DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA

Attention:

Dear

Reference is made to your Proposed Pediatric Study Request submitted on May 13, 2003 for Zinecard™ for Injection (dexrazoxane for injection) to NDA

To obtain needed pediatric information on dexrazoxane for injection, 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 dexrazoxane for injection in the treatment of children with cancer.

Please submit information from the following types of studies:

- **Types of studies:**

    1. An open-label clinical study evaluating dexrazoxane and doxorubicin pharmacokinetics (PK) in at least 18 pediatric patients receiving doxorubicin chemotherapy in combination with dexrazoxane for solid tumors or hematologic malignancy. The study report must include a detailed assay validation report.

    2. A Randomized Parallel Group Comparison Study of the Treatment of Childhood Acute Lymphoblastic Leukemia (ALL) in at least 100 high risk patients who receive combination chemotherapy including doxorubicin for ALL with or without dexrazoxane evaluating endpoints for tumor protection and cardiac toxicity.

    3. A Randomized Parallel Group Comparison Study of the Treatment of ALL and Advanced Stage Lymphoblastic non-Hodgkin's Lymphoma (NHL) in at least 400 patients who receive combination chemotherapy including doxorubicin with or without dexrazoxane evaluating endpoints for tumor protection and cardiac toxicity.

4. Long-term cardiac toxicity occurs after anthracycline therapy, some of which is related to the cumulative dose and to the time interval following exposure. The degree and duration of dexrazoxane protection against these adverse cardiac effects are uncertain, particularly in children who are cured of their malignancies. Therefore, you must commit to set up a registry of enrolled patients to facilitate long-term follow-up of cardiotoxicity and tumor recurrence in these patients. This registry could include patients continuing from the controlled trial and also patients recruited specifically for longer-term follow-up. The outcomes of interest are cardiotoxicity and tumor recurrence, obtained at roughly 2-year intervals. While actual follow-up data from this registry would not be required as part of your response to the Written Request, you must commit to obtaining such follow-up and provide a detailed plan in your response for establishing the registry.

- **Indication to be studied:**

  Cardioprotection in children receiving doxorubicin therapy

Age Group in which studies will be performed

1. For the PK study, approximately 6 patients in each of the following age groups: age 2 months to 6 years; 7 years to 12 years; and 13 years to 17 years.

2. For the phase 3 studies, the age groups will be those eligible for the specific protocols.

- **Study endpoints:**

1. The clinical PK study will determine the PK parameters of doxorubicin, doxorubicinol, and dexrazoxane including area under the curve (AUC), clearance, volume of distribution, and t1/2, calculated by noncompartmental or compartmental methods for dexrazoxane. This study must determine the PK parameters using the fixed ratio 1:10 of doxorubicin:dexrazoxane.

2. The two randomized studies must obtain safety data on cardiotoxicity, including both acute (during the chemotherapy) and late (continued monitoring to 4 years after completion of chemotherapy) effects, documented by the following: echocardiograms (ECHOs), troponin T levels (cTnT), any electrocardiographic monitoring deemed necessary, and chest x-rays. ECHO studies must be read by a blinded reviewer. Both raw data measurements and age- or BSA- adjusted values (as appropriate) must be submitted.

3. In study reports, the following cardiac events must be specifically reported: 1) a clinical diagnosis of congestive heart failure (CHF) by a cardiologist; 2) a serious cardiac adverse event [SAE-Cardiac, National Cancer Institute CTCAE version 3 criteria]; or 3) in ECHO evaluation, a change equal to or greater than 3 standard deviations from normal in depressed contractility or elevated afterload. Exploratory analyses of the relationship between troponin T elevation and ECHO measurements and the relationships between these measurements' subsequent clinical events must be performed.

4. For purposes of this Written Request, cardiac-event-free survival is defined as the time from randomization until death or first development of a cardiac event. Time-to-first-cardiac-event is defined as the time from randomization to first cardiac event, as defined above.

5. For purposes of this Written Request, cancer-event-free survival is defined as the time from randomization until death or first evidence of disease progression or recurrence.

- **Drug Information:**

  - Dosage form: Injection
  - Route of Administration: Intravenous
  - Regimen: As per protocol (300 mg/m^2 dexrazoxane per 30 mg/m^2 doxorubicin)

- **Drug specific safety concerns:**

  - Leukopenia and thrombocytopenia; typhlitis (neutropenic enterocolitis)
  - Cardiotoxicity, both during the chemotherapy and late (after completion of the chemotherapy up to 4 years), as indicated by effects on electrocardiogram, the chest x-ray, troponin T levels (cTnT), echocardiograms or clinical CHF events as described above.
  - The randomized studies must be analyzed to provide the estimate of the reduction in frequency and severity of cardiotoxicity of doxorubicin.
  - Possible tumor protection by dexrazoxane; the controlled studies must be analyzed to determine whether the continuous complete remission rate is reduced by dexrazoxane.

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

  - Use descriptive statistics for rates and proportions and log-rank analysis of time to events.
  - Submit the proposed PK study for FDA review and agreement prior to beginning the study.

  Meta-analysis plan: Submit for FDA review and agreement, prior to performing the meta-analysis, an analytic plan to assess the findings of cardioprotection in the two phase 3 studies, including assessment of the quantity and quality of available data and procedures for handling missing data. The plan must provide for a meta-analysis of the two controlled studies to assess further the possibility of a detrimental effect of dexrazoxane on the continuous complete remission rate and on event-free survival in children with high-risk ALL and NHL.

- **Labeling that may result from the studies:**

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

- **Format of the reports to be submitted:**

  The study protocol for the PK study and the full protocol for the meta-analysis for the two controlled studies, addressing issues outlined in this request, are to be submitted to the Agency for review. Do not commence either study before FDA review of these protocols.

Full study reports and analyses not previously submitted to the Agency addressing the issues outlined in this request including the full raw datasets, assessment, and interpretation are to be submitted to the Agency. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(s) must be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, or White. For ethnicity, one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

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

The final full study reports and analyses are due on or before December 31, 2006. 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 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.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

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

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the Federal Register a notification of availability.

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.

Sincerely,

Robert Temple, M.D.
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
6/17/04 04:59:01 PM