamic acid.

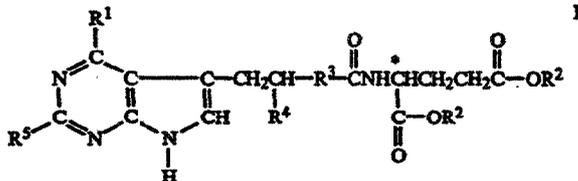
**7 Claims, No Drawings**

**N-(PYRROLO(2,3-D)PYRIMIDIN-3-YLACYL)-  
GLUTAMIC ACID DERIVATIVES**

**CROSS-REFERENCE TO RELATED  
APPLICATIONS**

This is a continuation of Ser. No. 07/448,742 filed Dec. 11, 1989 and Ser. No. 07/479,655 filed Feb. 8, 1990 both now abandoned.

The present invention pertains to glutamic acid derivatives having the formula:



in which:

R<sup>1</sup> is —OH or —NH<sub>2</sub>;

R<sup>2</sup> is hydrogen or a pharmaceutically acceptable cation;

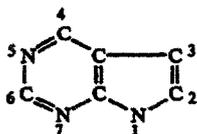
R<sup>3</sup> is 1,4-phenylene or 1,3-phenylene unsubstituted or substituted with chloro, fluoro, methyl, methoxy, or trifluoromethyl; thienediyl or furanediyl each unsubstituted or substituted with chloro, fluoro, methyl, methoxy, or trifluoromethyl; cyclohexanediyl; or alkanediyl;

R<sup>4</sup> is hydrogen, methyl, or hydroxymethyl;

R<sup>5</sup> is hydrogen, alkyl of 1 to 6 carbon atoms, or amino; and

the configuration about the carbon atom designated \* is S.

The compounds of this invention are herein described as embodying the pyrrolo[2,3-d]pyrimidine heterocyclic ring system which ring system is numbered as follows:



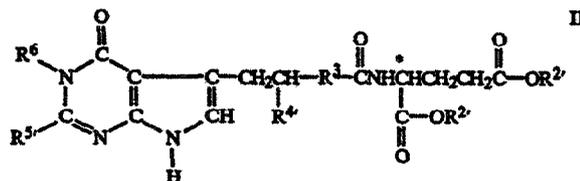
It will be appreciated that the pyrrolo[2,3-d]pyrimidines as depicted by Formula I are the tautomeric equivalent of the corresponding 5-H-6-oxo or 5-H-6-imino structures. Unless otherwise indicated, for simplicity's sake the compounds are depicted herein and named using the 6-hydroxy and 6-amino convention, it being understood the 5-H-6-oxo and 5-H-6-imino structures are fully equivalent.

The compounds of Formula I have an inhibitory effect on one or more enzymes which utilize folic acid, and in particular metabolic derivatives of folic acid, as a substrate. The compounds appear to be particularly active as inhibitors of thymidylate synthetase, which catalyses the methylation of deoxyuridylic acid to deoxythymidylic acid utilizing N<sup>5</sup>,N<sup>10</sup>-methylidene tetrahydrofolate as a coenzyme. The compounds thus can be used, alone or in combination, to inhibit the growth of those neoplasms which otherwise depend upon the inhibited enzyme.

The invention also pertains to the pharmaceutically acceptable salts of the compounds of Formula I, to

processes for the preparation of these compounds and their salts, to chemical intermediates useful in preparation of these compounds, to a method of combatting neoplastic growth in a mammal, and to pharmaceutical compositions containing these compounds or their salts.

A first group of useful chemical intermediates, which can be converted directly to the desired final compounds of Formula I through removal of protecting groups, are compounds of the formula:



in which:

R<sup>3</sup> is as defined above;

R<sup>2</sup> is hydrogen or a carboxy protecting group;

R<sup>4</sup> is hydrogen, methyl, hydroxymethyl, or hydroxymethyl carrying a hydroxy protecting group;

R<sup>5</sup> is hydrogen, alkyl, amino, or amino carrying a protecting group; and

R<sup>6</sup> is hydrogen or alkanoyloxy;

at least one of R<sup>2</sup>, R<sup>4</sup>, and R<sup>5</sup> being a carboxy protecting group, a hydroxy protecting group, or an amino protecting group, respectively.

The compounds of Formula I can be employed in the form of the free dicarboxylic acid, in which case both R<sup>2</sup> groups are hydrogen. Alternatively, the compounds often can be employed advantageously in the form of a pharmaceutically acceptable salt, in which case one or both R<sup>2</sup> groups are a pharmaceutically acceptable cation. Such salt forms, including hydrates thereof, are often crystalline and advantageous for forming solutions or formulating pharmaceutical compositions. Pharmaceutically acceptable salts with bases include those formed from the alkali metals, alkaline earth metals, non-toxic metals, ammonium, and mono-, di- and trisubstituted amines, such as for example the sodium, potassium, lithium, calcium, magnesium, aluminum, zinc, ammonium, trimethylammonium, triethanolammonium, pyridinium, and substituted pyridinium salts. The mono and disodium salts, particularly the disodium salt, are advantageous.

The group R<sup>3</sup> is a divalent group having at least two carbon atoms between the carbon atoms carrying the free valence bonds. R<sup>3</sup> for example can be a 1,4-phenylene or 1,3-phenylene ring which is unsubstituted or optionally substituted with chloro, fluoro, methyl, methoxy, or trifluoromethyl.

Alternatively, R<sup>3</sup> can be a thienediyl or furanediyl group, that is, a thiophene or furane ring from which two hydrogen atoms have been removed from two ring carbon atoms, as for example the thiene-2,5-diyl, thiene-3,5-diyl, thiene-2,4-diyl, and thiene-3,4-diyl ring systems and the furane-2,5-diyl, furane-3,5-diyl, furane-2,4-diyl, and furane-3,4-diyl ring systems, which ring systems can be unsubstituted or substituted with chloro, fluoro, methyl, methoxy, or trifluoromethyl. It will be appreciated that whereas in the abstract the thiene-3,5-diyl system is the equivalent of the thiene-2,4-diyl system, the two terms are utilized herein to denote the two isomeric forms resulting from the orientation of the thiophene ring within the remainder of the molecule:

e.g. the structure in which the depicted carboxy group adjacent to R<sup>3</sup> is in the 2-position of the thiophene ring and that in which the depicted carboxy group adjacent to R<sup>3</sup> is in the 3-position of the thiophene ring. The same conventions apply to the furane ring.

Alternatively, R<sup>3</sup> can be a cyclohexanediyl group, namely a divalent cycloalkane group of 6 carbon atoms such as cyclohexane-1,3-diyl and cyclohexane-1,4-diyl.

Alternatively, R<sup>3</sup> can be an alkanediyl, namely a straight or branched divalent aliphatic group of from 2 to 4 carbon atoms such as ethano, trimethylene, tetramethylene, propane-1,2-diyl, propane-2,3-diyl, butane-2,3-diyl, butane-1,3-diyl, and butane-2,4-diyl. It again will be appreciated that whereas in the abstract propane-1,2-diyl is the equivalent of propane-2,3-diyl, and butane-1,3-diyl the equivalent of butane-2,4-diyl, the two terms are utilized herein to denote the two isomeric forms resulting from the orientation of an unsymmetrical alkanediyl chain with respect to the remainder of the molecule.

The protecting groups designated by R<sup>2</sup>, R<sup>4</sup> and R<sup>5</sup> and utilized herein denote groups which generally are not found in the final therapeutic compounds but which are intentionally introduced at a stage of the synthesis in order to protect groups which otherwise might react in the course of chemical manipulations, thereafter being removed at a later stage of the synthesis. Since compounds bearing such protecting groups thus are of importance primarily as chemical intermediates (although some derivatives also exhibit biological activity), their precise structure is not critical. Numerous reactions for the formation and removal of such protecting groups are described in a number of standard works including, for example, "Protective Groups in Organic Chemistry", Plenum Press, London and New York, 1973; Greene, Th. W. "Protective Groups in Organic Synthesis", Wiley, New York, 1981; "The Peptides", Vol. I, Schröder and Lubke, Academic Press, London and New York, 1965; "Methoden der organischen Chemie", Houben-Weyl, 4th Edition, Vol.15/I, Georg Thieme Verlag, Stuttgart 1974, the disclosures of which are incorporated herein by reference.

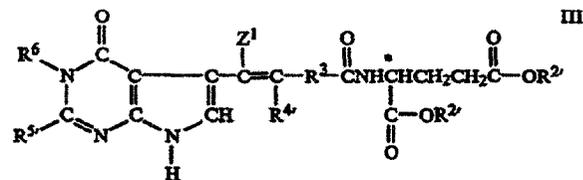
With respect to R<sup>2</sup>, a carboxy group can be protected as an ester group which is selectively removable under sufficiently mild conditions not to disrupt the desired structure of the molecule, especially a lower alkyl ester of 1 to 12 carbon atoms such as methyl or ethyl and particularly one which is branched at the 1-position such as t-butyl; and such lower alkyl ester substituted in the 1- or 2-position with (i) lower alkoxy, such as for example, methoxymethyl, 1-methoxyethyl, and ethoxymethyl, (ii) lower alkylthio, such as for example methylthiomethyl and 1-ethylthioethyl; (iii) halogen, such as 2,2,2-trichloroethyl, 2-bromoethyl, and 2-iodoethoxycarbonyl; (iv) one or two phenyl groups each of which can be unsubstituted or mono-, di- or tri-substituted with, for example lower alkyl such as tert.-butyl, lower alkoxy such as methoxy, hydroxy, halo such as chloro, and nitro, such as for example, benzyl, 4-nitrobenzyl, diphenylmethyl, di-(4-methoxyphenyl)methyl; or (v) aroyl, such as phenacyl. A carboxy group also can be protected in the form of an organic silyl group such as trimethylsilylethyl or tri-lower alkylsilyl, as for example trimethylsilyloxycarbonyl.

With respect to R<sup>4</sup>, a hydroxy group can be protected through the formation of acetals and ketals, as for example through formation of the tetrahydropyr-2-yloxy (THP) derivative.

With respect to R<sup>5</sup>, an amino group can be protected as an amide utilizing an acyl group which is selectively removable under mild conditions, especially formyl, a lower alkanoyl group which is branched  $\alpha$  to the carbonyl group, particularly tertiary alkanoyl such as pivaloyl, or a lower alkanoyl group which is substituted in the position  $\alpha$  to the carbonyl group, as for example trifluoroacetyl.

Preferred compounds of Formula I are those wherein R<sup>5</sup> is amino or hydrogen. Within this class, R<sup>1</sup> preferably is hydroxy, R<sup>3</sup> is 1,4-phenylene, and R<sup>4</sup> is hydrogen or hydroxymethyl. Also preferred within this class are the compounds in which R<sup>1</sup> is hydroxy, R<sup>3</sup> is thienediyl, and R<sup>4</sup> is hydrogen or hydroxymethyl.

The compounds of this invention can be prepared according to a first process through catalytic hydrogenation of a compound of the formula:



in which:

- Z<sup>1</sup> is hydrogen, or Z<sup>1</sup> taken together with R<sup>4</sup> is a carbon-carbon bond;
- R<sup>2</sup> is hydrogen or a carboxy protecting group;
- R<sup>3</sup> and R<sup>6</sup> are as defined above;
- R<sup>4</sup>, when taken independently of Z<sup>1</sup>, is hydrogen, methyl, hydroxymethyl, or hydroxymethyl substituted with a hydroxy protecting group; and
- R<sup>5</sup> is hydrogen, alkyl of 1 to 6 carbon atoms, amino, or an amino protecting group.

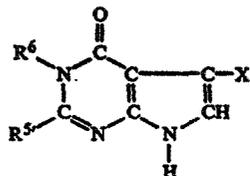
Suitable hydrogenation catalysts include noble metals and noble metal oxides such as palladium or platinum oxide, rhodium oxide, and the foregoing on a support such as carbon or calcium oxide.

When in Formula III, Z<sup>1</sup> taken together with R<sup>4</sup> is a carbon-carbon bond, that is, when a triple bond is present between the two carbon atoms to which Z<sup>1</sup> and R<sup>4</sup> are bound, R<sup>4</sup> in the hydrogenation product will be hydrogen. Absent any chirality in R<sup>3</sup> (or any protecting group encompassed by R<sup>2</sup>, R<sup>4</sup> and/or R<sup>5</sup>), the hydrogenation product will be a single enantiomer having the S-configuration about the carbon atom designated \*. This also is true when Z<sup>1</sup> and R<sup>4</sup> are each hydrogen, that is, when a double bond is present between the two carbon atoms to which Z<sup>1</sup> and R<sup>4</sup> are bound.

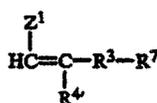
When, on the other hand, R<sup>4</sup> is other than hydrogen, a mixture of the R,S and S,S diastereomers is obtained. The diastereomeric mixture can be used therapeutically as such (after removal of the protecting groups) or can be separated mechanically as by chromatography. Alternatively, the individual diastereomers can be separated chemically by forming salts with a chiral acid, such as the individual enantiomers of 10-camphorsulfonic acid, camphoric acid, alphabromocamphoric acid, methoxyacetic acid, tartaric acid, diacetyltartaric acid, malic acid, pyrrolidone-5-carboxylic acid, and the like, and then freeing one or both of the individual diastereomeric bases, optionally repeating the process, so as to obtain either or both substantially free of the other; i.e., in a form having an optical purity of >95%.

The protecting groups encompassed by R<sup>2</sup>, R<sup>4</sup>, R<sup>5</sup>, and/or R<sup>6</sup> can be removed following hydrogenation through acidic or basic hydrolysis, as for example with hydrogen chloride to cleave an R<sup>4</sup> protecting group or with sodium hydroxide to cleave R<sup>2</sup> or R<sup>5</sup> protecting groups, thereby yielding the compounds of Formula I. Methods of removing the various protective groups are described in the standard references noted above and incorporated herein by reference.

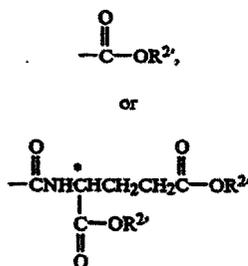
Compounds of Formula III can be prepared utilizing procedures analogous to those described in U.S. Pat. No. 4,818,819, utilizing however the corresponding halogenated pyrrolo[2,3-d]pyrimidine. Thus a pyrrolo[2,3-d]pyrimidine of the formula:



in which X is bromo or iodo, R<sup>5</sup>, and R<sup>6</sup> are as herein defined, is allowed to react with an unsaturated compound of the formula:



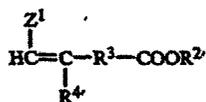
in which Z<sup>1</sup>, R<sup>3</sup> and R<sup>4</sup> are as herein defined, and R<sup>7</sup> is



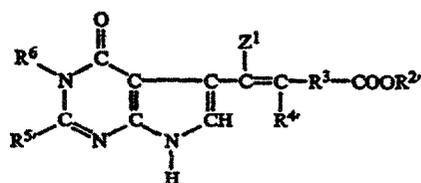
in which R<sup>2</sup> is as herein defined, in the presence of a palladium/trisubstituted phosphine catalyst of the type described in U.S. Pat. No. 4,818,819, the disclosure of which is incorporated herein by reference.

When R<sup>7</sup> is -CONHCH(COOR<sup>2</sup>)CH<sub>2</sub>CH<sub>2</sub>COOR<sup>2</sup>, the product of this coupling reaction is hydrogenated, and any protecting group removed, as described above.

Alternatively, a compound of Formula IV is allowed to react with a compound of the formula:



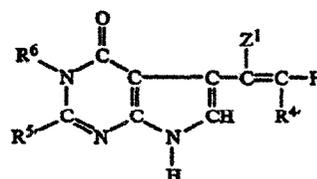
in which Z<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are as herein defined in the presence of a palladium/trisubstituted phosphine catalyst of the type described in U.S. Pat. No. 4,818,819 to yield an intermediate of the formula:



VII

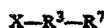
The product of Formula VII then can be hydrogenated, hydrolysed to remove the R<sup>2</sup> and R<sup>6</sup> protecting groups, and, optionally with intermediate protection of any amino group encompassed by R<sup>5</sup>, and coupled with a protected glutamic acid derivative in the manner described in U.S. Pat. No. 4,684,653 using conventional condensation techniques for forming peptide bonds such as DCC or diphenylchlorophosphonate, following which the protecting groups are removed.

In a further variant, compounds of Formula III can be prepared utilizing the procedures described in U.S. Pat. No. 4,818,819. Thus a compound of the formula:



VIII

in which Z<sup>1</sup>, R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> are as herein defined, is allowed to react with a compound of the formula:



IX

in which X, R<sup>3</sup>, and R<sup>7</sup> are as herein defined, in the presence of a palladium/trisubstituted phosphine catalyst of the type described in U.S. Pat. No. 4,818,819.

This variant of the process is particularly suitable for, but is not limited to, preparation of those compounds in which R<sup>4</sup> is hydroxymethyl, in which case R<sup>4</sup> in Formula VI is a protected hydroxymethyl group, as for example tetrahydropyran-2-yloxymethyl.

Compounds of Formula VIII also can be obtained by the methods of U.S. Pat. No. 4,818,819 by treating a compound of Formula IV with an unsaturated compound of the formula:



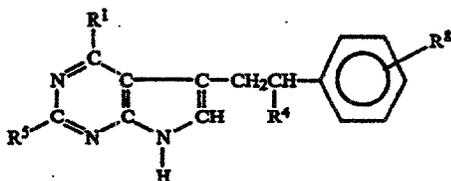
X

in which R<sup>4</sup> is methyl, a protected hydroxymethyl, or a trisubstituted silyl group in the presence of a palladium/trisubstituted phosphine catalyst of the type discussed above. This procedure is particularly suitable for, but is not limited to, preparation of those compounds in which R<sup>4</sup> is hydroxymethyl.

