DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Dear Mr. :

To obtain needed pediatric information on dactinomycin, 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 dactinomycin in the treatment of children with cancer.

Background:

The design of studies in pediatric oncologic drug development will depend, to a great extent, on the population, availability of therapeutic options or lack thereof, and currently existing information in pediatric or other populations. Therefore, it is often not possible to define the studies that need to be carried out until information becomes available. What can be described is a general approach and the expectations for follow-on 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. This is discussed in detail in the guidance for industry, *Pediatric Oncology Studies in Response to a Written Request.*

Dactinomycin has been studied in a number of pediatric tumors over the past 40 years. However, during that time, there have been no pharmacokinetic studies done in the pediatric population. Dosage strategies have been difficult in the youngest pediatric patients (< 3 years of age) because of increased toxicities. In addition, treatment failures are higher in the population of patients < 3 years of age. Pharmacokinetic, safety and efficacy trials need to be performed in patients < 3 years of age in order to maximize benefit and minimize serious toxicity. These studies must address whether young children are particularly susceptible to the toxic effects of dactinomycin and whether the efficacy of this agent, as it has been administered to children in the past is related to age.

Protocols for each of your studies must be submitted to the FDA for review, but they need not be submitted simultaneously. Each submission must review the overall development plan and justify the study design(s).

REQUESTED STUDIES:

Please submit information from the following types of studies:

Type of studies:

The data will come from one clinical trial (Study 1) and one retrospective analysis (Study 2):

Study 1: A prospective pharmacokinetic study in pediatric patients, 0 to <17 years of age with Wilms' tumor, rhabdomyosarcoma or other solid tumors.

Study 2: Analysis of current databases and ongoing clinical trials to determine the toxicity and efficacy of dactinomycin in treating pediatric patients with Wilms' tumor, rhabdomyosarcoma or other solid tumors.

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

Studies 1 and 2: Pediatric solid tumors such as Wilms' tumor and/or rhabdomyosarcoma

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

Studies 1 and 2: Pediatric patients 0 to <17 years of age with adequate representation of patients who are less than 3 years of age. A sufficient number of patients less than 1 year of age must be included in the trials to develop safety and efficacy data for this population.

Study endpoints:

Study 1: Population pharmacokinetic parameters for dactinomycin must be estimated, with evaluation of the impact of covariate clinical and demographic factors including body size and composition, tissue distribution/binding, cancer type and severity (extent of disease, site of primary disease, and stage and histology of tumor), concomitant therapy, age, and gender. If a sparse sampling approach is pursued, a sample size of at least 100 patients from 0 to <17 years of age must be studied, and must include sufficient numbers of patients less than 3 years of age as well as sufficient numbers of patients less than 1 year of age to achieve the pharmacokinetic objectives in each of these populations. If the number of patients is inadequate for reaching conclusive observations, additional patients may be enrolled and studied per the criteria described in the study protocol. The investigators must provide a clear justification for their proposed sample size and all blood sampling requirements and the methods for detecting dactinomycin need to be clearly outlined and justified.

Study 2: The toxicity and efficacy analyses must include clinically meaningful endpoints such as event free survival for efficacy and comprehensive toxicity assessments including hepatotoxicity and thrombocytopenia. Sufficient numbers of patients under 3 years of age and under 1 year of age need to be included to evaluate the relationship between age, dose, toxicity and efficacy in each of these populations.

Drug information:

Dosage form: Intravenous

Route of administration: Intravenous

Regimen: Tumor specific regimens as determined by weight and age.

Drug specific safety concerns:

Most recently, chemotherapy-induced hepatopathy with hepatic veno-occlusive disease (HVOD) being a manifestation of the most severe form of hepatopathy has been noted to be a significant problem, especially in those children under 3 years of age.

Other common adverse events associated with dactinomycin will be analyzed.

Statistical information, including power of study and statistical assessments:

Study 1: Pharmacokinetic results will be summarized using descriptive statistics. The proposal must describe the analytical approach to be used to examine specific covariate effects including indices of body size and composition, tissue distribution/binding, cancer type and severity, age, and gender. Analytical methods for exploring the relationship between various pharmacokinetic metrics and clinical outcomes (both efficacy and toxicity) must be described.

Study 2: Clinical toxicity and efficacy data will be summarized using multivariate descriptive statistics. Analytical methods for exploring the relationship between age, dose, efficacy and toxic effects must be described.

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 with analysis, assessment, and interpretation, not previously submitted to the Agency addressing the issues outlined in this request will be submitted. Pharmacokinetic study reports must include analytical method and assay validation, individual drug and/or metabolite concentration-time data and individual pharmacokinetic parameters.

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) should 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 should be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for submitting reports of the study(ies):

Reports of the above studies must be submitted to the Agency within 3 years of the date of this letter. 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 3, if we do not hear from you within 30 days of the date of this Written Request, we will refer this Written Request to the Director of the NIH. 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 IN RESPONSE TO WRITTEN REQUEST**" 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 - COMPLETE RESPONSE TO WRITTEN REQUEST**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

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 to 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, contact Paul Zimmerman, Regulatory Project Manager, at 301 594-5775.

Sincerely Yours,

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.

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Robert Temple
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