DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

National Institute of Health
Obstetric and Pediatric Pharmacology Branch
Center for Research for Mothers and Children
The *Eunice Kennedy Shriver* National Institute of Child Health
and Human Development
National Institutes of Health
6100 Executive Blvd Suite 4A01 MSC 7510
Bethesda, MD 20892-7510

Attention: Anne Zajicek MD, PharmD
Associate Branch Chief

Dear Dr. Zajicek:

Reference is made to your 9/17/08 Proposed Pediatric Study Request for isotretinoin (13-cis retinoic acid).

To obtain needed information on an age appropriate formulation of isotretinoin in pediatric patients, 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), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the trials in pediatric patients described below. These studies investigate use of isotretinoin in the treatment of children with High Risk (HR) Neuroblastoma.

Background:

Neuroblastoma is a malignancy of the sympathetic nervous system, and is the second most common extracranial malignancy (third most common tumor overall) of young children, accounting for 7-10% of pediatric malignancies. Median age at diagnosis is 23 months. Clinical stage at diagnosis is generally advanced with patients with high-risk tumors having dismal outcomes despite aggressive therapy. For children with high risk characteristics, standard therapy generally includes intensive chemotherapy followed by autologous bone marrow transplantation (ABMT). However, more than half of these patients will still relapse and succumb to their disease.

Vitamin A analogues (retinoids) are required for the maintenance of normal cell growth, differentiation, and loss within epithelial tissues. Various retinoids have been shown to suppress or reverse epithelial carcinogenesis and to prevent the development of invasive cancers in many animal systems. Retinoids act primarily in the post-carcinogen phases of promotion and progression, which makes them more useful for chemoprevention. However, isotretinoin, a naturally occurring analogue of Vitamin A, has been shown to induce maturation of malignant neuroblastoma cells to mature neural crest tissue in tissue culture. Furthermore, the clinical benefit of isotretinoin in extending event-free survival in children who have undergone ABMT has been shown in clinical trials.

The dose of isotretinoin utilized for treatment of Neuroblastoma (80 mg/m^2, PO, BID) represents the MTD of this agent and provides peak serum concentrations approaching or in excess of 5 μM for most patients. More specifically, pharmacokinetic studies performed on 16 patients in a phase I trial of isotretinoin showed significant interpatient and intrapatient variability in peak serum levels (mean peak serum 13-cis-RA concentration: 7.2 ± 5.3μM; trough concentration: 4.1 ± 2.7μM). It was further noted that peak serum concentrations above 10 μM were associated with a higher incidence of Grade 3 and 4 toxicities in patients. This poses a significant problem as oral isotretinoin is currently only available as 10-mg, 20-mg, 30-mg, and 40-mg soft gelatin capsules. These dosage forms cannot be swallowed by young children necessitating parental opening and handling of the capsule, including squeezing capsule contents into food or liquids. It is believed that incomplete emptying of capsules is a likely source of drug loss with resultant medication under-dosing. Furthermore handling has the potential to allow light-induced isomerization to all-trans retinoic acid, which has a different efficacy and toxicity profile than isotretinoin. Handling may also potentially cause harm in pregnant mothers and their fetuses because of isotretinoin's known teratogenicity. Recent data from the UK Children's Cancer Study Group (UKCCSG) study of 27 patients treated with isotretinoin revealed that peak concentrations were 2-3 fold lower than those noted above and that significant variability in concentrations was attributable to method of administration; children who had been able to swallow the capsule had an area under the concentration-time curve (AUC) that was nearly 2 fold larger than those who required the capsule to be opened and added to food.

Considering the data summarized above, the development of a pediatric (liquid) formulation of isotretinoin which enables simple administration in addition to accurate dose delivery would be a significant improvement over currently available formulations and a significant advancement in the treatment of pediatric neuroblastoma patients.

Design of studies for pediatric oncologic drug development is discussed in detail in the guidance for industry, *Pediatric Oncology Studies in Response to a Written Request*. Protocols for each of your studies should be submitted to the FDA for review. Each submission should review the overall development plan and justify the study design(s). Please consult the guidance for further details.

Please submit information from the following types of studies.

- *Type of study(ies)*:

These studies must take into account adequate (e.g., proportionate to study population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Study 1: A prospectively conducted, randomized, controlled study evaluating the efficacy of isotretinoin maintenance in the treatment of HR Neuroblastoma.

Study 2: A bioequivalence study using cross-over design with dense sampling in adults, using the highest capsule strength and comparing:

A. Accutane capsules given in a fasting state,
B. Accutane capsule contents with food or liquids (as used clinically in young children unable to swallow capsules in the Phase 3 trial)
C. New pediatric formulation given in a fasting state.

Study 3: Sparse-sampling PK study in children with HR neuroblastoma receiving the proposed pediatric formulation of isotretinoin.