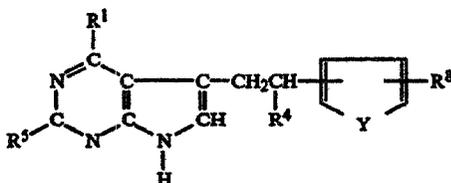
Although not always the case, the compounds of Formula IV in which R<sup>6</sup> is hydrogen can tend to be somewhat insoluble in solvents suitable for the reaction described in U.S. Pat. No. 4,818,819. In such instances, the compounds of Formula IV in which R<sup>6</sup> is hydrogen can be first treated with sodium hydride and a suitable alkyl alkanolate (such as chloromethyl pivalate) to introduce an alkanoyloxy group in the 5-position and increase solubility.

A useful subclass of compounds useful both as intermediates and for their effect on enzymes are derivatives

of Formula XI and XII lacking the glutamic acid side-chain:



and



in which:

- R<sup>1</sup> is —OH or —NH<sub>2</sub>;  
 R<sup>4</sup> is hydrogen, methyl, or hydroxymethyl;  
 R<sup>5</sup> is hydrogen, alkyl of 1 to 6 carbon atoms, or amino;  
 R<sup>8</sup> is hydrogen, chloro, fluoro, methyl, methoxy, trifluoromethyl, or carboxy; and  
 Y is —S— or —O—; and  
 the pharmaceutically acceptable salts thereof.

Compounds of Formulas XI and XII are obtained by allowing a compound of Formula VII to react with a compound of the formula:



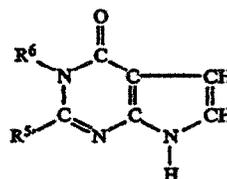
or



in which X, Y, and R<sup>8</sup> are as herein defined, by the methods of U.S. Pat. No. 4,818,819, namely in the presence of a palladium/trisubstituted phosphine catalyst, with the resulting coupled product being hydrogenated and hydrolysed to remove the R<sup>2</sup> protecting group. Typical compounds of Formulas XI and XII are 3-(2-phenylethyl)-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-[2-(3-fluorophenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-[2-(4-fluorophenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-[2-(4-carboxyphenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-[2-(4-methoxyphenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-[2-(4-methylphenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-(2-phenylethyl)-4-hydroxypyrrrolo[2,3-d]pyrimidine, 3-(2-phenylethyl)-4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine, 3-(2-phenyl-3-hydroxypropyl)-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-[2-(thien-2-yl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-[2-(thien-2-yl)ethyl]-4-hydroxypyrrrolo[2,3-d]pyrimidine, 3-[2-(thien-2-yl)ethyl]-4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine, 3-[2-(thien-3-yl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimi-

dine, 3-[2-(thien-3-yl)ethyl]-4-hydroxypyrrrolo[2,3-d]pyrimidine, 3-[2-(thien-3-yl)ethyl]-4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine, 3-[2-(fur-2-yl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-[2-(fur-2-yl)ethyl]-4-hydroxypyrrrolo[2,3-d]pyrimidine, 3-[2-(fur-2-yl)ethyl]-4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine, 3-[2-(fur-3-yl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, 3-[2-(fur-3-yl)ethyl]-4-hydroxypyrrrolo[2,3-d]pyrimidine, and 3-[2-(fur-3-yl)ethyl]-4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine.

As discussed above, the compounds of this invention can be prepared utilizing the palladium catalyzed coupling of various unsaturated compounds described in U.S. Pat. No. 4,818,819 and the glutamic acid coupling reactions described in U.S. Pat. No. 4,684,653, substituting the appropriate pyrrolo[2,3-d]pyrimidine for the pyrido[2,3-d]pyrimidine therein disclosed. The pyrrolo[2,3-d]pyrimidine intermediates of Formula IV above can be obtained by treating a compound of the formula:



XIII

in which R<sup>5</sup> and R<sup>6</sup> are as herein defined with N-iodosuccinimide to yield the corresponding 2,3-diiodopyrrolo[2,3-d]pyrimidine which then is treated with zinc and acetic acid to remove selectively the iodine atom in the 2-position, yielding the corresponding 3-iodopyrrolo[2,3-d]pyrimidine of Formula IV.

According to the foregoing processes, compounds of Formula II in which R<sup>1</sup> is —OH are obtained. When a compound of Formula I in which R<sup>1</sup> is —NH<sub>2</sub> is desired, a compound in which R<sup>1</sup> is —OH can be treated with 1,2,4-triazole and (4-chlorophenyl)dichlorophosphate and the product of this reaction then treated with concentrated ammonia.

As noted, the compounds of this invention have an effect on one or more enzymes which utilize folic acid, and in particular metabolic derivatives of folic acid, as a substrate. For example, N-(4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl)-L-glutamic acid demonstrates potent inhibitory effects against growth of human T-cell derived lymphoblastic leukemia cells (CCRF-CEM), exhibiting an IC<sub>50</sub> of 0.004 μ/ml. Cytotoxicity is not reversed by addition of purines such as hypoxanthine or by addition of aminoimidazolecarboxamide but is reversed by addition of thymidine, indicating specific inhibition in the thymidylate cycle and not in de novo purine synthesis. The compounds can be used, under the supervision of qualified professionals, to inhibit the growth of neoplasms including choriocarcinoma, leukemia, adenocarcinoma of the female breast, epidermid cancers of the head and neck, squamous or small-cell lung cancer, and various lymphosarcomas. The compounds can also be used to treat mycosis fungoides and psoriasis.

The compounds can be administered orally but preferably are administered parenterally, alone or in combination with other therapeutic agents including other anti-neoplastic agents, steroids, etc., to a mammal suffering from neoplasm and in need of treatment. Paren-

teral routes of administration include intramuscular, intrathecal, intravenous and intra-arterial. Dosage regimens must be titrated to the particular neoplasm, the condition of the patient, and the response but generally doses will be from about 10 to about 100 mg/day for 5-10 days or single daily administration of 250-500 mg, repeated periodically; e.g. every 14 days. While having a low toxicity as compared to other antimetabolites now in use, a toxic response often can be eliminated by either or both of reducing the daily dosage or administering the compound on alternative days or at longer intervals such as every three days. Oral dosage forms include tablets and capsules containing from 1-10 mg of drug per unit dosage. Isotonic saline solutions containing 20-100 mg/ml can be used for parenteral administration.

The following examples will serve to further illustrate the invention. In the NMR data, "s" denotes singlet, "d" denotes doublet, "t" denotes triplet, "q" denotes quartet, "m" denotes multiplet, and "br" denotes a broad peak.

#### EXAMPLE 1

##### 3-Iodo-4-hydroxy-6-Pivaloylaminopyrrolo[2,3-d]pyrimidine

A mixture of 3.0 g (0.02 mole) of 4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine and 8.4 g (0.07 mol) of pivaloyl chloride in 40 mL of pyridine is stirred for 30 minutes at from 80° to 90° C., the mixture then evaporated to dryness, and the residue dissolved in 30 mL of methanol. Addition of 10% aqueous ammonia yields 4.2 g (89%) of 4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine which can be further purified by chromatography through silica gel, eluting with 8% methanol in methylene chloride. mp 295° C. <sup>1</sup>NMR (d<sub>6</sub>-DMSO) δ 1.20 (s, 9H), 6.37 (d, J=3.4 Hz, 1H), 6.92 (d, J=3.4 Hz, 1H), 10.78 (s, 1H), 11.56 (s, 1H), 11.82 (s, 1H). Anal. Calc. for C<sub>11</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.16; H, 6.01; N, 23.67.

To a mixture of 4.7 g (20 mmol) of 4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine in 200 mL of dimethylformamide are added 9.9 g (44 mmol) of N-iodosuccinamide. The mixture is stirred at ambient temperature in the dark for 18 hours. Most of the dimethylformamide is removed by evaporation and the residual slurry poured into 300 mL of water. The resulting solid is collected by filtration and dried under vacuum over phosphorus pentoxide to yield 2,3-diiodo-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine which can be purified further by chromatography over silica eluting with 2.5% methanol in methylene chloride. mp >290° C. <sup>1</sup>NMR (d<sub>6</sub>-DMSO) δ 1.18 (s, 9H), 10.85 (s, 1H), 11.85 (s, 1H), 12.42 (s, 1H). Anal. Calc. for C<sub>11</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>I<sub>2</sub>: C, 27.18; H 2.49; N, 11.53; I, 52.22. Found: C, 27.51; H, 2.51; N, 11.27; I, 52.02.

In a similar fashion but starting with 4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine and 4-hydroxypyrrrolo[2,3-d]pyrimidine (7-deazahypoxanthine) there are respectively obtained 2,3-diiodo-4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine, mp 233° C., and 2,3-diiodo-4-hydroxypyrrrolo[2,3-d]pyrimidine, mp >205° C. (compound loses iodine). <sup>1</sup>NMR (d<sub>6</sub>-DMSO) δ 7.79 (s, 1H), 11.93 (s, 1H), 12.74 (s, 1H).

To a mixture of 4.86 g of 2,3-diiodo-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine in 100 mL of glacial acetic acid and 25 mL of water are added 1.3 g (20 mmol) of zinc powder. The mixture is stirred at ambient temperature for 18 hours, diluted with 500 mL

of water, and cooled. The solid is collected through filtration and dried under vacuum over phosphorus pentoxide to yield 3-iodo-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine which can be purified further by chromatography over silica eluting with 2.5% methanol in methylene chloride. mp >240° C. <sup>1</sup>NMR (d<sub>6</sub>-DMSO) δ 1.20 (s, 9H), 7.12 (d, J=1.8 Hz, 1H), 10.82 (s, 1H), 11.79 (s, 1H), 11.89 (s, 1H). Anal. Calc. for C<sub>11</sub>H<sub>13</sub>N<sub>4</sub>O<sub>2</sub>I: C, 36.69; H 3.64; N, 15.56; I, 35.24. Found: C, 36.91; H, 3.58; N, 15.65; I, 35.56.

In a similar fashion from 2,3-diiodo-4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine and 2,3-diiodo-4-hydroxypyrrrolo[2,3-d]pyrimidine, there are respectively obtained 3-iodo-4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine m.p 245° C., and 3-iodo-4-hydroxypyrrrolo[2,3-d]pyrimidine, mp >245° C. (compound loses iodine). <sup>1</sup>NMR (d<sub>6</sub>-DMSO) δ 7.20 (d, J=2.2 Hz, 1H), 7.82 (d, J=2.8 Hz, 1H), 11.85 (d, J=1.1 Hz, 1H), 12.17 (s, 1H).

#### EXAMPLE 2

##### Dimethyl

##### N-[4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate

To a mixture of 3.6 g (10 mmol) of well-dried 3-iodo-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine in 40 mL of dimethylformamide are added 4.0 g (13.19 mmol) of dimethyl N-(4-ethynylbenzoyl)-L-glutamate, 0.38 g of copper (I) iodide, 3 mL of triethylamine, and 1.0 g of tetrakis-(triphenylphosphine)palladium. This mixture is stirred at ambient temperatures for two hours and then poured into 500 mL of water. The solid is collected by filtration, air dried, and then refluxed in 200 mL of methanol. The mixture is cooled and the solid collected by filtration, dissolved in two liters of 10% methanol in methylene chloride, and chromatographed over silica. Initial black bands are rechromatographed and the combined colorless bands from the first and second runs are evaporated to give 3.5 g of dimethyl N-[4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate which can be purified further by recrystallization from 50% methanol in methylene chloride. mp 280°-285° C. <sup>1</sup>NMR (d<sub>6</sub>-DMSO) δ 1.21 (s, 9H), 1.96-2.15 (m, 2H), 2.44 (t, J=7.5 Hz, 2H) 3.56 (s, 3H), 3.62 (s, 3H), 4.40-4.45 (m, 1H), 7.43 (s, 1H), 7.53 (d, J=8.4 Hz, 2H), 7.87 (d, J=8.4 Hz, 2H), 8.82 (d, J=7.4 Hz, 1H), 10.95 (s, 1H), 11.95 (s, 1H). Anal. Calc. for C<sub>27</sub>H<sub>29</sub>N<sub>5</sub>O<sub>7</sub>: C, 60.56; H, 5.46; N, 13.08. Found: C, 60.55; H, 5.46; N, 12.89.

In a similar fashion by substituting an equivalent amount of dimethyl N-(pent-4-ynoyl)-L-glutamate, dimethyl N-(hept-6-enoyl)-L-glutamate, and dimethyl N-(hex-5-ynoyl)-L-glutamate for dimethyl N-(4-ethynylbenzoyl)glutamate in the foregoing procedure, there are obtained dimethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)pent-4-ynoyl]-L-glutamate, dimethyl N-[7-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)hept-6-enoyl]-L-glutamate, and dimethyl N-[6-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)hex-5-ynoyl]-L-glutamate.

Dimethyl N-(hex-5-ynoyl)-L-glutamate can be obtained in the manner described generally in U.S. Pat. No. 4,882,334 issued Nov. 21, 1989, the disclosure of which is incorporated herein by reference, by allowing hex-5-ynoic acid chloride (obtained by treating hex-5-ynoic acid with thionyl chloride) to react with dimethyl

L-glutamate in the presence of an acid acceptor such as triethylamine. Hex-5-ynoic acid in turn can be prepared, for example, by alkaline hydrolysis of 5-cyanopent-1-yne.

## EXAMPLE 3

## Diethyl

N-[4-(1-hydroxy-3-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-yl)benzoyl]glutamate

A mixture of 14.6 g of 3-iodo-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, 7.6 g of 2-(2-propynyloxy)-tetrahydropyran, 798 mg (10%) of palladium chloride, 2.36 g (20%) of triphenyl phosphine, 428 mg (5%) of cuprous iodide, 45 ml of triethyl amine and 700 ml of acetonitrile is heated at reflux under nitrogen for 12 hours. There then are added to the hot reaction mixture 3.2 g of 2-(2-propynyloxy)-tetrahydropyran and reflux is continued for an additional 12 hours. After heating for a total of 24 hours under reflux, the solvent is removed under reduced pressure, and the residue filtered through silica gel using 2% methanol in methylene chloride. This filtrate is concentrated and chromatographed on silica gel eluting with 20:1 ethyl acetate:hexane mixture to give 3-(3-tetrahydropyr-2-yloxyprop-1-yn-1-yl)-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine which is further purified by recrystallization with ethyl acetate.

A mixture of 2 g of 3-(3-tetrahydropyr-2-yloxyprop-1-yn-1-yl)-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, 40 ml of methanol, 20 ml of chloroform, 40 mg of 5% palladium on barium sulfate, and 40 mg of synthetic quinoline is stirred under 1 atmosphere hydrogen pressure for 40 min. The solvent then is removed by evaporation and the residue diluted with methylene chloride. The methylene chloride solution is filtered through silica gel with 2% methanol in methylene chloride to remove catalyst and the filtrate then concentrated to give an oil which upon adding ether yields 3-(3-tetrahydropyr-2-yloxyprop-1-en-1-yl)-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine which can be further purified through column chromatography eluting with ethyl acetate and recrystallization using ethyl acetate.

A mixture containing 3.48 g of 3-(3-tetrahydropyr-2-yloxyprop-1-en-1-yl)-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, 3.12g (1.2 equiv.) of diethyl N-(4-iodobenzoyl)glutamate, 546 mg (20%) of tris-(2-methylphenyl)phosphine, 201 mg (10%) of palladium acetate and 85.5 mg (5%) of cuprous iodide in 15 ml of triethylamine and 240 ml of acetonitrile is heated at reflux under nitrogen. After 12 hours, 1.17 g of diethyl N-(4-iodobenzoyl)glutamate are added and the reaction mixture is heated at reflux under nitrogen for an additional 12 hours. The reaction mixture then is concentrated under reduced pressure and the residue chromatographed on silica gel, eluting with 20:1 ethyl acetate:hexane. (Any recovered starting material can be recycled through the foregoing procedure.) The concentrated material is dissolved in 1:5 ethyl acetate:ether and this solution is refrigerated for 15 hours. The solid which forms is collected by filtration, washed with cold ethyl acetate and dried to yield diethyl N-[4-(1-(tetrahydropyr-2-yloxy)-3-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-en-2-yl)benzoyl]glutamate.

## EXAMPLE 4

## Dimethyl

N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethynyl]thien-2-ylcarbonyl-L-glutamate

A mixture of 2.0 g of 3-iodo-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, 1.2 g. of trimethylsilylacetylene, 0.1 g of palladium chloride, 0.23 g of triphenylphosphine, 0.06 g of cuprous iodide, and 2.6 g of triethylamine in 100 mL of acetonitrile is heated in a sealed tube for 1.5 hours at 50° C. and then at reflux for 3 hours. The solvent is removed under reduced pressure and the residue triturated with 1:1 ethyl acetate:hexanes and filtered. The solid thus collected is dissolved in methylene chloride and this solution is passed through a pad of silica gel eluting with 1% methanol on methylene chloride. The eluate is concentrated to yield 3-trimethylsilylethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine.

To a solution of 1.5 g of 3-trimethylsilylethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine in 100 mL of anhydrous tetrahydrofuran cooled to 0° C. are added under nitrogen 4.75 mL of 1M tetrabutylammonium fluoride in anhydrous tetrahydrofuran. After 5 minutes, the reaction mixture is allowed to attain room temperature and is then stirred for 2 hours. The solvent is removed under reduced pressure and the residue purified by chromatography over silica gel to yield 3-ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine.

