



NDA 20-038

Berlex Laboratories
15409 San Pablo Avenue
Richmond, CA 94804-0099

Attention: Anthony Bourdakis
Vice President
Regulatory Affairs and Quality Assurance

Dear Mr. Bourdakis:

Reference is made to your Proposed Pediatric Study Request submitted on July 9, 2001 for Fludara® (fludarabine phosphate) Injection to IND 26,875.

To obtain needed pediatric information on fludarabine phosphate, 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 Fludara in the treatment of children with cancer.

Background:

The development of pediatric oncology drugs merits special consideration. Compared to adult malignancies, pediatric cancers afflict small numbers of patients. 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 novel therapies. Early access to new drugs is one mechanism to achieve this goal.

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. Therefore, it is usually impossible to rely on pharmacokinetic and safety data alone to guide the use of these drugs in children. It is imperative that we evaluate the effectiveness and safety of new drugs in pediatric populations. In most cases, in the absence of available therapies to treat refractory stages of most pediatric cancers, the FDA expects to be able to use flexible regulatory approaches in developing and approving drugs for pediatric tumors, e.g., basing approval on an effect on tumor size or other surrogate marker likely to predict clinical benefit (Subpart H), and/or based on safety in smaller numbers of patients (Subpart E).

The intent of designing studies for development of drugs for pediatric oncology is to proceed in

the context of an overall development program. Drugs that lack dosing and pharmacokinetic information should begin with Phase 1 studies. Drugs that 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 2 studies, Phase 3 studies may be initiated. See the guidance for circumstances when it may be appropriate to request an exclusivity determination or advisory opinion at the end of either Phase 1 or 2. The FDA recommends that the rationale and context in an overall pediatric oncology drug development program be included with each study.

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, initially a Phase 1 protocol should be submitted for review, but the submission of Phase 2 or pilot study protocols may be deferred.

Please submit information from the following types of studies (at least one study in each phase of development described below):

- ***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; 18-25 patients may be sufficient. CCG 097 may qualify as a study in this category.

Phase 2 or pilot study: Enrollment of at least 14 pediatric patients with refractory or relapsed acute leukemia. The study should be performed at facilities that have the experience, support, and expertise to care for children with cancer. CCG 0895 may qualify as a study in this category.

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

Refractory or relapsed acute leukemias

- ***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 or pilot 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, fever, chills, infection, nausea and vomiting, weakness, peripheral neuropathy, diarrhea, rash, pulmonary hypersensitivity reaction.

- ***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 Dianne Spillman, Regulatory Health Project Manager, at (301) 594-5746.

Sincerely Yours,

{See appended electronic signature page}

Rachel Behrman, M.D.
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/

Robert Temple
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