DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 40,061

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indicanapolis, IN 46285

Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs

Dear Dr. Brophy:

Reference is made to your Proposed Pediatric Study Request submitted on May 24, 2001 for ALIMTA® (LY231514) to IND 40,061.

To obtain needed pediatric information on ALIMTA® (LY231514), the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the trials in pediatric patients described below. These studies investigate the potential use of ALIMTA® in the treatment of children with cancer.

Background:

The development of pediatric oncology drugs presents certain challenges but is also facilitated by current practices. Compared to most adult malignancies, pediatric cancers afflict small numbers of patients, making formal outcome studies difficult. On the other hand, because the majority of pediatric patients receive their cancer therapy as participants in clinical research protocols, participation in Phase 3 oncology trials has become the *standard of care* in pediatric oncology. Children with cancer are usually treated at specialized centers by pediatric oncologists who are members of a national pediatric cooperative study group. One of the highest priorities of these groups is to develop improved therapies and effective treatment for patients who are refractory to current therapy. Early access to new drugs is one mechanism to achieve this goal.

Although in some cases pediatric claims can be based on results in adults with appropriate PK and safety information in the pediatric population, the many known and potential differences in the biology of pediatric and adult tumors usually will not permit the extrapolation of clinical activity from adults to children. It is usually necessary, therefore, to evaluate the effectiveness, as well as the safety, of new drugs in pediatric populations. In the absence of available therapies to treat refractory stages of most pediatric cancers, the FDA would ordinarily expect to rely on demonstration of tumor response as a basis of approval; other endpoints would probably be used where there is existing therapy for a stage of disease. In refractory settings, and with rare diseases, it may be appropriate to rely on relatively small amounts of safety data.

The design of studies in pediatric oncologic drug development, as is generally true, will depend, to a great extent, on the population, therapeutic options or lack thereof, and existing information in pediatric or other populations. It is, therefore, often not possible to define the needed studies until such information becomes available but it is possible to describe a general approach and the expectations for follow-on studies. Drugs that lack dosing and pharmacokinetic information should begin with Phase 1 studies. Drugs that already have dosing and pharmacokinetic data in pediatric patients should be tested in Phase 2 or pilot studies. If appropriate, a specific disease may be targeted; otherwise, several studies in a variety of tumor types, such as brain tumors, solid tumors, or hematologic tumors should be planned. Depending upon the outcome of the Phase 1 studies, Phase 2 studies may be initiated, and if necessary, Phase 3 studies. Alternatively, drug development may need to be terminated after phase 1 because of unacceptable toxicity or lack of activity and it may be appropriate to request an exclusivity determination, as the needed information pertinent to pediatric use will have been obtained. A more detailed discussion of this approach can be found in the guidance for industry, *Pediatric Oncology Studies in Response to a Written Request*.

What direction development should take will depend on the results of early studies and should be discussed after those results are available. Protocols for each of your studies should be submitted to the FDA for review, but they need not be submitted simultaneously. For example, if you begin with a Phase 1 study, the Phase 1 protocol should be submitted for review; submission of the Phase 2 protocol(s) may be deferred until results are available. Each submission should review the overall development plan and justify the study design(s).

Please submit information from the following types of studies:

- ***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 or pilot studies: Enrollment of at least 14 pediatric patients per trial, in refractory or relapsed tumors. Studies should be performed at facilities that have the experience, support, and expertise to care for children with cancer.

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

  Refractory or relapsed pediatric malignancies

- ***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 studies or pilot studies 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 study(ies):***

  Reports of the above studies must be submitted to the Agency on or before December 31, 2004. Please keep in mind that pediatric exclusivity attaches to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Please submit protocols for the appropriate studies to your investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports on the outcome of the studies should be submitted to a new drug application (NDA) or as a supplement to an approved NDA with the proposed labeling you believe would be warranted based on the data derived from these studies. When submitting the reports, please 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. Please also 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, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if changes to this Written Request are agreed to by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, contact Debra Vause, Regulatory Project Manager, at (301) 594-5724.

Sincerely Yours,

Rachel E. Behrman, M.D., M.P.H.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Rachel Behrman
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