A mixture of 1.70 g. of 3-ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, 2.30 g. of dimethyl N-(5-bromothien-2-ylcarbonyl)-L-glutamate (prepared as described in U.S. Pat. No. 4,882,333 issued Nov. 21, 1989, the disclosure of which is incorporated herein by reference), 44 mg. of palladium chloride, 130 mg. of triphenylphosphine, 25 mg. of cuprous iodide, and 1.13 mL. of triethylamine in 30 mL. of acetonitrile is heated at reflux for 3 hours and then cooled to ambient temperature. The solvent is removed under reduced pressure and the residue column chromatographed (Waters 500) eluting with 1:19 methanol:methylene chloride to yield dimethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethynyl]thien-2-ylcarbonyl-L-glutamate.

By substituting equivalent amounts of diethyl N-(4-bromothien-2-ylcarbonyl)-L-glutamate, and diethyl N-(5-bromothien-3-ylcarbonyl)-L-glutamate in the foregoing procedure, there are respectively obtained diethyl N-[4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)thien-2-ylcarbonyl]-L-glutamate and diethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)thien-3-ylcarbonyl]-L-glutamate.

Diethyl N-[4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)fur-2-ylcarbonyl]-L-glutamate and diethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)fur-3-ylcarbonyl]-L-glutamate can be similarly obtained from diethyl N-(4-bromofur-2-ylcarbonyl)-L-glutamate and diethyl N-(5-bromofur-3-ylcarbonyl)-L-glutamate, respectively.

Similarly from dimethyl N-(2-fluoro-4-iodobenzoyl)-L-glutamate and dimethyl N-(3-fluoro-4-iodobenzoyl)-L-glutamate (prepared as described in U.S. Pat. No. 4,889,859 issued Dec. 26, 1989, the disclosure of which is incorporated herein by reference), there are respec-

tively obtained dimethyl N-[2-fluoro-4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate and dimethyl N-[3-fluoro-4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate.

## EXAMPLE 5

Dimethyl  
N-[4-(4-hydroxypyrrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate

By allowing 3-iodo-4-hydroxypyrrrolo[2,3-d]pyrimidine to react with dimethyl N-(4-ethynylbenzoyl)-L-glutamate in the manner described in Example 2, there is obtained dimethyl N-[4-(4-hydroxypyrrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate which is purified by chromatography over silica, m.p. 160° C. (dec.). <sup>1</sup>NMR (d<sub>6</sub>-DMSO)δ1.98-2.15 (m, 2H), 2.45 (t, J=7.5 Hz, 2H) 3.57 (s, 3H), 3.64 (s, 3H), 4.40-4.45 (m, 1H), 7.51 ((d, J=2.5 Hz, 1H), 7.55 (d, J=8.2 Hz, 2 H), 7.87 (s, 1H), 7.90 (d, J=8.2 Hz, 1 H), 11.97 ((d, J=3.7 Hz, 1 H), 12.31 (s, 1H).

Alternatively, by substituting equivalent amounts of methyl 4-ethynylbenzoate, 4-ethynyltoluene, 4-ethynylbenzene, 4-ethynylchlorobenzene, 4-ethynylfluorobenzene, 3-ethynylfluorobenzene, and 1-methoxy-4-ethynylbenzene in the procedure of Example 2, there are obtained methyl 4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoate, 3-(4-methylphenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, 3-phenylethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, 3-(4-chlorophenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, 3-(4-fluorophenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, 3-(3-fluorophenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine, and 3-(4-methoxyphenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine.

Use of 3-iodo-4-hydroxypyrrrolo[2,3-d]pyrimidine in place of 3-iodo-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine with methyl 4-ethynylbenzoate, 4-ethynyltoluene, 4-ethynylbenzene, 4-ethynylchlorobenzene, 4-ethynylfluorobenzene, 3-ethynylfluorobenzene, and 1-methoxy-4-ethynylbenzene yields respectively methyl 4-(4-hydroxypyrrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoate, 3-(4-methylphenyl)ethynyl-4-hydroxypyrrrolo[2,3-d]pyrimidine, 3-phenylethynyl-4-hydroxypyrrrolo[2,3-d]pyrimidine, 3-(4-chlorophenyl)ethynyl-4-hydroxypyrrrolo[2,3-d]pyrimidine, 3-(4-fluorophenyl)ethynyl-4-hydroxypyrrrolo[2,3-d]pyrimidine, and 3-(4-methoxyphenyl)ethynyl-4-hydroxypyrrrolo[2,3-d]pyrimidine.

Ten grams of 3-iodo-4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidine are allowed to react with 2.19 g of 80% sodium hydride oil dispersion and 75 ml of dimethylformamide with the exclusion of moisture. After 30 minutes, 6.02 g of chloromethyl pivalate are added. This mixture is stirred for three hours poured into water, and neutralized with acetic acid. The solid is chromatographed on silica gel with acetone-dichloromethane to yield 3-iodo-4-hydroxy-1,5-bis-(pivaloyloxy)-6-methylpyrrolo[2,3-d]pyrimidine, m.p. 155° C. initially, followed by 3-iodo-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine, m.p. 236° C.

Use of 3-iodo-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine in the procedure of Example 2 then yields dimethyl N-[4-(4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate, m.p. 196° C. Anal. Calc. for C<sub>29</sub>H<sub>32</sub>N<sub>4</sub>O<sub>8</sub>:

C, 61.70; H 5.71; N, 9.92. Found: C, 61.90; H, 5.71; N, 9.95.

Use of 3-iodo-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine in place of 3-iodo-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine with methyl 4-ethynylbenzoate, 4-ethynyltoluene, 4-ethynylbenzene, 4-ethynylchlorobenzene, 4-ethynylfluorobenzene, 3-ethynylfluorobenzene, and 1-methoxy-4-ethynylbenzene yields methyl 4-(4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoate, 3-(4-methylphenyl)ethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine, 3-phenylethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine, 3-(4-chlorophenyl)ethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine, 3-(4-fluorophenyl)ethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine, and 3-(4-methoxyphenyl)ethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine.

## EXAMPLE 6

Dimethyl  
N-[4-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamate

A mixture of 1.0 g of dimethyl N-[4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate in 250 mL of 50% methanol in methylene chloride and 0.8 g of 3% palladium-on-carbon is hydrogenated at 50 p.s.i. for three hours, filtered, and concentrated under reduced pressure. The solid is collected by filtration and dried to yield 0.72 g of dimethyl N-[4-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamate- mp 247° C. <sup>1</sup>NMR (d<sub>6</sub>-DMSO)δ1.21 (s, 9H), 1.90-2.12 (m, 2H), 2.42 (t, J=7.4 Hz, 2H), 2.92 (t, J=4 Hz, 2H), 2.97 (t, J=4 Hz, 2H), 3.55 (s, 3H), 3.61 (s, 3H), 4.38-4.45 (m, 1H), 6.61 (s, 1H), 7.27 (d, J=8.2 Hz, 2 H), 7.75 (d, J=8.2 Hz, 2 H), 8.64 (d, J=7.4 Hz, 1 H), 10.75 (s, 1H), 11.22 (s, 1H). Anal. Calc. for C<sub>27</sub>H<sub>33</sub>N<sub>5</sub>O<sub>7</sub>: C, 60.10; H 6.17; N, 12.98. Found: C, 59.94; H, 6.15; N, 12.72.

## EXAMPLE 7

Dimethyl  
N-[5-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]thien-2-ylcarbonyl]-L-glutamate

By subjecting dimethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethynyl]thien-2-ylcarbonyl]-L-glutamate to the hydrogenation procedure of Example 6, there is obtained dimethyl N-[5-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]thien-2-ylcarbonyl]-L-glutamate.

Similarly the following compounds are subjected to the hydrogenation of Example 6:

- dimethyl N-[2-fluoro-4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate;
- dimethyl N-[3-fluoro-4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate;
- diethyl N-[4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)thien-2-ylcarbonyl]-L-glutamate;

- (d) diethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)thien-3-ylcarbonyl]-L-glutamate;
- (e) dimethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)pent-4-ynoyl]-L-glutamate;
- (f) dimethyl N-[7-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)hept-6-enoyl]-L-glutamate;
- (g) dimethyl N-[6-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)hex-5-ynoyl]-L-glutamate;
- (h) methyl 4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoate;
- (i) 3-(4-methylphenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
- (j) 3-phenylethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
- (k) 3-(4-chlorophenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
- (l) 3-(4-fluorophenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
- (m) 3-(3-fluorophenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
- (n) 3-(4-methoxyphenyl)ethynyl-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
- (o) methyl 4-(4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoate;
- (p) 3-(4-methylphenyl)ethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine;
- (q) 3-phenylethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine;
- (r) 3-(4-chlorophenyl)ethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine;
- (s) 3-(4-fluorophenyl)ethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine;
- (t) 3-(4-methoxyphenyl)ethynyl-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine;
- (u) methyl 4-(4-hydroxypyrrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoate;
- (v) 3-(4-methylphenyl)ethynyl-4-hydroxypyrrrolo[2,3-d]pyrimidine;
- (w) 3-phenylethynyl-4-hydroxypyrrrolo[2,3-d]pyrimidine;
- (x) 3-(4-chlorophenyl)ethynyl-4-hydroxypyrrrolo[2,3-d]pyrimidine;
- (y) 3-(4-fluorophenyl)ethynyl-4-hydroxypyrrrolo[2,3-d]pyrimidine; and
- (z) 3-(4-methoxyphenyl)ethynyl-4-hydroxypyrrrolo[2,3-d]pyrimidine.
- There are respectively obtained:
- (a) dimethyl N-[2-fluoro-4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethyl)benzoyl]-L-glutamate;
- (b) dimethyl N-[3-fluoro-4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethyl)benzoyl]-L-glutamate;
- (c) diethyl N-[4-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethyl)thien-2-ylcarbonyl]-L-glutamate;
- (d) diethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-ylethyl)thien-3-ylcarbonyl]-L-glutamate;
- (e) dimethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)pentyl]-L-glutamate;
- (f) dimethyl N-[7-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)heptyl]-L-glutamate;
- (g) dimethyl N-[6-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)hexyl]-L-glutamate;
- (h) methyl 4-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoate;

- (i) 3-[2-(4-methylphenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
- (j) 3-(2-phenylethyl)-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
- (k) 3-[2-(4-chlorophenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
- (l) 3-[2-(4-fluorophenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
- (m) 3-[2-(3-fluorophenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
- (n) 3-[2-(4-methoxyphenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine;
- (o) methyl 4-[2-(4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoate;
- (p) 3-[2-(4-methylphenyl)ethyl]-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine;
- (q) 3-(2-phenylethyl)-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine;
- (r) 3-[2-(4-chlorophenyl)ethyl]-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine;
- (s) 3-[2-(4-fluorophenyl)ethyl]-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine;
- (t) 3-[2-(4-methoxyphenyl)ethyl]-4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidine;
- (u) methyl 4-[2-(4-hydroxypyrrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoate;
- (v) 3-[2-(4-methylphenyl)ethyl]-4-hydroxypyrrrolo[2,3-d]pyrimidine;
- (w) 3-(2-phenylethyl)-4-hydroxypyrrrolo[2,3-d]pyrimidine;
- (x) 3-[2-(4-chlorophenyl)ethyl]-4-hydroxypyrrrolo[2,3-d]pyrimidine;
- (y) 3-[2-(4-fluorophenyl)ethyl]-4-hydroxypyrrrolo[2,3-d]pyrimidine; and
- (z) 3-[2-(4-methoxyphenyl)ethyl]-4-hydroxypyrrrolo[2,3-d]pyrimidine.

## EXAMPLE 8

## Diethyl N-[4-55

1-(Tetrahydropyr-2-yloxy)-3-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-yl]benzoyl]glutamate

A solution of 1.16 g of diethyl N-[4-(1-(tetrahydropyr-2-yloxy)-3-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-en-2-yl)benzoyl]glutamate and 174 mg (20%) of amorphous platinum (IV) oxide in 150 ml of glacial acetic acid is hydrogenated for 10 hours at 50 psi. The reaction mixture is diluted with 50 ml of methanol and filtered through Celite. The filtrate is concentrated and diluted with ethyl acetate. The solid which forms after cooling for 15 hour is collected by filtration, washed with cold ethyl acetate and dried to give diethyl N-[4-(1-(tetrahydropyr-2-yloxy)-3-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-yl)benzoyl]glutamate.

## EXAMPLE 9

## Dimethyl

N-[4-0[2-(4-hydroxypyrrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamate

A mixture of 1.1 g of dimethyl N-[4-(4-hydroxypyrrrolo[2,3-d]pyrimidin-3-ylethynyl)benzoyl]-L-glutamate in 100 mL of 50% methanol in methylene chloride and 0.8 g of 3% palladium-on-carbon is hydrogenated at 50 p.s.i. for 24 hours, filtered, and concentrated under reduced pressure. Ether is added to the residue and the solid is collected by filtration and dried to yield 0.67 g of

dimethyl N-[4-[2-(4-hydroxyaminopyrrolo [2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamate. mp 170°-172° C. <sup>1</sup>NMR (d<sub>6</sub>-DMSO) δ1.94-2.14 (m, 2H), 2.44 (t, J=7.4 Hz, 2H), 2.93-3.02 (m, 2H), 3.57 (s, 3H), 3.63 (s, 3H), 4.40-4.70 (m, 1H), 6.71 (s, 1H), 7.29 (d, J=8.2 Hz, 2 H), 7.77 (m, 3 H), 8.66 (d, J=7.4 Hz, 1 H), 11.52 (s, 1H), 11.71 (s, 1H).

In a similar fashion from dimethyl N-[4-(4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamate, there is obtained according to this procedure dimethyl N-[4-[2-(4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamate, m.p. 163° C.

## EXAMPLE 10

N-[4-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamic Acid

A mixture of 1.5 g of dimethyl N-[4-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamate in 10 mL of 1N sodium hydroxide is stirred at ambient temperatures for three days to form the sodium salt of N-[4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamic acid. This is neutralized with glacial acetic acid. The solid which forms is collected by filtration and recrystallized from 50% methanol in methylene chloride to give 0.8 g (67%) of N-[4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamic acid. <sup>1</sup>NMR (d<sub>6</sub>-DMSO) δ 1.80-2.00 (m, 2H), 2.10-2.30 (m, 2H), 2.77-2.820 (m, 2H), 2.89-2.93 (m, 2H), 4.13-4.19 (m, 2H), 6.25 (d, J=1.3 Hz, 1H), 7.23 (d, J=8.1 Hz, 2 H), 7.69 (d, J=8.1 Hz, 2 H), 8.13 (d, J=6.7 Hz, 1 H), 10.55 (s, 1H).

## EXAMPLE 11

Diethyl

N-[4-[1-hydroxy-3-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-yl]benzoyl]glutamate

The solution of 0.94 g of diethyl N-[4-(1-(tetrahydropyr-2-yloxy)-3-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-yl)benzoyl]glutamate in 40 ml of 0.1N methanolic hydrogen chloride is stirred at ambient temperatures for 2 hours. The reaction mixture is neutralized with a solution of 205 mg of sodium carbonate in 10 ml of water and most of methanol removed by evaporation under reduced pressure. One hundred milliliters of methylene chloride are added and the solution is washed twice with 20 ml of water, dried over anhydrous magnesium sulfate, and concentrated. The residue is triturated with 1:2 ethyl acetate and ether, filtered, and dried to give diethyl N-[4-[1-hydroxy-3-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-yl]benzoyl]glutamate.

## EXAMPLE 12

N-[4-[1-hydroxy-3-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-yl]benzoyl]glutamic Acid

A solution of 0.3 g of diethyl N-[4-[1-hydroxy-3-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-yl]benzoyl]glutamate in 9 ml of 1N aqueous sodium hydroxide is stirred under nitrogen at ambient temperature for 72 hours. The reaction mixture is rendered slightly acidic (pH=-4) with 1N hydrochloric acid and filtered. The solid thus collected is washed with water (5 ml) and cold ethanol (5 ml) and dried to give N-[4-(1-hydroxy-3-(4-hydroxy-6-aminopyr-

rolo[2,3-d]-pyrimidin-3-yl)prop-2-yl]benzoyl]glutamic acid.

Similarly from dimethyl N-(2-fluoro-4-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamate and dimethyl N-[3-fluoro-4-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamate there are respectively obtained according to the foregoing procedure N-(2-fluoro-4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl)-L-glutamic acid, m.p. 230° (foaming), 300° C (dec.) and N-[3-fluoro-4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamic acid, m.p. >300° C. (dec.).

In an analogous fashion to the foregoing procedure, there are respectively obtained from diethyl N-[4-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]thien-2-ylcarbonyl]-L-glutamate, diethyl N-[5-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]thien-3-ylcarbonyl]-L-glutamate, dimethyl N-[5-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]fur-2-ylcarbonyl]-L-glutamate, and dimethyl N-[5-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]thien-2-ylcarbonyl]-L-glutamate, the compounds N-[4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]thien-2-ylcarbonyl]-L-glutamic acid, N-[5-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]thien-3-ylcarbonyl]-L-glutamic acid, N-[5-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]fur-2-ylcarbonyl]-L-glutamic acid, m.p. 200°-203° C., and N-[5-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]thien-2-ylcarbonyl]-L-glutamic acid, m.p. 241°-243° C.

Similarly obtained from dimethyl N-[5-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)pentanoyl]-L-glutamate, dimethyl N-[7-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)heptanoyl]-L-glutamate, and dimethyl N-[6-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)hexanoyl]-L-glutamate, are, respectively, N-[5-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)pentanoyl]-L-glutamic acid, N-[7-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)heptanoyl]-L-glutamic acid, and N-[6-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)hexanoyl]-L-glutamic acid.

