DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT #5

NDA 021462

Eli Lilly and Company
Attention: Daniel R. Brady, Ph.D., RAC
Lily Corporate Center
Indianapolis, IN 46285

Dear Dr. Brady:

Please refer to your correspondences dated March 23, 2010; April 12, 2010; and April 23, 2010; requesting changes to FDA's October 5, 2001, Written Request for pediatric studies for Alimta® (pemetrexed). We also refer to our July 3, 2002, correspondence that re-issued the October 5, 2001, Written Request under the Best Pharmaceuticals for Children Act and our May 7, 2004, correspondence that amended the Written Request.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on October 5, 2001, and as amended on May 4, 2004, remain the same. (Text added is underlined. Text deleted is ~~strikethrough~~.)

• ***Type of studies:***

Phase 2: Enrollment of at least 10 pediatric patients in each of the following disease strata: osteosarcoma, Ewing sarcoma/peripheral PNET, (b) (4) and neuroblastoma (b) (4) At least nine patients should be enrolled in a rhabdomyosarcoma stratum. The study should be performed at facilities that have the experience, support, and the expertise to care for children with cancer.

• ***Timeframe for submitting reports of the studies:***

Reports of the above studies must be submitted to the Agency on or before ~~July~~ October 15, 2010. Please keep in mind that pediatric exclusivity attached to existing patient protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Reports of the studies that meet the terms of the Written Request dated October 5, 2001, and re-issued July 3, 2002, as amended by this letter, must be submitted to the Agency as part of a new drug application or supplement to an approved new drug application on or before (b) (4) October 15, 2010, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a investigational new drug application with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission

"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- In accordance with section 505A(e)(2), if:

  1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  3) you have not marketed the formulation within one year after the Agency publishes such notice,

  the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that pemetrexed is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).

- In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

  - the type of response to the Written Request (i.e., complete or partial response);
  - the status of the application (i.e., withdrawn after the supplement has been filed or pending);
  - the action taken (i.e., approval, approvable, not approvable); or
  - the exclusivity determination (i.e., granted or denied).

- If your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results.

Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

If you have any questions, call Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products, HFD 150
Center for Drug Evaluation and Research

Attachment

NDA 021462

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Indianapolis, IN 46285

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We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on October 5, 2001, and as amended on April 16, 2007, remain the same.

Background:

The design of studies in pediatric oncologic drug development is discussed in detail in the guidance for industry, Pediatric Oncology Studies in Response to a Written Request.
http://www.fda.gov/cder/guidance/3745dft.pdf

Protocols for each of your studies should be submitted to the FDA for review prior to initiation of the studies. 'Each submission should review the overall development plan and justify the study designs.

• ***Type of studies:***

Phase 1: A dose finding study, including pharmacokinetics, with doses determined for all appropriate age groups. The number of patients entered should be sufficient to achieve Phase 1 objectives, which may be in the range of 18-25.

Phase 2: Enrollment of at least 10 pediatric patients in each of the following disease strata: osteosarcoma, Ewing sarcoma/peripheral PNET, and neuroblastoma. At least nine patients should be enrolled in a rhabdomyosarcoma stratum. The study should be performed at facilities that have the experience, support, and the expertise to care for children with cancer.

• ***Indication(s) to be studied (i.e.• objective of each study):***

Phase 1: Refractory solid tumors

Phase 2: Refractory or relapsed pediatric patients with osteosarcoma, Ewing sarcoma/peripheral PNET, rhabdomysarcoma and neuroblastoma.

• ***Age group in which study(ies) will be performed:***

Infants> 1 month of age to adolescents

• *Study endpoints:*

The Phase 1 study should have maximum tolerated dose (MTD) (or biologically effective dose = BED) as a primary endpoint with measurements of blood (and CSF if appropriate) concentrations, and clearance as secondary endpoints. A traditional or sparse sampling technique may be used to estimate the PK parameters and develop pharmacokinetic-pharmacodynamic relationship.

The Phase 2 study should have a disease-specific surrogate or clinically relevant endpoint.

• ***Drug Information:***

Dosage form: Age appropriate formulation
Route of administration: Intravenous
Regimen: As determined by Phase 1 study

• ***Drug specific safety concerns:***

Myelosuppression, hearing loss, nephrotoxicity

• ***Statistical information, including power of study and statistical assessments:***

Statistics appropriate to the phase of the study.

• ***Labeling that may result from the study(ies):***

Appropriate sections of the label may be changed to incorporate the findings of the studies.

• ***Format of reports to be submitted:***

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

• ***Timeframe for submitting reports of the studies:***

Reports of the above studies must be submitted to the Agency on or before October 15, 2010. Please keep in mind that pediatric exclusivity attached to existing patient protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

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- In accordance with section 505A(e)(2), if:

    4) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
    5) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
    6) you have not marketed the formulation within one year after the Agency publishes such notice,

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Sincerely,

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Richard Pazdur, M.D.
Director
Office of Oncology Drug Products, HFD 150
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21462	GI-1	ELI LILLY AND CO	ALIMTA (PEMETREXED DISODIUM) 500MG VIALS
IND-40061	GI-1	ELI LILLY AND CO	LY231514 DISODIUM

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

/s/

RICHARD PAZDUR
07/02/2010