Study 4: A food effect study in adults emphasizing foods typically consumed by pediatric patients in target age range.

- *Indication to be studied/Objective of each study:*

Study 1: To determine efficacy of isotretinoin in pediatric patients with HR neuroblastoma

Study 2: To determine relative bioavailability of the proposed pediatric formulation of isotretinoin in adult volunteers.

Study 3: To determine the pharmacokinetics of the proposed pediatric formulation of isotretinoin, using sparse PK sampling technique, in pediatric patients with HR neuroblastoma.

Study 4: To determine the food effect on the pharmacokinetics of isotretinoin for the proposed pediatric formulation in adult volunteers

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

Study 1: 1-18 years, inclusive, at the time of diagnosis.

Study 2: Adults, age > 18 years.

Study 3: 1-18 years.

Study 4: Adults, age > 18 years.

- *Number of patients to be studied:*

Study 1: 560 patients.

Study 2: 12 volunteers completing study.

Study 3: 28 patients (a minimum of 4 subjects need to be enrolled in the 1 to < 2 years age group, 8 subjects in the 2 to < 6 years age group).

Study 4: 12 volunteers completing study.

- *Study endpoints*

Study 1: Event-free survival (EFS)

Study 2: Isotretionin pharmacokinetic parameters, including relative bioavailability, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, T_{max}, $t_{1/2}$, and their descriptive statistics should be evaluated.

Study 3: Relevant pharmacokinetic endpoints including clearance, volume of distribution, and AUC should be derived through approaches such as optimal sparse sampling in all patients. Such data should then be appropriately analyzed using methods such as nonlinear mixed effects modeling.

Study 4: Isotretionin pharmacokinetic parameters, including $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, T_{max}, $t_{1/2}$, and their descriptive statistics should be evaluated.

- *Drug information*

Study 1:

- *Dosage form:* Accutane (Roche) soft gel capsule.
- *route of administration:* oral
- *regimen:* 80 mg/m^2 PO BID for two consecutive weeks each month x 6 months

Study 2:

- *dosage form:* Accutane (Roche) soft gel capsule and the proposed pediatric liquid formulation
- *route of administration:* oral
- *regimen:* 40 mg, single dose.

Study 3:

- *dosage form:* The proposed pediatric liquid formulation
- *route of administration:* oral
- *regimen:* 80 mg/m^2 PO BID for two consecutive weeks each month x 6 months

Study 4:

- *dosage form:* The proposed pediatric liquid formulation
- *route of administration:* oral
- *regimen:* 40 mg, single dose.

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives marketing approval), 2) the Agency publishes the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice reflecting the fact that the approved pediatric formulation has not been marketed, in accordance with section 505A(e)(2).

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Drug specific safety concerns*:

You must assess relative incidence of hypercalcemia, rash, anemia, thrombocytopenia, chelitis, conjunctivitis, transaminitis, elevated alkaline phosphatase, nausea, emesis, diarrhea, anorexia, abdominal pain and distention. The latter toxicities should be compared following collection of adverse event data and evaluated in the context of pharmacokinetic data as dose-limiting toxicities have been correlated with peak serum levels of $\geq$ 10 μM in previous studies.

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

Study 1:

A detailed statistical analysis plan should be submitted to include:

1. Clearly stated primary/secondary endpoint(s), hypotheses to be tested, and the analysis methods for testing the hypotheses using these endpoints;

2. An evaluation of EFS as a time-to-event endpoint,

3. Assessment of the effect of switching treatment arms,

4. Specification of the timing and the stopping rules of any interim analyses,

5. Description of the effects of missing assessments and drop-outs,

6. Clarification of frequency of assessments,

7. Clarification of case report form capture of method of isotretinoin drug administration (swallowed whole, opened and added to food, drug withdrawn from capsule with syringe),

8. Evaluation of age as a prognostic factor,

9. Analysis for the effect of isotretinoin stratified by chemotherapy (CT) or ABMT to correct the effect of CT/BMT,

10. Pre-specification of the method for analyzing the effect of isotretinoin, with clarification of performance of statistical inferences,

11. Each of the two analyses, ABMT analysis and isotretinoin analysis, using $p < 0.05$; including discussion of correlation of the data from ABMT analysis with the data from isotretinoin analysis, and issues of multiple comparisons.

Studies 2, 3, and 4: descriptive statistics

- *Labeling that may result from the study(ies)*:

You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that isotretinoin is safe

and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*:

You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) 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, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

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

Reports of the above studies must be submitted to the Agency on or before 10 years of the date of this letter. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:*

Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) 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.

Reports of the study(ies) should be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are 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 to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. 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, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/cder/pediatric/index.htm

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.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Paul Zimmerman, Project Manager, at 301-796-1489.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research