## EXAMPLE 13

N-[4-[2-(4-hydroxypyrrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamic Acid

A mixture of 0.5 g of dimethyl N-[4-[2-(4-hydroxypyrrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamate in 3 mL of 1N sodium hydroxide is stirred at ambient temperatures for three days to form the sodium salt of N-[4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamic acid. This is neutralized with hydrochloric acid. The solid which forms is collected by filtration and recrystallized from methanol by addition of water to give 0.35 g (75%) of N-[4-[2-(4-hydroxypyrrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamic acid. m.p. >230° C., <sup>1</sup>NMR (d<sub>6</sub>-DMSO) δ1.88-2.12 (m, 2H), 2.33 (t, J=7.3 Hz, 2H), 2.97 (m, 4H), 4.33-4.40 (m, 1H), 6.70 (d, J=1.2 Hz, 1H), 7.28 (d, J=7.0 Hz, 2 H), 7.76 (m, 3H), 8.50 (d, J=7.6 Hz, 1H), 11.48 (s, 1H), 11.67 (s, 1H), 12.40 (br, 1H).

In a similar fashion from dimethyl N-[4-[2-(4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamate, there is obtained

according to the foregoing procedure first the sodium salt of N-[4-[2-(4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamic acid which upon neutralization with glacial acetic acid yields N-[4-[2-(4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamic acid, m.p. 291 ° C. <sup>1</sup>NMR (d<sub>6</sub>-DMSO) 8.32 (m, 4H), 2.48 (s, 3H), 2.96 (m, 4H), 4.26 (m, 1H), 6.60 (s, 1H), 7.26 (d, J=8.0 Hz, 1H), 7.75 (d, J=7.76 Hz, 1H), 8.44 (d, J=2.96 Hz, 1H), 11.26 (s, 1H), 11.59 (s, 1H).

By subjecting methyl 4-[2-(4-hydroxy-5-pivaloyloxy-6-methylpyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoate; 3-[2-(4-methylphenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine; 3-(2-phenylethyl)-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine; 3-[2-(4-chlorophenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine; 3-[2-(4-fluorophenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine; 3-[2-(3-fluorophenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine; 3-[2-(4-methoxyphenyl)ethyl]-4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidine; and methyl 4-[2-(4-hydroxy-6-pivaloylaminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoate to the foregoing procedure, there are respectively obtained 4-[2-(4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoic acid; 3-[2-(4-methylphenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine; 3-(2-phenylethyl)-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine; 3-[2-(4-chlorophenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine; 3-[2-(4-fluorophenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine; 3-[2-(3-fluorophenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, m.p. 295°-298°; 3-[2-(4-methoxyphenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine, m.p. 280°-284° C.; and 4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoic acid, m.p. >300° C.

#### EXAMPLE 14

Representative inhibition values against CCRF-CEM 5 cell cultures for typical compounds are as follows:

Compound	IC <sub>50</sub> (μg/ml)
4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoic acid	>20.00
N-[4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamic acid	0.004
3-[2-(4-methoxyphenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine	>20.00
N-[2-fluoro-4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamic acid	0.008
N-[3-fluoro-4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamic acid	0.019
3-[2-(3-fluorophenyl)ethyl]-4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidine	>20.00
N-[5-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]thien-2-ylcarbonyl]-L-glutamic acid	0.025
N-[5-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]fur-2-ylcarbonyl]-L-glutamic acid	>20.00
N-[4-[2-(4-hydroxy-6-methylpyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamic acid	0.0084
N-[4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamic acid	1.20

The cytotoxicity of these compounds is not reversed by the addition of hypoxanthine or AICA, suggesting

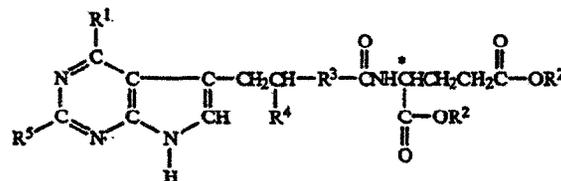
they do not inhibit the purine de novo biosynthesis pathway, but is reversed by thymidine, indicating thymidylate synthetase is the main target. Cytotoxicity is also reversed by addition of leucovorin, indicating the cytotoxicity is due to antagonism of a folate-related mechanism.

In vivo activity can be seen from the following representative data for N-[4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamic acid against the L5178Y/TK- tumor line in DBA/2 mice (female), administration being ip in a total volume of 0.5 mL daily for eight days:

	Dose %	Inhibition	Toxicity	Tumor Weight
Control	0.0	0	0/6	3606 ± 2099
Control	0.0	0	0/6	5533 ± 1234
	200.00	100	0/7	0 ± 0
	100.00	100	0/7	0 ± 0
	50.00	100	0/6	0 ± 0
	25.00	100	0/7	0 ± 0
	12.50	98	0/7	102 ± 166

What is claimed is:

1. A compound of the formula:



in which:

R<sup>1</sup> is —OH or —NH<sub>2</sub>;

R<sup>2</sup> is hydrogen or a pharmaceutically acceptable cation;

R<sup>3</sup> is 1,4-phenylene unsubstituted or substituted with chloro, fluoro, methyl, methoxy, or trifluoromethyl;

R<sup>4</sup> is hydrogen, or methyl;

R<sup>5</sup> is amino; and

the configuration about the carbon atom designated \* is S.

2. A compound according to claim 1 wherein R<sup>1</sup> is —OH; R<sup>3</sup> is 1,4-phenylene, and R<sup>4</sup> is hydrogen.

3. The compound according to claim 1 which is N-[4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamic acid.

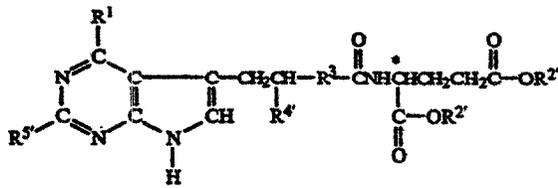
4. The compound according to claim 1 which is N-[4-[1-hydroxy-3-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)prop-2-yl]benzoyl]glutamic acid.

5. The compound according to claim 1 which is N-[2-fluoro-4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamic acid.

6. The compound according to claim 1 which is N-[3-fluoro-4-[2-(4-hydroxy-6-aminopyrrolo[2,3-d]pyrimidin-3-yl)ethyl]benzoyl]-L-glutamic acid.

7. A compound of the formula:

21



in which:

22

R<sup>1</sup> is —OH or —NH<sub>2</sub>;R<sup>2</sup> is hydrogen, a pharmaceutically acceptable cation, or a carboxy protecting group;R<sup>3</sup> is 1,4-phenylene unsubstituted or substituted with chloro, fluoro, methyl, methoxy, or trifluoromethyl;R<sup>4</sup> is hydrogen, or methyl;R<sup>5</sup> is amino or amino substituted with an amino protecting group; and

the configuration about the carbon atom designated \* is S.

\* \* \* \* \*

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**United States  
Patent and  
Trademark Office**

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**Maintenance Fee Statement**

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The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. **TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).**

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. **THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.**

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,344,932	183	1050	0	07/674,541	09/06/94	03/22/91	04	NO	PAID
000000										

ITEM NBR	ATTY DKT NUMBER

1

960-118D

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**EXHIBIT IV**

*Lilly*

**Lilly Research Laboratories**

A Division of Eli Lilly and Company

Lilly Corporate Center  
Greenwood, Indiana 46285  
Tel: 317-276-2000

**July 8, 1992**

**Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room 2-14  
12420 Parklawn Drive  
Rockville, Maryland 20852**

**Re: Initial Submission - LY231514 Disodium for Injection - Serial No. 000**

**In accordance with CFR § 312.20, we are submitting an Investigational New Drug Application (in four volumes) for the new drug substance, LY231514 Disodium.**

**LY231514 Disodium is a folic acid antimetabolite and a specific antagonist of thymidylate synthase and will be tested as an oncolytic chemotherapeutic agent for solid neoplasms.**

**Accompanying this letter is Form FDA 1571 information supporting Phase I studies of LY231514 Disodium. Section 6(a) contains the protocol (H3E-MC-JMAB-001) for the initial safety and pharmacokinetic study. In accordance with the telephone conversation with Ms. Ellen Cutler (CSO) on July 8, 1992, the Form FDA 1572 is being submitted for 6 (b), (c) and (d) with the exception of the curriculum vitae (item 2 of the Form 1572).**

**In accordance with the request outlined in the letter of April 27, 1992, the following information is provided:**

- 1. Protocol Title: A Phase I Trial of LY231514 Administered as a Bolus Infusion Every Seven Days**
- 2. Protocol Number: H3E-MC-JMAB-001**
- 3. Minimum Qualifications of Principal Investigator: Licensed, Board Certified and Practicing Oncologist**

4. Daniel D. Von Hoff, M.D., F.A.C.P., the principal investigator meets the above qualifications.  
University of Texas Health Science Center  
Department of Medicine Oncology  
Section of Clinical Drug Development  
7703 Floyd Curl Drive  
San Antonio, Texas 78284-7884
5. Name and address of the Institutional Review Boards are listed in the Form 1572 and in item 3.3.4 of the protocol.
6. Names and qualifications of sub investigators working under the supervision of Dr. Von Hoff:

The following subinvestigators are board certified and/or practicing oncologists.

Karen Bowen, M.D.  
Howard A. Burris, III, M.D.  
John R. Eckardt, M.D.  
Stephen Kalter, M.D.  
Pamela New, M.D.  
Timothy J. O'Rourke, M.D.  
Peter M. Ravdin, M.D.  
David A. Rinaldi, M.D.  
Gladys I. Rodriguez, M.D.  
Mace L. Rothenberg, M.D.  
Lon Smith, M.D.  
James Wall, M.D.  
Geoffery R. Weiss, M.D.

The following subinvestigators are licensed pharmacists experienced in assisting in clinical studies.

James Koeller, M.S.  
John G. Kuhn, Pharm. D.

THIS DOCUMENT CONTAINS TRADE SECRETS,  
OR COMMERCIAL OR FINANCIAL INFORMATION,  
PRIVILEGED OR CONFIDENTIAL, DELIVERED  
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INFORMATION WILL NOT BE MADE AVAILABLE  
TO THE PUBLIC WITHOUT THE EXPRESS  
WRITTEN CONSENT OF ELI LILLY AND COMPANY.

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b> PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION <b>INVESTIGATIONAL NEW DRUG APPLICATION (IND)</b> <b>(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)</b>		Form Approved: OMB No. 0910-0014 Expiration Date: December 31, 1991 See OMB Statement on Reverse.
1. NAME OF SPONSOR ELI LILLY AND COMPANY		2. DATE OF SUBMISSION JULY 8, 1992
3. ADDRESS (Number, Street, City, State and Zip Code) Lilly Corporate Center Indianapolis, Indiana 46285		4. TELEPHONE NUMBER (Include Area Code) (317) 276-2000
5. NAME(S) OF DRUG (Include all available names: Trade, Generic, Chemical, Code) Compound LY231514, Thymidylate Synthase (TSI)		6. IND NUMBER (if previously assigned)
7. INDICATION(S) (Covered by this submission) NA		
8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: <input checked="" type="checkbox"/> PHASE 1 <input type="checkbox"/> PHASE 2 <input type="checkbox"/> PHASE 3 <input type="checkbox"/> OTHER _____ (Specify)		
9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.  DMF 4700 DMF 1546 DMF 5919		
10. IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.		SERIAL NUMBER <u>000</u>
11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply)		
<input checked="" type="checkbox"/> INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) <span style="float: right;"><input type="checkbox"/> RESPONSE TO CLINICAL HOLD</span>		
PROTOCOL AMENDMENT(S): <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> CHANGE IN PROTOCOL <input type="checkbox"/> NEW INVESTIGATOR	INFORMATION AMENDMENT(S): <input type="checkbox"/> CHEMISTRY/MICROBIOLOGY <input type="checkbox"/> PHARMACOLOGY/TOXICOLOGY <input type="checkbox"/> CLINICAL	IND SAFETY REPORT(S): <input type="checkbox"/> INITIAL WRITTEN REPORT <input type="checkbox"/> FOLLOW-UP TO A WRITTEN REPORT
<input type="checkbox"/> RESPONSE TO FDA REQUEST FOR INFORMATION		<input type="checkbox"/> ANNUAL REPORT <span style="float: right;"><input type="checkbox"/> GENERAL CORRESPONDENCE</span>
<input type="checkbox"/> REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED		<input type="checkbox"/> OTHER _____ (Specify)
<b>CHECK ONLY IF APPLICABLE</b>		
JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.		
<input type="checkbox"/> TREATMENT IND (21 CFR 312.35(b)) <input type="checkbox"/> TREATMENT PROTOCOL (21 CFR 312.35(a)) <input type="checkbox"/> CHANGE REQUEST/NOTIFICATION (21 CFR 312.35(c))		
<b>FOR FDA USE ONLY</b>		
CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

## CONTENTS OF APPLICATION

This application contains the following items: (check all that apply)

- 1. Form FDA 1571 [21 CFR 312.23 (a) (1)]
- 2. Table of contents [21 CFR 312.23 (a) (2)]
- 3. Introductory statement [21 CFR 312.23 (a) (3)]
- 4. General investigational plan [21 CFR 312.23 (a) (3)]
- 5. Investigator's brochure [21 CFR 312.23 (a) (5)]
- 6. Protocol(s) [21 CFR 312.23 (a) (6)]
  - a. Study protocol(s) [21 CFR 312.23 (a) (6)]
  - b. Investigator data [21 CFR 312.23 (a) (6)(iii)(b)] or completed Form(s) FDA 1572
  - c. Facilities data [21 CFR 312.23 (a) (6)(iii)(b)] or completed Form(s) FDA 1572
  - d. Institutional Review Board data [21 CFR 312.23 (a) (6)(iii)(b)] or completed Form(s) FDA 1572
- 7. Chemistry, manufacturing, and control data [21 CFR 312.23 (a) (7)]
  - Environmental assessment or claim for exclusion [21 CFR 312.23 (a) (7)(iv)(e)]
- 8. Pharmacology and toxicology data [21 CFR 312.23 (a) (8)]
- 9. Previous human experience [21 CFR 312.23 (a) (9)]
- 10. Additional information [21 CFR 312.23 (a) (10)]

13 IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION?  YES  NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION?  YES  NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14 NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

J. H. Holcombe, M.D.

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

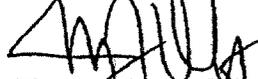
Same as 14 above

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16 NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE

M. W. Talbott, Ph.D., Director  
Medical Regulatory Affairs

17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE



18 ADDRESS (Number, Street, City, State and Zip Code)

Eli Lilly and Company (MC598) (11/3)  
Lilly Corporate Center  
Indianapolis, Indiana 46285

19. TELEPHONE NUMBER  
(Include Area Code)

(317) 276-2574

20. DATE

JULY 8, 1992

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

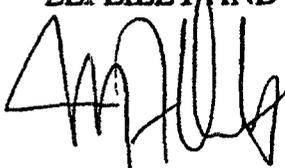
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

A copy of the Form FDA 1572 and appropriate curriculum vitae for the primary investigator and subinvestigators are being retained in our files per your instructions in the April 27, 1992, letter.

Please call me at (317) 276-2574 or Dr. Andy Stewart at (317) 276-4113 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY



M. W. Talbott, Ph.D.  
Director  
Medical Regulatory Affairs

Enc.

cc: Ms. E. Cutler, Consumer Safety Officer (letter only)

Eli Lilly and Company will notify the Food and Drug Administration if the investigation is discontinued and the reason therefore.

Eli Lilly and Company will notify each investigator if a new drug application is approved or if the investigation is discontinued. The Institutional Review Boards will also be notified if the IND is withdrawn because of safety reasons.

As a general rule, all materials for study are supplied to investigators without charge. If the drug is to be sold, the Food and Drug Administration will be so notified and an explanation of why sale is required will be rendered and should not be regarded as commercialization of the new drug.

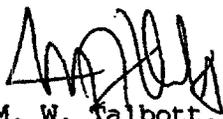
Clinical studies in humans will not be initiated prior to 30 days after the date of receipt of the Investigational New Drug Application by the Food and Drug Administration unless the 30-day delay is waived by the Food and Drug Administration upon showing by Eli Lilly and Company of good reason for such waiver. Eli Lilly and Company will defer or restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days.

Eli Lilly and Company will, when requested by the Food and Drug Administration, provide an environmental impact analysis report.

All non clinical laboratory studies have been, or will be, conducted in compliance with the good laboratory practice regulations or, if such studies have not been conducted in compliance with such regulations, a statement will be provided that describes in detail all differences between the practices used in conducting the study and those required in the regulations.

Very truly yours,

ELI LILLY AND COMPANY



M. W. Talbott, Ph.D.  
Director  
Medical Regulatory Affairs

MWT:sm

To the Reviewers:

To co-ordinate our activities with yours, we suggest that any wires or written communications, regardless of subject, concerning this file be directed to:

M. W. Talbott, Ph.D., Director  
Medical Regulatory Affairs  
Lilly Research Laboratories  
Lilly Corporate Center  
Indianapolis, Indiana 46285

Any telephone calls relating to manufacturing-controls should be made to:

Dr. D. J. Miner                    276-4509\*

or in his absence to:

Dr. R. A. Raths                    276-4248\*

Any calls relating to toxicology-pharmacology should be made to the Greenfield Laboratories of Eli Lilly and Company to:

Dr. D. M. Morton                    467-4301\*

or in his absence to:

Dr. J. L. Emmerson                    467-4306\*

Any calls dealing with clinical reports or with labels and literature should be made to Dr. Talbott between 7:30 a.m. and 4:15 p.m. (EST).

