



Dear :

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

Background:

Daunomycin (also known as daunorubicin) is an anthracycline antineoplastic drug used in the treatment of acute lymphocytic leukemia and other malignancies in childhood. There are no data on the pharmacokinetics of daunorubicin in obese children, and only limited data on daunorubicin pharmacokinetics in children in general.

Like many anticancer agents, daunorubicin has a narrow therapeutic index. Myelosuppression and stomatitis are common acute toxicities. Cardiomyopathy is an important dose-dependent late effect that is being recognized with increasing frequency. Despite its frequent use, however, daunorubicin's pharmacokinetics and pharmacodynamics have not been studied systematically in children and very little is known about the relationship between pharmacokinetic parameters and covariates like obesity, body composition, age, gender, or ethnicity. Dosing is usually calculated based on body surface area (BSA) or body weight, based on the concept that hepatic and renal function correlate with BSA. A rational basis for dose modifications in children who are overweight or obese, in particular, is lacking. This represents a significant gap in our knowledge of the safe and appropriate use of this important agent. A better understanding of the relationship between body composition and pharmacokinetics could provide a better rationale for proper drug dosing.

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 studies:

1. A study to evaluate the relationship between body composition and daunorubicin pharmacokinetics in children, and to examine the influence of gender, age and ethnicity on daunorubicin pharmacokinetics in patients 21 years of age or younger.

2. A study to compare the pharmacokinetics of daunorubicin in underweight, middle-weight and obese pediatric patients with high risk acute lymphoblastic leukemia, and to examine the relationship between the pharmacokinetics in the weight groups and rapid early responder vs. slow early responder/induction failure status in these patients.

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

Study 1

Patients < 21 years of age with any diagnosis, who are receiving chemotherapy that includes daunorubicin administered as an infusion of any duration < 24 hours including bolus and all short infusion schedules.

Study 2

Patients obese, middle weight or underweight ≥ 10 and < 20 years of age who are undergoing induction chemotherapy for high risk acute lymphocytic leukemia (ALL).

Age group in which studies will be performed:

Study 1

Patients < 21 years of age.

Study 2

Patients ≥ 10 and < 20 years of age.

Study endpoints:

Study 1

Primary:

- To determine the pharmacokinetics (CL, V_d , C_{max} , AUC, and K_e) of daunorubicin in children.

Secondary:

- To evaluate the relationship between body composition (percent body fat) and daunorubicin pharmacokinetics in children.
- To determine whether daunorubicin pharmacokinetics are correlated with gender, age or ethnic background in children.

Study 2

Primary:

- To compare the pharmacokinetics (CL, V_d , C_{max} , AUC, and K_e) of daunorubicin among obese, middle weight and underweight children ≥ 10 and < 20 years of age undergoing induction chemotherapy for high risk ALL.

Secondary:

- To examine the relationship between the daunorubicin exposure and rapid early responders versus slow early responder/induction failure status.

- To examine the relationship between the daunorubicin exposure and toxicity.

Drug information:

Study 1 and 2

- *dosage form*: intravenous
- *route of administration*: intravenous infusion

Study 1

- *regimen*: infusions of any duration < 24 hours as part of a chemotherapy regimen that includes daunorubicin.

Study 2

- *regimen*: short infusions as part of induction chemotherapy (prednisone + PEG L-asparaginase + vincristine + daunorubicin)

Drug specific safety concerns:

Dose-limiting toxicities include myelosuppression and cardiotoxicity. Other toxicities include mucositis, alopecia, rash, acute nausea and vomiting, diarrhea and abdominal pain. Extravasation may cause severe local tissue necrosis, cellulitis or thrombophlebitis. Rare anaphylactoid reactions can occur.

Statistical information, including power of study and statistical assessments:

Study 1

The relationship between daunomycin and daunomycinol PK parameters with BMI and percent body fat should be examined using linear regression methods. Additional multivariate analysis of the data should also be performed to assess the influence of body surface area (BSA), liver function enzymes (ALT), bilirubin, age, gender, and ethnicity on daunorubicin PK parameters.

Study 2

PK parameters should be compared across the obese, normal weight and underweight groups. Multivariate analysis should be performed to examine the relationship between PK parameters and BMI status (as well as BMI as a continuous variable) and the role of covariates such as white cell counts. Multiple logistic regression should be performed to examine the relationship between PK parameters, responder status, and toxicities.

Sample size:

Study 1

A sample size of 100 would be sufficient to detect a minimum correlation coefficient (between a specific PK parameter and BMI) of 0.32 with an α of 0.05 and 90% power. For such a correlation, this would mean that 10% of the variability in the PK parameter being evaluated (e.g., clearance) could be explained by the effect of BMI on that parameter.

Study 2

A total sample size sufficient to detect a meaningful difference in PK parameters between the three groups (obese, middle weight, and underweight).

Labeling that may result from the studies:

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

Format of reports to be submitted:

You must submit full study reports (including data sets and individual data listings), not previously submitted to the Agency, addressing the issues outlined in this request with full analysis, assessment, and interpretation. 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 studies 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 studies:

Reports of the above studies must be submitted to the Agency within 4 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 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.

Study reports should be submitted as **a supplement to an approved NDA** with proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting such 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.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (<http://clinicaltrials.gov> & <http://prsinfo.clinicaltrials.gov/>). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or lifethreatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site <http://prsinfo.clinicaltrials.gov>.

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 _____, Project Manager, at _____.

Sincerely,

Karen D. Weiss, M.D.
Deputy Director
Office of Oncology Drug Products
Office of New Drugs
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/

Karen Weiss

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