DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 63,641

ILEX Products, Inc.
4545 Horizon Hill Blvd.
San Antonio, TX 78229-2263

Attention: Mike Bernstein, MPH
Senior Director, Regulatory Affairs

Dear Mr. Bernstein:

Reference is made to your Investigational New Drug application (IND) for clofarabine.

To obtain needed pediatric information on clofarabine, 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 clofarabine in the treatment of children with hematological malignancies and solid tumors.

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 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).

Please submit information from the following types of studies:

- *Type of studies*:

  Phase 1 study in hematologic malignancies: A dose finding study, including pharmacokinetics, with doses determined for all appropriate age groups in pediatric hematologic malignancies. The number of patients entered must be sufficient to achieve Phase 1 objectives. Historically, this has been accomplished with the range of 18-25 patients for other drugs.

  Phase 1 study in solid tumors: A dose finding study, including pharmacokinetics, with doses determined for all appropriate age groups in pediatric solid tumors. The number of patients entered must be sufficient to achieve Phase 1 objectives. Historically, this has been accomplished with the range of 18-25 patients for other drugs.

  Phase 2 study in hematologic malignancies: Enrollment of at least 14 pediatric patients with the same tumor type per trial, in refractory or relapsed hematologic malignancies. Studies should be performed at facilities that have the experience, support, and expertise to care for children with cancer.

  Phase 2 study in solid tumors: Enrollment of at least 14 pediatric patients with the same tumor type per trial, in refractory or relapsed solid tumors. Studies should be performed at facilities that have the experience, support, and expertise to care for children with cancer.

- *Indications to be studied:*

  Refractory or relapsed pediatric hematologic malignancies and solid tumors

- *Age group in which studies will be performed*:

  Infants > 1 month of age to adolescents up to 18 years of age with a distribution of patients that reflects the demographics of the diseases under study

- *Study endpoints*

  The Phase 1 studies should have maximum tolerated dose (MTD) and must have standard pharmacokinetic (PK) parameters such as half-life of the parent drug and major metabolites, maximum concentration, clearance and area under the curve as endpoints. A traditional or sparse sampling technique may be used to estimate the PK parameters and develop pharmacokinetic-pharmacodynamic relationship.

- *Drug information*
  - *dosage form:* Age appropriate formulation
  - *route of administration:* Intravenous
  - *regimen:* As determined by Phase 1 study

- *Drug specific safety concerns*:

  Neutropenia, thrombocytopenia, bleeding, infections, anemia, death

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

  Statistical analysis appropriate to the phase of the study including descriptive statistics for the Phase 2 studies must be submitted.

- *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 and all raw data for pharmacokinetic analysis must be submitted. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities.

- *Timeframe for submitting reports of the study(ies):*

  Reports of the above studies must be submitted to the Agency on or before December 31, 2005. Please keep in mind that pediatric exclusivity attaches only 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.

- *Response to Written Request:*

  As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an 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 of the studies should be submitted as a new drug application (NDA) or as a supplement to an approved NDA with the proposed labeling changes 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 any changes to this Written Request are agreed upon by the Agency.

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

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 594-5761.

Sincerely,

{see electronic signature page}

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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