Dr. M. W. Talbott                    276-2574\*  
846-2345\* (Home)

or in his absence to:

Dr. A. J. Stewart                    276-4113\*  
251-8836\* (Home)

Dr. A. Pedersen                    276-2796\*  
253-5186\* (Home)

\* Area Code 317

On holidays, Saturdays, or Sundays, call the above personnel at home using the telephone numbers indicated.

By way of explanation, Drs. Miner and Raths are in the Development Division; Drs. Emmerson and Morton are in the Toxicology Division; and Drs. Talbott, Stewart, and Pedersen are in the Medical component. It is through Dr. Talbott's office that FDA submissions for this file are made.

Close liaison among the three divisions will result in any messages, no matter how received, being brought to the attention of all concerned.

MWT:sm



**Lilly Research Laboratories**  
A Division of Eli Lilly and Company

Lilly Corporate Center  
Greenwood, Indiana 46205  
(317) 276-2000

September 10, 1992

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology and Pulmonary  
Drug Products, HFD-150  
Attn.: Document Control Room 17B-20  
5600 Fishers Lane  
Rockville, Maryland 20857-1706

**Re: IND 40,061 - LY231514 (Thymidylate Synthase Inhibitor) - Serial No.: 003**

Please refer to the conference call held on August 24, 1992, and the Memorandum of Agreement summarizing the discussion and conclusions submitted August 28, 1992.

In accordance with the agreement the following documentation is being submitted:

1. Amended Protocol H3E-MC-JMAB(a).
2. Revised toxicology summary for the Clinical Investigator Brochure (pages 3.8 - 3.14).
3. Toxicology Report (Leucovorin Rescue of Beagle Dog Given Lethal Doses of LY231514 Disodium in Study D01692).
4. Manufacturing responses to points 4 and 5 in the August 7, 1992, FAX from the FDA.

For your convenience, a copy of the following documents are also attached:

- Memorandum of Agreement of the August 24, 1992, conference call.
- Copy of the FDA FAX of August 7, 1992, notifying Eli Lilly of the clinical hold.

In accordance with the agreement that the clinical study could be initiated concurrently with the submission of these documents, clinical trial materials are being shipped to the principal investigator (Dr. Daniel Von Hoff, University of Texas, San Antonio, Texas).

Food and Drug Administration  
IND 40,061 - LY231514  
September 10, 1992  
Page 2

Please call me at (317) 276-2574 or Dr. Andy Stewart at (317) 276-4113 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY



M. W. Talbott, Ph.D.  
Director  
Medical Regulatory Affairs

Enc.

cc: Ms. Ellen Cutler (1)

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b> <b>PUBLIC HEALTH SERVICE</b> <b>FOOD AND DRUG ADMINISTRATION</b> <b>INVESTIGATIONAL NEW DRUG APPLICATION (IND)</b> <b>(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)</b>		Form Approved: OMB No. 0910-001 Expiration Date: December 31, 1999 See OMB Statement on Reverse.
1. NAME OF SPONSOR <b>ELI LILLY AND COMPANY</b>		2. DATE OF SUBMISSION <b>September 10, 1992</b>
3. ADDRESS (Number, Street, City, State and Zip Code) <b>Lilly Corporate Center</b> <b>Indianapolis, Indiana 46285</b>		4. TELEPHONE NUMBER (Include Area Code) <b>(317) 276-2000</b>
5. NAME(S) OF DRUG (Include all available names: Trade, Generic, Chemical, Code) <b>Compound LY231514 Disodium (Thymidylate Synthase Inhibitor)</b>		6. IND NUMBER (If previously assign) <b>IND 40,061</b>
7. INDICATION(S) (Covered by this submission) <b>NA</b>		
8. PHASE (S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: <input checked="" type="checkbox"/> PHASE 1 <input type="checkbox"/> PHASE 2 <input type="checkbox"/> PHASE 3 <input type="checkbox"/> OTHER _____ (Specify)		
9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN APPLICATION. <b>NA</b>		
10. IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.		SERIAL NO. <b>_ 00</b>
11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply)		
<input type="checkbox"/> INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) <input type="checkbox"/> RESPONSE TO CLINICAL HOLD		
PROTOCOL AMENDMENT(S): <input type="checkbox"/> NEW PROTOCOL <input checked="" type="checkbox"/> CHANGE IN PROTOCOL <input type="checkbox"/> NEW INVESTIGATOR	INFORMATION AMENDMENT(S): <input checked="" type="checkbox"/> CHEMISTRY/MICROBIOLOGY <input checked="" type="checkbox"/> PHARMACOLOGY/TOXICOLOGY <input checked="" type="checkbox"/> CLINICAL	IND SAFETY REPORT(S): <input type="checkbox"/> INITIAL WRITTEN REPORT <input type="checkbox"/> FOLLOW-UP TO A WRITTEN REPC
<input checked="" type="checkbox"/> RESPONSE TO FDA REQUEST FOR INFORMATION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> GENERAL CORRESPONDENCE		
<input type="checkbox"/> REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED <input type="checkbox"/> OTHER _____ (Specify)		
<b>CHECK ONLY IF APPLICABLE</b>		
<b>JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.</b>		
<input type="checkbox"/> TREATMENT IND 21 CFR 312.35(b) <input type="checkbox"/> TREATMENT PROTOCOL 21 CFR 312.35(a) <input type="checkbox"/> CHANGE REQUEST/NOTIFICATION 21 CFR 312.35(c)		
<b>FOR FDA USE ONLY</b>		
CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

THIS DOCUMENT CONTAINS TRADE SECRETS,  
OR COMMERCIAL OR FINANCIAL INFORMATION,  
PRIVILEGED OR CONFIDENTIAL, DELIVERED  
IN CONFIDENCE AND RELIANCE THAT SUCH  
INFORMATION WILL NOT BE MADE AVAILABLE  
TO THE PUBLIC WITHOUT THE EXPRESS WRITTEN  
CONSENT OF ELI LILLY AND COMPANY.

EXHIBIT VI



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

IND 40,061

Eli Lilly and Company  
Lilly Corporate Center  
Indianapolis, Indiana 46285

SEP 11 1992

Attention: M. W. Talbott, Ph.D.  
Director, Medical Regulatory Affairs

Dear Dr. Talbott:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Compound LY231514.

We also refer to our August 7, 1992 facsimile transmission in which you were notified that your IND is on clinical hold and to the August 24, 1992 telephone conference between members of your company and this Division. In that telephone conference you were notified that you may initiate the clinical investigation simultaneously upon submission of the following information to the FDA.

1. A revised protocol including the rationale for the proposed 10 mg/m<sup>2</sup> starting dose of Compound LY231514, the criteria for leucovorin administration, and the dose, route and schedule of leucovorin.
2. The extended toxicology report and the leucovorin study report.
3. The revised Investigator's Brochure.

We have the following additional comments and requests.

4. Provide additional information and controls for the starting material N-4-iodobenzoyl-L-glutamic acid diethyl ester.
5. The drug product should be formulated at 100% of the label claim. A 10% excess must be justified.

Additional comments may be forwarded as our review continues.

NEW SEP 17 1992

IND 40,061  
Page 2

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations promulgated thereunder. Those responsibilities include reporting any unexpected fatal or life-threatening experiences by telephone to this Agency no later than three working days after receipt of the information and the submission of annual progress reports.

Sincerely yours,

*Gregory Burke*

Gregory Burke, M.D., Ph.D.  
Director  
Division of Oncology and  
Pulmonary Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

A copy of this submission can be found in 30 red books at the end of this file.  
www.lilly.com

*Lilly*

Lilly Research Laboratories  
A Division of Eli Lilly and Company  
Lilly Corporate Center  
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

October 24, 2002

**Pre-Submission for Original Application, NDA 21-462**

Central Document Room  
Center for Drug Evaluation and Research  
Food and Drug Administration  
12229 Wilkins Avenue  
Rockville, MD 20852

**Re: NDA 21-462, Alimta<sup>®</sup> (pemetrexed, LY231514) – Pre-Submission**

This letter accompanies the enclosed pre-submission of an original New Drug Application (NDA) for Alimta<sup>®</sup> (pemetrexed, LY231514) in combination with cisplatin for the indication of malignant pleural mesothelioma.

This pre-submission is provided in electronic format on a digital tape according to the January 1999 "Guidance for Industry Providing Regulatory Submissions in Electronic Format – NDAs." The electronic submission size is approximately 5.3 gigabytes for this portion of the submission. All electronic media have been checked by representatives of Lilly Information Technology and have been verified to be free of known viruses. The virus checking software was Norton Antivirus Corporate Edition version 7.51.847 using Virus Definitions 41009c created on October 9, 2002 and Scan Engine 4.1.0.6. As specified in the above Guidance, a paper review copy containing 37 volumes is included in this submission.

The Division of Oncology Drug Products (DODP) and Lilly have met to discuss this NDA at Pre-NDA meetings on January 30, 2002 and again on September 6, 2002.

This NDA is being submitted as a "rolling" submission as per the Fast Track Designation for Alimta in this indication granted by the FDA on June 10, 2002. As per agreements between Lilly and DODP at the September 6, 2002 Pre-NDA meeting, this NDA submission will be done in four stages as indicated below:

- o Stage A (October 31, 2002)
- o Stage B (March 31, 2003)
- o Stage C (April 15, 2003)
- o Stage D (September 30, 2003)

Note: Stage D submission date is contingent upon reaching agreement with FDA DNDC I in December 2002 on the acceptability of the compatibility and comparability data package and planned studies supporting the change to a comparable container closure system.

As agreed in an October 1, 2002 meeting with CDER and CBER personnel, Bio-Imaging Technologies, Inc. (BITI), Lilly's vendor who is preparing the imaging scan data, will be submitting a set of DVD's containing the imaging data (together with a set on CD's for archiving) for the patients in the phase 3 mesothelioma registration trial (JMCH). BITI will submit the imaging data by December 30, 2002. These electronic media containing the media imaging data will be sent directly to Debra Vause of DODP as per agreement at this meeting.

This pre-submission contains Stage A of the rolling NDA. Stage A contains the following:

- Item 1 – index and certain administrative documents
- Item 2 – draft labeling only
- Item 5 – complete nonclinical pharmacology and toxicology
- Item 6 – all human pharmacology and bioavailability / bioequivalence documentation with the exception of the two pharmacokinetic reports on the Alimta/aspirin and Alimta/ibuprofen interaction studies (these will be provided in Stage B of the rolling submission)
- Item 8 – the following two critical clinical study reports demonstrating efficacy of Alimta in malignant pleural mesothelioma:
  - JMCH – Phase 3 registration study of Alimta plus cisplatin versus single agent cisplatin in chemo-naive malignant pleural mesothelioma patients
  - JMDR – Phase 2 study of single agent Alimta in chemo-naive malignant pleural mesothelioma patients
  - Reference publications
- Item 11 – datasets relating to clinical pharmacology and clinical study reports for the studies identified in Items 6 and 8 above
- Item 12 – clinical report forms (CRFs) for notable patients (deaths, serious adverse events, discontinuation because of adverse events, and responders) in the two clinical studies identified in Item 8 above

Please note that Alimta for malignant pleural mesothelioma was granted Orphan Drug Designation on August 28, 2001. As a result of the Orphan Drug Designation, the sponsor is:

- 1) Not required to provide evidence of safety and efficacy in pediatric populations (From the FDA meeting minutes of the January 30, 2002 Pre-NDA meeting sent from DODP to Lilly on March 6, 2002, "Please note that you have been granted Orphan Drug status on August 28, 2001 therefore the Pediatric Final Rule (63 FR 66632) does not apply.")
- 2) Exempt from submitting the PDUFA User's fee. The User Fee ID# is 4249 as indicated on Form 3397 which is provided in Item 1 of Stage A.

In order to coordinate our activities with yours, we suggest that any facsimile (FAX) or other written communications regarding this file, regardless of subject, be directed to:

Debasish Roychowdhury, M.D.  
Director, U.S. Regulatory Affairs  
Eli Lilly and Company  
Lilly Research Laboratories  
Lilly Corporate Center  
Indianapolis, IN 46285  
FAX number (317) 433-2255

Telephone calls or E-Mails regarding overall submission or clinical / preclinical matters should be made to:

- Mr. John F. Worzalla  
Regulatory Research Scientist, U.S. Regulatory Affairs  
(317) 276-5052 (work)  
(866) 478-6616 (pager)  
FAX: (317) 276-1652  
E-Mail address: [worzalla@lilly.com](mailto:worzalla@lilly.com)  
(317) 251-0957 (home)

In Mr. Worzalla's absence please contact:

- Dr. Debasish Roychowdhury  
(317) 433-6604 (work)  
(317) 332-4268 (cellular)  
FAX: (317) 433-2255  
E-mail address: [dfr@lilly.com](mailto:dfr@lilly.com)  
(317) 566-0935 (home)

Telephone calls regarding chemistry, manufacturing or control issues should be made to:

- Mr. Jeffrey R. Ferguson  
(317) 433-5615 (work)  
(317) 502-2208 (cellular)  
FAX: (317) 276-1887  
E-mail address: [ferguson\\_jeffrey\\_r@lilly.com](mailto:ferguson_jeffrey_r@lilly.com)  
(317) 818-9070 (home)

In Mr. Ferguson's absence please contact:

- Diane Zezza, Ph.D.,  
Director, Global Regulatory Affairs, CM&C  
(317) 433-9882 (work)  
(317) 997-5491 (cellular)  
(877) 793-1062 (pager)  
FAX (317) 276-1887  
E-mail address: [zezza\\_d@lilly.com](mailto:zezza_d@lilly.com)

On holidays or weekends, please call Mr. Worzalla, Dr. Roychowdhury or Mr. Ferguson at home using the telephone numbers provided.

Close liaison between the Lilly representatives listed above will result in any messages, no matter how received, being brought to the attention of all concerned. Please let us know if there are any additional ways we may be of assistance during the review of this NDA. Lilly appreciates your continued assistance and cooperation.

The sponsor has been informed that DODP will schedule a meeting approximately 45 days after DODP receives Stage A of the NDA where the sponsor will give a presentation containing an overview of the NDA and reasons why the NDA should be approved. The sponsor requests that the week of December 9 be considered for this presentation if that meets with FDA schedules.

Sincerely,

Eli Lilly & Company

*John F. Worzalla*

John F. Worzalla  
Regulatory Research Scientist  
U.S. Regulatory Affairs

Enclosures

cc: Ms. Debra Vause, Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Drug Products, HFD-150  
1451 Rockville Pike  
Rockville, Maryland 20852-1448



www.lilly.com

Lilly Research Laboratories  
A Division of Eli Lilly and Company  
Lilly Corporate Center  
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

March 24, 2003

**Pre-Submission for Original Application, NDA 21-462**

Central Document Room  
Center for Drug Evaluation and Research  
Food and Drug Administration  
12229 Wilkins Avenue  
Rockville, MD 20852

**Re: NDA 21-462, Alimta<sup>®</sup> (pemetrexed, LY231514) – Pre-Submission – Stage B**

This letter accompanies the enclosed pre-submission of an original New Drug Application (NDA) for Alimta<sup>®</sup> (pemetrexed, LY231514) in combination with cisplatin for the indication of malignant pleural mesothelioma. This submission constitutes Stage B of the "rolling submission" of NDA 21-462 as explained below. Stage A of the NDA was submitted on October 24, 2002.

Submission of Stage B completes the non-clinical and clinical portions of NDA 21-462. When Item 4 (Chemistry, Manufacturing and Control) is provided the NDA will be complete. Please note that drug substance information for Item 4 will be provided as Stage C of the "rolling submission" by April 15, 2003 and the drug product information for Item 4 will be provided as Stage D of the "rolling submission" by September 30, 2003.

This pre-submission is provided in electronic format on a digital tape according to the January 1999 "Guidance for Industry Providing Regulatory Submissions in Electronic Format – NDAs.". The electronic submission size is approximately 1.5 gigabytes for this portion of the submission. All electronic media have been checked by representatives of Lilly Information Technology and have been verified to be free of known viruses. The virus checking software was Norton Antivirus Corporate Edition version 7.51.847 using Virus Definition File 50312q created on March 12, 2003 and Scan Engine 4.1.0.6. As specified in the above Guidance, a paper review copy containing 27 volumes is included in this submission.

The Division of Oncology Drug Products (DODP) and Lilly have met to discuss this NDA at Pre-NDA meetings on January 30, 2002 and again on September 6, 2002.

This NDA is being submitted as a "rolling" submission as per the Fast Track Designation for Alimta in this indication granted by the FDA on June 10, 2002. As per agreements between Lilly and DODP at the September 6, 2002 Pre-NDA meeting, this NDA submission will be done in four stages as indicated below:

- o Stage A (by October 31, 2002—actual submission was on October 24, 2002)
- o Stage B (by March 31, 2003)
- o Stage C (by April 15, 2003)
- o Stage D (by September 30, 2003)

This pre-submission contains Stage B of the rolling NDA. Stage B includes the following:

- Item 1 – Table of contents, index and certain administrative documents
- Item 2 – Proposed labeling (please note that the package insert labeling may be updated when Stage D is submitted in September of 2003 to reflect any changes needed for the drug product compatibility and stability portions of the package insert)
- Item 3 – Application summary
- Item 6 – Two new pharmacokinetic (PK) reports (addendum 1 and addendum 2 to study JMAW) on the Alimta/aspirin and Alimta/ibuprofen interaction studies. These two new PK reports are provided in an electronic version along with the previous PK reports submitted in Stage A of the rolling NDA.
- Item 8 – Study reports for the five remaining critical clinical studies (JMAP, JMAU, JMAW, JMAY and JMBZ) and the remaining clinical study reports (see Table of Contents for Item 8 for the listing of studies provided in Stage B). These study reports are provided in an electronic version along with the previous study reports (JMCH and JMDR) submitted in Stage A of the rolling NDA.

Item 8 also contains the following to complete the clinical package:

- Integrated Summary of Efficacy
- Integrated Summary of Safety
- Integrated Summary of Benefit/Risk
- Item 11 – Datasets relating to the clinical pharmacology reports for the JMAW addenda and for other clinical studies not previously submitted in Stage A
- Item 12 – Clinical report forms (CRFs) for notable patients (deaths, serious adverse events, discontinuation because of adverse events, and responders) for the five remaining critical studies (JMAP, JMAU, JMAW, JMAY and JMBZ)
- Item 19 – Financial disclosure for the seven clinical studies (JMCH, JMDR, JMAP, JMAU, JMAW, JMAY and JMBZ) as agreed to by DODP at the January 30, 2002 Pre-NDA meeting
- Item 20 – Other – the Risk Management Plan

Please note that the Alimta malignant pleural mesothelioma indication was granted Orphan Drug Designation on August 28, 2001. As a result of the Orphan Drug Designation, the sponsor is:

- 1) Not required to provide evidence of safety and efficacy in pediatric populations
- 2) Exempt from submitting the PDUFA User's fee. The User Fee ID# is 4249 as indicated on Form 3397 provided in Item 1 of Stage A.

The following contact information was previously provided with Stage A in October 2002. There have been no changes in the contact information. In order to coordinate our activities with yours, we suggest that any facsimile (FAX) or other written communications regarding this file, regardless of subject, be directed to:

Debasish Roychowdhury, M.D.  
Director, U.S. Regulatory Affairs  
Eli Lilly and Company  
Lilly Research Laboratories  
Lilly Corporate Center  
Indianapolis, IN 46285  
FAX number (317) 433-2255

Telephone calls or E-Mails regarding overall submission or clinical / preclinical matters should be made to:

- Mr. John F. Worzalla  
Regulatory Research Scientist, U.S. Regulatory Affairs  
(317) 276-5052 (work)  
(866) 478-6616 (pager)  
FAX: (317) 276-1652  
E-Mail address: [worzalla@lilly.com](mailto:worzalla@lilly.com)  
(317) 251-0957 (home)

In Mr. Worzalla's absence please contact:

- Dr. Debasish Roychowdhury  
(317) 433-6604 (work)  
(317) 332-4268 (cellular)  
FAX: (317) 433-2255  
E-mail address: [dfr@lilly.com](mailto:dfr@lilly.com)  
(317) 566-0935 (home)

Telephone calls regarding chemistry, manufacturing or control issues should be made to:

- Mr. Jeffrey R. Ferguson  
(317) 433-5615 (work)  
(317) 502-2208 (cellular)  
FAX: (317) 276-1887  
E-mail address: [ferguson\\_jeffrey\\_r@lilly.com](mailto:ferguson_jeffrey_r@lilly.com)  
(317) 818-9070 (home)

In Mr. Ferguson's absence please contact:

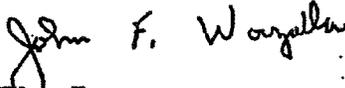
- Diane Zezza, Ph.D.,  
Director, Global Regulatory Affairs, CM&C  
(317) 433-9882 (work)  
(317) 997-5491 (cellular)  
(877) 793-1062 (pager)  
FAX (317) 276-1887  
E-mail address: [zezza\\_d@lilly.com](mailto:zezza_d@lilly.com)

On holidays or weekends, please call Mr. Worzalla, Dr. Roychowdhury or Mr. Ferguson at home using the telephone numbers provided.

Close liaison between the Lilly representatives listed above will result in any messages, no matter how received, being brought to the attention of all concerned. Please let us know if there are any additional ways we may be of assistance during the review of this NDA. Lilly appreciates DODP's continued assistance and cooperation.

Sincerely,

Eli Lilly & Company



John F. Weizalla  
Regulatory Research Scientist  
U.S. Regulatory Affairs

Enclosures

cc: Ms. Patricia Garvey, Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Drug Products, HFD-150  
1451 Rockville Pike  
Rockville, Maryland 20852-1448

Lilly Research Laboratories  
A Division of Eli Lilly and Company  
Lilly Corporate Center  
Indianapolis, Indiana 46285 U.S.A.

THIS SUBMISSION CAN BE FOUND IN 3 RED BINDERS AT THE END OF THIS FILE

Phone 317 276 2000

March 27, 2003

**Pre-Submission for Original Application, NDA 21-462**

Central Document Room  
Center for Drug Evaluation and Research  
Food and Drug Administration  
12229 Wilkins Avenue  
Rockville, MD 20852

**Re: NDA 21-462, Alimta<sup>®</sup> (pemetrexed, LY231514) – Pre-Submission – Stage C**

This letter accompanies the enclosed pre-submission of an original New Drug Application (NDA) for Alimta<sup>®</sup> (pemetrexed, LY231514) in combination with cisplatin for the indication of malignant pleural mesothelioma. This submission constitutes Stage C of the “rolling” submission of NDA 21-462 and contains the complete drug substance chemistry, manufacturing and control (CMC) information for pemetrexed disodium heptahydrate. The specific content of Stage C is outlined below. Stage A and Stage B of the NDA were submitted on October 24, 2002 and March 24, 2003, respectively, and represent, collectively, the complete pre-clinical and clinical sections of the NDA. Stage D of the “rolling” submission for NDA 21-462 is targeted for submission by September 30, 2003 and will contain the complete drug product sections, and thereby complete all NDA submission content requirements.

Stage A and Stage B of the NDA were submitted and organized according to 21 CFR.314.50 and followed the January 1999 “Guidance for Industry Providing Regulatory Submissions in Electronic Format – NDAs”. However as previously discussed and agreed with Division of New Drug Chemistry I (DNDC I) personnel, the CMC sections (Item 4) of this NDA will be provided using the ICH Common Technical Document (CTD) format and numbering. To combine both formats within Stage C, Item 4 contains the complete drug substance information using the CTD format that additionally incorporates the general principles of electronic formatting outlined in the January 1999 “Guidance for Industry Providing Regulatory Submissions in Electronic Format – NDAs”. Item 1 of Stage C contains review aides comparing the CTD to the standard NDA submission format and numbering to facilitate review of the CMC sections in Item 4.

The Stage C submission is supplied in electronic format on one CD-ROM. The size of the submission is less 4 MB. The electronic media has been checked and verified to be free of known viruses. The virus checking software was Norton Antivirus Corporate Edition version 7.51.847 using Virus Definition File 50312q created on March 12, 2003 and Scan Engine 4.1.0.6. As specified in the above Guidance, a paper review copy containing 3 volumes is included in this submission.

As agreed during the September 6, 2002 Pre-NDA meeting, Item 1 of this submission also contains a certification stating that the drug substance manufacturing, packaging and control sites listed in Stage C are ready for pre-approval inspections, if required. Additionally, this pre-submission contains the following:

**Item 1 (NDA Index and Administrative Documents)**

**Item 3 (Application Summary- Drug Substance)**

**Item 4 (Chemistry, Manufacturing and Control)**

Drug substance sections provided in CTD format, consisting of the Quality Overall Summary (QOS – Module 2.3.S) and the Quality Body of Data (Module 3.2.S) sections.

**Item 7 (Microbiology)**

This section is not applicable for this NDA submission.

**Item 14 (Patent Certification)**

Patent certification was provided with Stage A.

**Item 15 (Establishment Description)**

This section is not applicable in this NDA submission.

**Item 16 (Debarment Certification)**

Debarment Certification was provided with Stage A.

**Item 17 (Field Copy Certification)**

Field Copy Certification for the drug substance content is provided in Item 1.

**Item 20 (Other)**

Note to Reviewer and Stage C review aid.

The submission contact information, previously provided with Stage A and Stage B, is included below for your convenience. In order to coordinate our activities with yours, we suggest that any facsimile (FAX) or other written communications regarding this file, regardless of subject, be directed to:

Debasish Roychowdhury, M.D.  
Director, U.S. Regulatory Affairs  
Eli Lilly and Company  
Lilly Research Laboratories  
Lilly Corporate Center  
Indianapolis, IN 46285  
FAX number (317) 433-2255

Telephone calls regarding chemistry, manufacturing or control issues contained in Stage C should be made to:

- Mr. Jeffrey R. Ferguson  
(317) 433-5615 (work)  
(317) 502-2208 (cellular)  
FAX: (317) 276-1887  
E-mail address: [ferguson\\_jeffrey\\_r@lilly.com](mailto:ferguson_jeffrey_r@lilly.com)  
(317) 818-9070 (home)

In Mr. Ferguson's absence please contact:

- Diane Zezza, Ph.D.,  
Director, Global Regulatory Affairs, CM&C

(317) 433-9882 (work)  
(317) 997-5491 (cellular)  
(877) 793-1062 (pager)  
FAX (317) 276-1887  
E-mail address: [zezza\\_d@lilly.com](mailto:zezza_d@lilly.com)

Telephone calls or E-Mails regarding overall submission or clinical / preclinical matters should be made to:

- Mr. John F. Worzalla  
Regulatory Research Scientist, U.S. Regulatory Affairs  
(317) 276-5052 (work)  
(866) 478-6616 (pager)  
FAX: (317) 276-1652  
E-Mail address: [worzalla@lilly.com](mailto:worzalla@lilly.com)  
(317) 251-0957 (home)

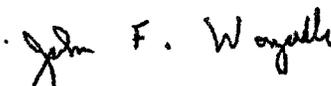
In Mr. Worzalla's absence please contact:

- Dr. Debasish Roychowdhury  
(317) 433-6604 (work)  
(317) 332-4268 (cellular)  
FAX: (317) 433-2255  
E-mail address: [dfr@lilly.com](mailto:dfr@lilly.com)  
(317) 566-0935 (home)

On holidays or weekends, please call Mr. Worzalla, Dr. Roychowdhury or Mr. Ferguson at home using the telephone numbers provided.

Close liaison between the Lilly regulatory representatives listed above will result in any messages, no matter how received, being brought to the attention of all concerned. Please let us know if there are any additional ways we may be of assistance during the review of this NDA. Lilly appreciates your continued assistance and cooperation.

Sincerely,  
Eli Lilly & Company

  
John F. Worzalla  
Regulatory Research Scientist  
U.S. Regulatory Affairs

Enclosures

cc: Ms. Patricia Garvey, Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Drug Products, HFD-150  
1451 Rockville Pike  
Rockville, Maryland 20852-1448



September 29, 2003

**Completion of Original Application, NDA 21-462**

Central Document Room  
Center for Drug Evaluation and Research  
Food and Drug Administration  
12229 Wilkins Avenue  
Rockville, MD 20852

**Re: NDA 21-462, Alimta<sup>®</sup> (pemetrexed, LY231514) – Final-Submission – Stage D**

This letter accompanies the enclosed submission containing all outstanding content of the chemistry, manufacturing and control (CMC) sections and thereby completes all NDA submission content requirements for Alimta<sup>®</sup> (pemetrexed, LY231514) in combination with cisplatin for the indication of malignant pleural mesothelioma.

This submission constitutes Stage D of the "rolling" submission of NDA 21-462 and contains the complete drug product CMC information for Pemetrexed for Injection. Additionally, updated drug product labeling and a safety update are provided in this submission. The specific content of Stage D is outlined below.

Stage A and Stage B of the NDA were submitted on October 24, 2002 and March 24, 2003, respectively, and represent, collectively, the complete pre-clinical and clinical sections of the NDA. Stage C of the NDA was submitted on March 27, 2003 and contained the complete drug substance portion of the CMC sections of the NDA. Stage C of NDA 21-462 was amended with additional drug substance lot release data in the CMC information amendment dated September 3, 2003. As previously agreed during the DODP September 6, 2002 Pre-NDA meeting, information provided in pre-submissions Stage A, Stage B and Stage C are not included in this submissions.

Stage A and Stage B of the NDA were submitted and organized according to 21 CFR.314.50 and followed the January 1999 "Guidance for Industry Providing Regulatory Submissions in Electronic Format – NDAs". However as previously discussed and agreed with Division of New Drug Chemistry I (DNDC I) personnel, the CMC sections

(Item 4 submitted in Stages C and D) of this NDA are provided using the ICH Common Technical Document (CTD) format and numbering. To combine both formats within Stage D, Item 4 contains the complete drug product information using the CTD format that additionally incorporates the general principles of electronic formatting outlined in the January 1999 "Guidance for Industry Providing Regulatory Submissions in Electronic Format – NDAs". Item 20 contains a review aide comparing the CTD to the standard NDA submission format and numbering to facilitate review of Item 4.

The Stage D submission is supplied in electronic format on one CD-ROM. The size of the submission is approximately 79MB. The electronic media has been checked and verified to be free of known viruses. The virus checking software was Norton Antivirus Corporate Edition version 7.51.847 using Virus Definition File 50918g created on September 4, 2003 and Scan Engine 4.1.0.6. As specified in the above Guidance, a paper review copy is included with this submission.

As agreed during the September 6, 2002 Pre-NDA meeting, Item 1 of this submission also contains a certification stating that the drug product manufacturing, packaging and control sites listed in Stage D are ready for pre-approval inspections, if required. Additionally, this submission contains the following:

**Item 1 (NDA Index and Administrative Documents)**

**Item 2 (Updated Draft Labeling)**

The enclosed draft labeling has been updated with additional CMC information on the drug product. Also, Table 9 under "Other Adverse Events" has been updated as explained in the information amendment to NDA 21-462 sent to FDA on April 3, 2003 (copy of April 3, 2003 amendment provided in Appendix 1 to Item 2).

**Item 3 (Application Summary- Drug Substance and Drug Product)**

The Application Summary consists of the annotated labeling and CMC summary information. Labeling annotations specific to drug substance sections contained in Stage C do not contain live links within Stage D. Appendix 1 to the Application Summary contains a "Manual Cross-Reference Links Spreadsheet" summarizing the annotated label cross-references to the Stage C (drug substance) submission.

**Item 4 (Chemistry, Manufacturing and Control)**

Drug product sections provided in CTD format, consisting of the Quality Overall Summary (QOS -- Module 2.3.P), Quality Body of Data (Module 3.2.P), Appendices (Module 3.2.A), and US Regional Information (Module 3.2.R) sections.

**Item 7 (Microbiology)**

This section is not applicable for this NDA submission.

**Item 9 (Safety Update Report)**

The first safety update was provided as an amendment to NDA 21-462 on July 23, 2003. A second updated safety update is being provided with this submission; also a copy of the first safety update that was earlier provided on July 23 is being provided with this submission.

**Item 13 (Patent Information)**

Patent information was provided back with Stage A, but this did not include completed FDA 3542a forms. Completed 3542a forms are being provided with this submission.

**Item 14 (Patent Certification)**

Patent certification was provided with Stage A.

**Item 15 (Establishment Description)**

This section is not applicable in this NDA submission.

**Item 16 (Debarment Certification)**

Debarment Certification was provided with Stage A.

**Item 17 (Field Copy Certification)**

Field Copy Certification for the drug product content is provided in Item 1.

**Item 20 (Other)**

Note to Reviewer and Stage D review aid.

The submission contact information, previously provided with Stage A, Stage B and Stage C is included below for your convenience. In order to coordinate our activities with yours, we suggest that any facsimile (FAX) or other written communications regarding this file, regardless of subject, be directed to:

Debasish Roychowdhury, M.D.  
Director, U.S. Regulatory Affairs  
Eli Lilly and Company  
Lilly Research Laboratories  
Lilly Corporate Center  
Indianapolis, IN 46285  
FAX number (317) 433-2255

Telephone calls regarding chemistry, manufacturing or control issues contained in Stage C and D should be made to:

Mr. Jeffrey R. Ferguson  
Regulatory Research Scientist, Global Regulatory CM&C  
(317) 433-5615 (work)  
(317) 502-2208 (cellular)  
FAX: (317) 276-1887  
E-mail address: [ferguson\\_jeffrey\\_r@lilly.com](mailto:ferguson_jeffrey_r@lilly.com)  
(317) 818-9070 (home)

In Mr. Ferguson's absence please contact:

Diane Zezza, Ph.D.,  
Director, Global Regulatory Affairs, CM&C  
(317) 433-9882 (work)  
(317) 997-5491 (cellular)  
FAX (317) 276-1887  
E-mail address: [zezza\\_d@lilly.com](mailto:zezza_d@lilly.com)  
(317) 733-8604 (home)

Telephone calls or E-Mails regarding overall submission or clinical / preclinical matters should be made to:

Mr. John F. Worzalla  
Regulatory Research Scientist, U.S. Regulatory Affairs  
(317) 276-5052 (work)  
(866) 478-6616 (pager)  
FAX: (317) 276-1652  
E-Mail address: [worzalla@lilly.com](mailto:worzalla@lilly.com)  
(317) 251-0957 (home)

In Mr. Worzalla's absence please contact:

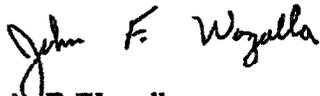
Dr. Debasish Roychowdhury  
(317) 433-6604 (work)  
(317) 332-4268 (cellular)  
FAX: (317) 433-2255  
E-mail address: [dfr@lilly.com](mailto:dfr@lilly.com)  
(317) 566-0935 (home)

On holidays or weekends, please call Mr. Worzalla, Dr. Roychowdhury, Mr. Ferguson or Dr. Zezza at home using the telephone numbers provided.

Close liaison between the Lilly regulatory representatives listed above will result in any messages, no matter how received, being brought to the attention of all concerned. Please let us know if there are any additional ways we may be of assistance during the review of this NDA. Lilly appreciates your continued assistance and cooperation.

Sincerely,

Eli Lilly & Company



John F. Worzalla  
Regulatory Research Scientist  
U.S. Regulatory Affairs

Enclosures

cc: Ms. Patricia Garvey, Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Drug Products, HFD-150  
1451 Rockville Pike  
Rockville, Maryland 20852-1448

## Note to Reviewer NDA 21-462

### Alimta<sup>®</sup> (pemetrexed, LY231514) for the Indication of Malignant Pleural Mesothelioma

#### ***Pre-Submission***

This Note to Reviewers accompanies Stage D of a "rolling submission" under Fast Track designation as agreed to by Division of Oncology Drug Products at the September 6, 2002 Pre-NDA Meeting.

#### ***Introduction***

Lilly is submitting this NDA to gain approval to market Alimta (pemetrexed, LY231514) in combination with cisplatin for the indication of treatment of patients with malignant pleural mesothelioma. Alimta is an antifolate agent that targets several key folate-dependent enzymes in the de novo biosynthesis of thymidine and purine nucleotides. Malignant pleural mesothelioma is a rare type of cancer for which there is no current standard of treatment and there is no FDA approved therapy. Alimta was granted orphan-drug designation for the indication of malignant pleural mesothelioma by the Office of Orphan Products Development on August 28, 2001 (request #01-1451). Alimta was granted Fast Track designation for malignant pleural mesothelioma by the Division of Oncology Drug Products (DODP) on June 10, 2002.

This submission constitutes Stage D of the "rolling" submission of NDA 21-462 and contains the complete drug product CMC information for Pemetrexed for Injection. Additionally, updated drug product labeling and a safety update are provided in this submission. The specific content of Stage D is outlined below.

Stage A and Stage B of the NDA were submitted on October 24, 2002 and March 24, 2003, respectively, and represent, collectively, the complete pre-clinical and clinical sections of the NDA. Stage C of the NDA was submitted on March 27, 2003 and contained the complete drug substance portion of the CMC sections of the NDA. Stage C of NDA 21-462 was amended with additional drug substance lot release data in the CMC information amendment dated September 3, 2003. As previously agreed during the DODP September 6, 2002 Pre-NDA meeting, information provided in pre-submissions Stage A, Stage B and Stage C are not included in this submissions.

## ***Naming Conventions***

### **Drug Substance and Product**

Throughout this document, Alimta may be referred to by a variety of terms including LY231514, pemetrexed disodium (USAN), pemetrexed (INN) or Alimta (proprietary name). In its early stages of development, Alimta was also referred to as MTA (for Multi-Targeted Antifolate) or TSI (for Thymidylate Synthase Inhibitor), and thus these terms may also have been used.

The Division of Medication Errors and Technical Support (DMETS) completed a preliminary review of the propose proprietary name, Alimta. On June 14, 2002 DMETS stated that it has no objection to the use of the proposed proprietary drug name. DMETS cautioned that the FDA would re-review the proprietary name during the NDA review process.

## ***NDA Submission Information: Stage D Final Submission Containing Drug Product CMC Information***

### **Format and Organization of Stage D**

Stage A and Stage B of the NDA were submitted and organized according to 21 CFR.314.50 and followed the January 1999 "Guidance for Industry Providing Regulatory Submissions in Electronic Format - NDAs". However as previously discussed and agreed with Division of New Drug Chemistry I (DNDC I) personnel, the CMC sections (Item 4 submitted in Stages C and D) of this NDA are provided using the ICH Common Technical Document (CTD) format and numbering. To combine both formats within Stage D, Item 4 contains the complete drug product information using the CTD format that additionally incorporates the general principles of electronic formatting outlined in the January 1999 "Guidance for Industry Providing Regulatory Submissions in Electronic Format - NDAs". Item 20 contains a review aide comparing the CTD to the standard NDA submission format and numbering to facilitate review of the CMC sections in Item 4.

**Stage D Submission Content**

Stage D of the NDA contains the following sections and content:

**Cover Letter**

Sponsor contact information is provided in the cover letter.

**Item 1 (NDA Index and Administrative Documents)****Item 2 (Updated Draft Labeling)**

The enclosed draft labeling has been updated with additional CMC information on the drug product. Also, Table 9 under "Other Adverse Events" has been updated as explained in the information amendment to NDA 21-462 sent to FDA on April 3, 2003 (copy of April 3, 2003 amendment provided in Appendix 1 at the end of this section).

**Item 3 (Application Summary- Drug Substance and Drug Product)**

The Application Summary consists of the annotated labeling and CMC summary information. Labeling annotations specific to drug substance sections contained in Stage C do not contain live links within Stage D. Appendix 1 to the Application Summary contains a "Manual Cross-Reference Links Spreadsheet" summarizing the annotated label cross-references to the Stage C (drug substance) submission.

**Item 4 (Chemistry, Manufacturing and Control)**

Drug product sections provided in CTD format, consisting of the Quality Overall Summary (QOS - Module 2.3.P), Quality Body of Data (Module 3.2.P), Appendices (Module 3.2.A), and US Regional Information (Module 3.2.R) sections.

**Item 7 (Microbiology)**

This section is not applicable for this NDA submission.

**Item 9 (Safety Update Report)**

As agreed between DODP and Lilly at the September 6, 2002 Pre-NDA meeting, this submission (Stage D) contains a second safety update reflecting updates since the first safety update submitted to NDA 21-462 on July 23, 2003. A copy of the first safety update that was earlier provided on July 23 is being provided with this submission.

**Item 13 (Patent Information)**

Patent information was provided back with Stage A, but this did not include completed FDA 3542a forms. Completed 3542a forms are being provided with this submission.

**Item 14 (Patent Certification)**

Patent certification was provided with Stage A.

**Item 15 (Establishment Description)**

This section is not applicable in this NDA submission.

**Item 16 (Debarment Certification)**

Debarment Certification was provided with Stage A.

**Item 17 (Field Copy Certification)**

Field Copy Certification for the drug product content is provided in Item 1.

**Item 20 (Other)**

Note to Reviewer and Stage D review aid.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-462

Eli Lilly & Company  
Attention: John F. Worzalla  
Regulatory Research Scientist, U.S. Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Mr. Worzalla:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Alimta® (pemetrexed, LY231514)  
Review Priority Classification: Priority (P)  
Date of Application: September 29, 2003  
Date of Receipt: September 30, 2003  
Our Reference Number: NDA 21-462

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 29, 2003 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be March 31, 2003.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

RECEIVED OCT 20 2003

NDA 21-462

Page 2

U.S. Postal Service:

Center for Drug Evaluation and Research  
Division of Oncology Drug Products, HFD-150  
Attention: Division Document Room, 3067  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Drug Products, HFD-150  
Attention: Document Room 3067  
1451 Rockville Pike  
Rockville, Maryland 20852

If you have any questions, call Patty Garvey, Regulatory Project Manager, at (301) 594-5766.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur  
Director  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**  
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/s/  
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Dotti Pease  
10/10/03 02:40:58 PM  
signing for Richard Pazdur, M.D.

RECEIVED OCT 20 2003



FILING COMMUNICATION

NDA 21-462

Eli Lilly & Company  
Attention: John F. Worzalla  
Regulatory Research Scientist, U.S. Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Mr. Worzalla:

Please refer to your September 29, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alimta® (pemetrexed, LY231514).

We also refer to your submissions dated October 24, November 22, December 6, 2002; January 10, 28, February 13, 27, March 24, 27, April 3, May 9, 12, 29, June 18, 26, July 29, 30, August 8, 15, 21, 28, September 2, 3, 4, 9, 12, 15, 16, 19, 22, 29, October 6, 7, 20, and November 4, 5, 6, and 7, 2003.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on November 29, 2003 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Patty Garvey, Regulatory Project Manager, at (301) 594-5766.

Sincerely,

*{See appended electronic signature page}*

Dotti Pease  
Chief, Project Management Staff  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/  
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Patricia Garvey  
11/19/03 01:41:35 PM  
Signed for Dotti Pease

RECEIVED NOV 25 2003



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 21-462

Eli Lilly & Company  
Attention: John F. Worzalla  
Regulatory Research Scientist, U.S. Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Mr. Worzalla:

Please refer to your new drug application (NDA) dated September 29, 2003, received September 30, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alimta® (pemetrexed, LY231514).

We acknowledge receipt of your submissions dated October 24, November 22, December 6, 2002; January 10, 28, February 13, March 24, 27, April 3, May 9, 12, 29, June 18, 26, 30, July 29, 30, August 8, 15, 21, 28, September 2, 3, 4, 9, 12, 15, 16, 19, 22, 29, October 6, 7, 20, November 4, 5, 6, 14, 18, 24, 26, December 1, 4, 5, 10, 11, 12, 15, 16, 29, 2003, and January 12, 2004.

This new drug application provides for the use of Alimta® (pemetrexed, LY231514) in the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are otherwise not candidates for curative surgery.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon attached labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and the patient package insert). Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission “FPL for approved NDA 21-462.” Approval of this submission by FDA is not required before the labeling is used.

NDA 21-462

Page 2

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Oncology Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising  
And Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The Med-Watch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at [www.fda.gov/medwatch/report/mmp.htm](http://www.fda.gov/medwatch/report/mmp.htm).

If you have any questions, call Patty Garvey, Regulatory Project Manager, at (301) 594-5766.

Sincerely,  
{See appended electronic signature page}

Robert Temple, M.D.  
Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure: labeling

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

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/s/

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Robert Temple  
2/4/04 07:52:20 PM

### **3.H.2.1. Regulatory History**

#### **3.H.2.1.1. Regulatory History and Agreements**

The original IND for LY231514 was submitted on 8 July 1992 and was assigned IND number 40,061 by the FDA on 14 July 1992.

The first human dose of LY231514 was administered on 29 September 1992.

Four End of Phase 2 (EOP2) meetings have occurred between the Division of Oncology Drugs (DODP) and Lilly at which the malignant pleural mesothelioma (MPM) indication was discussed. The initial EOP2 meetings on MPM took place on 23 September 1998 (Biopharmaceutics) and 25 September 1998 (Clinical). Lilly requested an additional EOP2 meeting to discuss the possibility for accelerated approval in MPM, and this meeting was held on 25 June 1999. Another EOP2 meeting was held between DODP and Lilly on 1 March 2000 to discuss the ramifications of the addition of folic acid and vitamin B<sub>12</sub> supplementation for the ongoing registration trial (JMCH) in MPM.

LY231514 for MPM received Orphan Drug designation from the Office of Orphan Drug Products on 28 August 2001.

The first pre-NDA meeting for the MPM indication was held on 31 January 2002.

LY231514 for MPM received Fast Track Designation by the FDA on 10 June 2002, and thus a second pre-NDA meeting was held on 6 September 2002 to discuss the mechanism for a rolling submission for the LY231514 MPM NDA. The first portion of the LY231514 rolling NDA was sent to the FDA on 24 October 2002. Lilly made a 45-day presentation to DODP on 3 December 2002, during which the sponsor presented the basis for approval of the LY231514 MPM NDA.

Table 3.H.3 summarizes the significant FDA meetings, communications, and IND submissions over the clinical development history of LY231514 for the MPM indication.

**Table 3.H.3. History of Regulatory Correspondence**

Date	IND Serial # or Type of Communication	Comments
7/8/92	#000 Submitted IND	Lilly submitted the original IND application for LY231514 disodium.
7/14/92	FDA Letter to Lilly	FDA assigns IND # 40,061 to LY231514 disodium (communication received by Lilly on 7/21/92).
9/29/92	N/A	First human dose of LY231514 given in the Phase 1 study H3E-MC-JMAB.
07/13/98	#125 Request for EOP2 Meeting	Lilly requested an EOP2 Meeting to discuss dose and schedule of LY231514 and the MPM, NSCLC, and head and neck cancer indications. Lilly proposed discussions on efficacy endpoints, active controls, analysis plans, and safety related to patient exposure, as these issues related to the timing and quality of an NDA submission and review.
07/29/98	#126 Briefing Document	Lilly provided the scientific rationale for the use of LY231514 and gave the development history. Lilly posed questions to the FDA regarding MPM, NSCLC, head and neck cancer, NSAID usage, population PK, renal impairment, hepatic impairment, multivariate analysis, risk to benefit ratio, and the use of unidimensional measurements.
09/08/98	#130 Revisions to Briefing Document	Lilly told the FDA it wanted the EOP2 Meeting to focus on MPM and NSCLC, and Lilly is withdrawing the questions related to the head and neck cancer indication. Lilly posed some additional questions relating to the use of concentrated solution for injection and the use off-the-shelf vitamins in place of folic acid.
09/23/98	EOP2 Meeting #1 (Biopharm) between Lilly and the FDA	At the EOP2 Biopharmaceutics meeting between the FDA and Lilly, the FDA said that PK data will be reviewed, but it may be inadequate to rule out the absence of interaction between LY231514 and ibuprofen, and that further animal data would be considered with examples from each class of NSAIDs. The FDA was interested in having PK population data as soon as possible for review, and Lilly will follow guidelines for analysis of renal impairment study. Lilly agreed that patients will be followed for liver function, and the FDA agreed that the preclinical studies were in order concerning toxicity and PK studies.

(continued)

Table 3.H.3.

## History of Regulatory Correspondence (continued)

Date	IND Serial # or Type of Communication	Comments
09/25/98	EOP2 Meeting #2 (Clinical) between Lilly and the FDA	At the EOP2 Clinical meeting between the FDA and Lilly, the FDA recommended a dose of 500 mg/m <sup>2</sup> , survival as primary endpoint in MPM, and that clinical related symptoms (pain, shortness of breath, etc.) should be used for gaining approval if survival advantage cannot be demonstrated. FDA said unidimensional measurements were uncertain to provide information to determine response rate. The FDA said that it would be a better study if tumor-related symptoms were assessed in a blinded trial, and that accelerated approval based on response rate was unlikely in MPM. The FDA said that although approval for a first indication usually requires two studies, the FDA might be willing to grant approval (depending on the quality of the data) based on a single trial in MPM with supporting evidence from a trial "in a closely-related disease, ie, NSCLC." The FDA stated the addition of vitamins to the LY231514 arm without data that efficacy is not reduced is risky, and the FDA would like to know the basis for the determination that the addition of vitamins would not affect efficacy.
11/06/98	#134 Annual Report	The 1998 Annual Report contained a section on multivariate analysis where the toxicities reported for LY231514 patients could be predicted from pretherapy homocysteine levels.
02/12/99	#150 Protocol Amendment	Lilly submitted protocol amendment (a) to the MPM registration trial, JMCH. This protocol amendment incorporated the changes suggested by the FDA in the End of Phase 2 Meeting on 25 September 1998. This is the version of the protocol used to enroll the initial patients. The major changes in this amendment included: (1) the starting dose was reduced to 500 mg/m <sup>2</sup> ; (2) survival was made the new primary endpoint; (3) the secondary endpoints were redefined; (4) the trial was single-blinded (at the patient level) for tumor-related symptoms; and (5) administration of vitamins was removed from the study.

(continued)

**Table 3.H.3. History of Regulatory Correspondence (continued)**

Date	IND Serial # or Type of Communication	Comments
03/08/99	FAX from FDA to Lilly	The FDA sent Lilly their medical review of the 08 February 1999 submission (rationale for single-blinding) and the 12 February 1999 submission protocol amendment JMCH(a). The FDA wanted to know when final survival analysis would occur for JMCH. The FDA also said that the clinical benefit endpoint was not validated. The FDA again pointed out that JMCH must be double-blind – “Since the FDA is considering one positive trial in MPM plus a positive trial in a closely-related malignancy as the basis for approval, the one MPM trial must be rigorous and above reproach.” The FDA wanted to know the minimum time requirement that 50% of patients must have achieved to be evaluable and the number of patients enrolled/evaluable for the interim analysis. The FDA said that if JMCH is single-blind, then clinical benefit assessment will not be considered an option for full approval. The FDA strongly urged Lilly to design and perform a second, randomized pivotal trial in MPM, e.g., cisplatin + LY231514 compared with cisplatin + gemcitabine.
03/29/99	SN 158 CMC Meeting Package	Lilly submitted a pre-meeting information package for the scheduled 14 April 1999 teleconference between FDA and Lilly representatives. The focus of the teleconference was the selection of starting materials for the LY231514 disodium septahydrate process.
4/12/99	FDA FAX regarding briefing document dated 29 March 1999	FDA replied to Lilly’s CMC meeting package dated 29 March 1999 (SN 158) to cancel the 14 April 1999 teleconference and to confirm that the FDA agreed with Lilly’s proposed selection of starting materials for the septahydrate (heptahydrate) drug substance synthesis.
4/20/99	FAX from FDA to Lilly	The FDA completed their review of amendment JMCH(a) submitted on 12 February 1999. The FDA stated that (1) the rationale for the interim analysis was unclear, particularly because the interim was based on clinical benefit endpoints rather than survival (the primary endpoint for the final analysis). Thus, an efficacy advantage at the interim might not be sufficient for approval. (2) The interim Type I error level, based on assumptions about correlation between clinical benefit and survival, may be too high or low. (3) Although the stratification scheme is acceptable, there may be some problems in the actual analysis. (4) There may not be enough patients for balancing against such a large number of randomization factors. (5) Lilly must be explicit as to whether the final survival analysis is an adjusted or unadjusted log-rank test. (Note this FAX was sent to Lilly originally on 20 April 1999 and re-sent on 24 June 1999.)

(continued)

**Table 3.H.3. History of Regulatory Correspondence (continued)**

Date	IND Serial # or Type of Communication	Comments
06/10/99	#170 Briefing Document	Lilly submitted the briefing document for the second EOP2 meeting on 25 June 1999. The briefing document posed questions related to accelerated approval, the use of unidimensional measurements, time to tumor progression as a surrogate for survival, clinical benefit as a valid endpoint and the single agent Phase 2 trial in MPM. An attachment to the briefing document provided Lilly's responses to the FDA statistical review of JMCH(a) on 20 April 1999.
06/25/99	EOP2 Meeting (Responses and Accelerated Approval) between Lilly and the FDA	FDA stated that it "is still concerned about the ability to assess response adequately in MPM. However if responses can be convincingly demonstrated and there are clinically relevant and statistically significant differences on all three endpoints (response rate, time to progression and clinical benefit), the results would be sufficient for accelerated approval." Lilly stated its commitment to complete the 280 patient trial in MPM even if the results were positive at interim analysis. The FDA will consider unidimensional measurements provided data support a correlation between unidimensional and bidimensional lesions in patients who exhibit both types. For clinical benefit, FDA said it would give more weight to separate assessment of each component of proposed composite clinical benefit endpoint. Also if clinical benefit is to suffice for approval, then double-blinding is strongly advised. FDA requested Lilly submit written statistical plan for analysis of clinical benefit. FDA stated, "We remind you of our agreement that the randomized control trial in NSCLC is essential to support the single randomized control trial in MPM".
9/15/99	#182 Response to Stat Review	Lilly submits response to 20 April 1999 statistical review of JMCH. Lilly provides further information and algorithm for clinical benefit endpoint and addresses FDA statistical concerns re: protocol amendments JMCH(b) and JMDR(a).
11/08/99	#191 Annual Report	1999 Annual Report contained updated homocysteine – toxicity safety analysis (pp. 1-5), and cover letter pointed out relationship between high baseline homocysteine levels and severe toxicity noted in LY231514 trials. Lilly will recommend collection of baseline homocysteine levels in all new protocols and increased vigilance for patients who present with high baseline homocysteine.

(continued)

**Table 3.H.3. History of Regulatory Correspondence (continued)**

Date	IND Serial # or Type of Communication	Comments
11/24/99	#194 IND Safety Report	Further analysis of homocysteine levels in LY231514 patients led to the conclusion that high baseline homocysteine levels are correlated with increased risk of hematologic and non-hematologic toxicities. A letter was sent to LY231514 investigators informing them to exclude patients with high baseline homocysteine levels ( $\geq 12 \mu\text{M}$ ).
12/03/99	#195 IND Safety Report Follow-Up	A letter was sent to investigators on the MPM registration trial (JMCH) informing them to no longer exclude patients with high baseline homocysteine, but rather to supplement patients with folic acid and vitamin B <sub>12</sub> . This submission also included updated LY231514 safety analysis showing details of relationship between baseline homocysteine and toxicity in LY231514 patients.
12/10/99	#196 IND Safety Report Follow-Up	This submission included letters to investigators in trials other than JMCH informing them to no longer exclude patients with high baseline homocysteine, but rather to supplement patients with folic acid and vitamin B <sub>12</sub> . This submission also included a copy of the abbreviated safety analysis that was sent to the investigators. The letter to investigator and the abbreviated safety report was not sent to investigators on JMCH, JMAF, JMAS, JMAU and JMBV and the reasons these investigators were excluded are detailed.
12/21/99	#199 "Dear Investigator" Letter and Protocol Amendments	A "Dear Investigator" letter (dated 17 December 1999) was sent to the FDA along with protocol amendments specifying vitamin supplementation. It was recommended to investigators that they not enroll new patients prior to local IRB approval of the amendment. Lilly submitted protocol amendments for other studies to institute vitamin supplementation in these protocols (JMAV, JMAW, JMBT, JMCD and JMDL).
12/21/99	FAX from FDA to Lilly	The FDA Medical Officer reviewed submissions #191 and #195, and the Medical Officer does not support adding vitamins to the ongoing pivotal, randomized trial in MPM. He gave several reasons to support his position including (1) no statistical plan to evaluate and compare data to prior accumulated data, (2) adding vitamins appears to deviate from the sponsor's commitment to complete JMCH even if the results are positive at interim analysis, and (3) the information in the annual report for LY231514 toxicity does not appear to support the addition of vitamins. The FDA Medical Officer added that Lilly "may want to design a randomized trial of LY231514 +/- vitamins in MPM."

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Table 3.H.3.

## History of Regulatory Correspondence (continued)

Date	IND Serial # or Type of Communication	Comments
12/22/99	#200 Protocol Amendment JMCH(c)	Amendment (c) to the MPM registration trial, JMCH, was submitted. This amendment instituted addition of folic acid and vitamin B <sub>12</sub> for patients on JMCH and gives instructions for vitamin supplementation for new patients or for continuation on patients who began without vitamin supplementation. The amendment specifies what constitutes folic acid supplementation compliance and additionally gives a plan for a safety analysis in which the toxicity would be compared for cycles in which patients did and did not receive folic acid.
12/22/99	#201 Lilly Response to FDA Communication	In response to 21 December 1999 FDA communication, Lilly provided rationale for adding vitamins to the ongoing MPM registration trial – this included (1) Lilly statistical analysis plan [SAP] for JMCH, (2) Lilly's commitment to completing JMCH and (3) updated data on mortality in both arms of JMCH (five deaths on LY231514 plus cisplatin arm versus one death on cisplatin alone arm).
01/06/00	FAX from FDA to Lilly	FDA Medical Officer reiterated that after reviewing submissions #200 and #201, he still did not support the addition of vitamins to the ongoing pivotal MPM trial.
2/14/00	#206 Protocol Amendments JMCH(d), JMDR (b) and JMDR(c)	Protocol Amendment JMCH(d) provided re-wording to increase clarity. Protocol Amendment JMDR(b) instituted folic acid and vitamin B <sub>12</sub> supplementation for the single agent Phase 2 LY231514 trial in MPM. Protocol Amendment JMDR(c) provided re-wording to increase clarity.
02/16/00	#207 Briefing Document for 01 March Meeting	Lilly provided briefing document for upcoming 01 March 2000 meeting to discuss vitamin supplementation in ongoing MPM registration trial, JMCH. Included with this briefing document as an attachment was a list of communications between the FDA and Lilly concerning LY231514 for MPM.
3/1/01	EOP2 Meeting #3 (Vitamins)	EOP2 Meeting was held to discuss addition of vitamins to ongoing MPM registration trial. Lilly agreed to continue the MPM registration trial with vitamins using a recalculated sample size to provide adequate power (see 06 April 2000 entry for FDA minutes of this meeting). After 150 patients are treated on revised protocol, a pooled survival analysis will be done with the approximately 150 patients not supplemented with vitamins.. Lilly will provide vitamin dosing information and a new statistical plan for Study JMCH.

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**Table 3.H.3. History of Regulatory Correspondence (continued)**

Date	IND Serial # or Type of Communication	Comments
03/08/00	#212 Follow-Up Questions to March 1 Meeting	Lilly made Expedited Review Request for DODP response regarding the issue of supporting trials. At the March 1 meeting with the FDA, Dr. Pazdur stated in the consensus answer to Question #3, that the "FDA will get back to the sponsor on the number of trials in NSCLC and no commitment is made at this meeting.
03/20/00	#216 Lilly Version of March 1 Meeting Minutes	Lilly submitted their version of the meeting minutes from the March 1, 2000 meeting. Lilly asked that several items be noted that were not captured in minutes taken by the FDA during the meeting. Also Lilly provided answers to "Additional Comments from the FDA" that were provided in writing at the 01 March meeting (one comment on clinical benefit response and another comment on justification for use of vitamins). Additionally Lilly provided answers to FDA comments on protocol amendment JMCH(d) that was submitted 14 February 2000 (serial # 206) and a revised SAP for JMCH.
04/06/00	FAX from FDA to Lilly	FDA sent to Lilly the official meeting minutes of the 01 March 2000 meeting where vitamin supplementation in the ongoing MPM registration trial was discussed. The FDA minutes did not incorporate any of the notes or clarifications proposed by Lilly in the Lilly version of the meeting minutes (submission #216 on 20 March 2000).
4/25/00	FAX from FDA to Lilly	FDA response to Lilly submission #212 (Lilly question regarding supporting trials); FDA said that 2 <sup>nd</sup> line NSCLC could serve as the supporting trial for MPM indication, but that Phase 2 trials would not support the MPM indication
4/26/00	#224 Protocol Amendment JMDR(d)	Protocol amendment JMDR(d) stated the sample size was increased to assure that the trial would contain 41 vitamin supplemented patients; the lung density data would no longer be collected in this trial
5/19/00	FAX from FDA to Lilly	FDA responded with statistical comments to the Lilly 20 March 2000 submission of the Lilly statistical plan for JMCH. FDA asked for clarification of the interim survival for JMCH and the effects of the interim analysis on the final survival analysis. The FDA asked or clarification on the primary analysis for an accelerated approval and demonstration that a Type I error inflation will not result without the appropriate alpha adjustment. Also the FDA asked Lilly to specify either logrank or Wilcoxon analysis for the interim and final analyses; if both analyses will be considered as primary, then the alpha level should be adjusted for multiple analyses.

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**Table 3.H.3. History of Regulatory Correspondence (continued)**

Date	IND Serial # or Type of Communication	Comments
06/08/00	SN 233 EOP2 CMC Questions	Lilly submitted an amendment to the IND to confirm its planned approach on three topics: the API stability simulator, the matrixing of upright and inverted vials for drug product primary stability (for solution formulation), and the inclusion of two long-term storage conditions in the API primary stability study.
6/21/00	Teleconference between DODP and Lilly	A teleconference was held between FDA and Lilly to discuss supporting trials. The FDA agreed that the second line registration trial in NSCLC could support the MPM indication. FDA strongly discouraged a MPM submission on interim analysis of the secondary endpoints (response rate, time to tumor progression or "symptom benefit" without mature survival data. FDA also stated that "survival data would lead to a definitive conclusion regarding LY231514's clinical benefit."
7/12/00	#242 Protocol Amendment JMCH(e)	Protocol amendment JMCH(e) increased the sample size to allow for 280 patients that had been supplemented with vitamins (per 01 March 2000 EOP2 meeting); also amendment stated that lung density measurements were no longer being collected in this trial as sufficient data has been obtained. Additionally the amendment presented a revised primary efficacy analysis.
8/11/00	FDA FAX response to EOP2 CMC Questions	FDA (Ms. Vause) FAX dated 11 August 2002 provided FDA's responses to Lilly's questions dated 08 June 02 (SN 233). FDA agreed that the API stability simulator and primary stability study test conditions [(Lilly Questions (1) and (3))]. Further, FDA recommended a modification to our proposed matrix design for the drug product primary stability plan (Lilly Question 2).
8/28/00	SN 253 Response to FDA FAX dated 11 August 2000	This submission was made in response to the FDA FAX received 11 August 2000. Lilly agreed to FDA's suggestion in response to question 2 and reversed the upright/inverted schedules for the 25 mL presentation. We have revised the P1 protocol from page 19 of the original briefing document as shown.
8/23/00	FAX from FDA to Lilly	FDA response to Lilly's 06 July 2000 request for a special protocol assessment for Study JMEI (LY231514 vs docetaxel in second line NSCLC). In the submission of July 6, Lilly asked if JMEI will support the MPM claim. The FDA responded that the study is well controlled and will support the MPM claim, but that the proposed assessment of non-inferiority is not acceptable. Thus Study JMEI would need to demonstrate superiority to support the MPM claim

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Table 3.H.3.

## History of Regulatory Correspondence (continued)

Date	IND Serial # or Type of Communication	Comments
8/31/00	FAX from FDA to Lilly	FDA response to Lilly's 12 July 2000 submission (protocol amendment JMCH(f)). If lung density is dropped as a secondary endpoint, the results of the exploratory analysis of the 170 patients with lung densities should be submitted. FDA stated that although not all patients may have sufficient tissue for review of histopathology, the slides should be available for review by an independent pathologist. The rigor to the study will be decreased without independent review of all cases. FDA recommends a uniform, single dose of folic acid and vitamin B <sub>12</sub> , otherwise the results are subject to bias and uncertainty for review of the NDA and labeling. Pleural rind when considered for assessment of tumor response or progression should be prospectively identified at baseline. FDA wanted clarification of the interim analysis p-value. The final analysis on survival should be based on the protocol-specified number of deaths (also the interim analysis). FDA decried submission of interim analysis based on secondary endpoints without mature survival data.
2/6/01	#291 Protocol Amendment JMCH(f)	Lilly submitted protocol amendment JMCH(f). This amendment provided that the interim analysis of Study JMCH would be based on the primary endpoint of survival rather than on the secondary endpoints. In addition the alpha spend at the interim analysis was lowered to 0.01 to preserve a higher significance level testing at the final analysis. Lilly reiterated that the interim analysis will be performed under the auspices of a Data Monitoring Board comprised exclusively of members external to Lilly and that any decision to submit an NDA after the interim analysis will be based on the recommendation of this DMB.
3/20/01	#298 Request for Special Protocol Assessment	Lily requested a 45 day Special Protocol Assessment of the draft protocol for a second MPM registration trial, JMEW. The title of this trial is "A Randomized Phase 3 Trial Comparing LY231514 plus Best Supportive Care versus Best Supportive Care Alone in Previously Treated Patients with Locally Advanced or Metastatic Malignant Pleural Mesothelioma."

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Table 3.H.3.

## History of Regulatory Correspondence (continued)

Date	IND Serial # or Type of Communication	Comments
5/01/01	FAX from FDA to Lilly	DODP requested Lilly address several issues in NDA for LY231514. The first issue involved drug-drug interactions in conjunction with the 02 May 2001 EOP2 meeting to discuss the proposed registration trial of LY231514 plus gemcitabine in pancreatic cancer. DODP also asked, "What is the status of in vitro studies to determine whether LY231514 is an inhibitor, substrate or an inducer of cytochrome P-450 isozymes?" DODP also brought up the topic of organ dysfunction studies: "At the End-of-Phase 2 meeting with FDA on 23 September 1998, the sponsor committed to conducting renal impairment studies with LY231514 in accordance with the FDA Guidance for Industry on Renal Impairment studies. What is the current status of these studies?"
5/7/01	Communication from FDA to Lilly	Lilly received (11 May 2001) the FDA communication dated 07 May 2001 with DODP special clinical protocol assessment for the second line MPM trial, JMEW submitted as SN 298 on 20 March 2001. DODP agreed with the design of JMEW, the patient population, the comparator and also that Study JMEW could be supportive to a front line claim in MPM. DODP recommended that the number of stratification factors in JMEW be reduced.
5/10/01	#314 Charter for Data Monitoring Board	Lilly submitted charter for Data Monitoring Board (DMB) for MPM registration Study JMCH. The DMB will oversee the interim analysis of JMCH. Members of the DMB are all external to Lilly and only the DMB is authorized to review completely unblinded the interim efficacy and safety analysis. The interim analysis on JMCH will be based on primary endpoint of overall survival and the trial will not be stopped based on the results of the interim analysis.
5/21/01	Lilly Submission to the Office of Orphan Products	Lilly submitted request for Orphan Product Designation for LY231514 for MPM to the Office of Orphan Products Development. This submission was based on (1) the prevalence of MPM has been estimated at only 3930 cases in the US and (2) scientific rationale for the use in MPM.

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Table 3.H.3.

## History of Regulatory Correspondence (continued)

Date	IND Serial # or Type of Communication	Comments
5/29/01	#320 Response to 01 May FDA Biopharm Issues	Lilly responded to the 01 May FDA biopharm issues. (1) Regarding the drug-drug interaction studies for LY231514 with gemcitabine, Lilly stated that a trial is already being done using the general cancer patient population to study interactions between LY231514 and gemcitabine. (2) Regarding in vitro studies of cytochrome P-450 isozymes, Lilly stated that LY231514 would be predicted to not cause significant inhibition of the metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9 and CYP1A2. Because LY231514 is excreted largely unchanged in human urine, studies to determine whether LY231514 is a substrate for CYP-450 enzymes have not been carried out. Also enzyme induction studies have not been carried out with LY231514 since any significant enzyme induction in humans is not likely with a once every 21 day schedule. (3) Lilly gave an update on the clinical renal insufficiency Study JMAW and asked if the completed PK and clinical safety analyses could be submitted as part of the 120 day safety update rather than at the time of the NDA submission.
6/4/01	#323 Safety Update	Lilly submitted a safety update on the effects of folic acid and vitamin B <sub>12</sub> supplementation that was promised in SN 195 (03 December 1999) and again in the briefing document (SN 207 on 16 February 2000) for the 01 March 2000 EOP2 meeting. The results of this analysis showed that folic acid and vitamin B <sub>12</sub> supplementation led to a profound reduction in LY231514-related deaths as well as significant reductions in episodes of Grade 3 hematologic and Grade 3/4 nonhematologic toxicities associated with LY231514.
6/20/01	Teleconference with FDA regarding Biopharm issues	Teleconference was held between FDA and Lilly to discuss Biopharm issues. FDA stated that Lilly's 29 May 2001 responses to Issues #1 (drug-drug interactions between LY231514 and gemcitabine) and #2 (in vitro cytochrome P-450 studies) were acceptable responses. Regarding the third issue (organ dysfunction) FDA stated that the renal insufficiency study is potentially relevant to the drug's approval, and that FDA will wait for the results of the MPM interim analysis before making their decision and that this issue will be revisited at the pre-NDA meeting. The FDA again stated that the endpoint for the interim analysis of the MPM registration trial, JMCH, must be survival.

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