DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

IND 35,555
NDA 20-449

Sanofi-aventis U.S. Inc.
Attention: Diane C. Louie, M.D., M.P.H.
Director, Regulatory Affairs
200 Crossing Boulevard
Mail Code: BX4-212C
Bridgewater, NJ 08807

Dear Dr. Louie:

Reference is made to your January 31, 2007, Proposed Pediatric Study Request submitted to IND 35,555, for Taxotere (docetaxel) Injection Concentrate, 20 and 80 mg.

To obtain needed pediatric information on docetaxel, 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 Taxotere® in the treatment of children with cancer.

Background:

The development of pediatric oncology drugs presents certain difficulties but is also facilitated by current practices. Compared to most adult malignancies, pediatric cancers afflict small numbers of patients, making formal outcome studies difficult. On the other hand, because the majority of pediatric patients receive their cancer therapy as participants in clinical research protocols, participation in investigational 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 study group. One of the highest priorities of these groups is to develop improved therapies and effective treatment for patients refractory to current therapy. Early access to new drug combinations is one mechanism to achieve this goal.

Although in some cases pediatric claims can be based on results in adults with appropriate PK and safety information in the pediatric population, the many 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. It is usually necessary, therefore, to evaluate the effectiveness, as well as the safety, of new drugs in pediatric populations. In the absence of available therapies to treat refractory stages of most pediatric cancers, the FDA would ordinarily expect to rely on demonstration of tumor response as a basis of approval; other endpoints would probably be used in disease stages where there is existing therapy. In refractory settings, and with rare disease, it is generally appropriate to rely on relatively small amounts of safety data.

The design of studies in pediatric oncologic drug development is discussed in detail in the guidance for industry, Pediatric Oncology Studies in Response to a Written Request.
http://www.fda.gov/cder/guidance/3756dft.pdf

Protocols for each of your studies should be submitted to the FDA for review prior to initiation of the studies. Each submission should review the overall development plan and justify the study design(s).

- *Types of studies needed:*

  Study 1: A dose-finding phase 1 study of Taxotere® monotherapy in patients with relapsed refractory solid tumors, including pharmacokinetics, with doses determined for all appropriate age groups.

  Study 2: A Phase 2 single-arm study to determine the response rate and safety of Taxotere® monotherapy in patients with relapsed/refractory Ewing sarcoma, rhabdosarcoma and undifferentiated sarcoma, osteosarcoma, neuroblastoma, medulloblastoma, and astrocytoma.

  Study 3: A randomized study to evaluate the addition of Taxotere® to the combination of cisplatin-5-fluorouracil (CF) versus CF in the induction treatment of nasopharyngeal carcinoma (NPC)

- *Indications to be studied:*

  Study 1: Refractory or relapsed pediatric solid tumors.

  Study 2: Refractory or relapsed Ewing sarcoma, rhabdosarcoma and undifferentiated sarcoma, osteosarcoma, neuroblastoma, medulloblastoma, and astrocytoma.

  Study 3: Newly diagnosed NPC stage T2-4

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

  Study 1: Infants >1 month of age to adolescents up to 21 years of age, with a distribution of patients that reflects the demographics of the diseases under study.

  Study 2: Infants >1 month of age to adolescents up to 21 years of age, with a distribution of patients that reflects the demographics of the diseases under study.

  Study 3: Infants >1 month of age to adolescents up to 21 years of age

- *Study endpoints:*

  Study 1: primary endpoint - determination of maximum tolerated dose
  Secondary endpoints - PK, safety, and response rate by RECIST criteria.

Study 2: primary endpoint - objective response rate defined by RECIST criteria
Secondary endpoints - safety and tolerability

Data from studies 1 and 2 should be combined to develop pharmacokinetic and pharmacodynamic (PK-PD) models to explore exposure-response relationships for measures of safety and effectiveness.

Study 3: Primary endpoint - Complete response rate (CR) following 3 cycles of induction chemotherapy according to RECIST criteria

Secondary endpoints - pharmacokinetic analysis based on sparse PK sampling, overall response rate on completion of radiotherapy, overall survival, predictive value of EBV-DNA in peripheral blood

- *Drug information:*
  - *dosage form: IV*
  - *route of administration*: Intravenous
  - *regimen:*
    - Study 1 dose escalation with a starting dose of 55 mg/m^2 of Taxotere® administered intravenously every 21 days.
    - Study 2 Taxotere® 125 mg/m^2 administered intravenously every 21 days
    - Study 3:
      - Experimental Regimen
        - Taxotere® 75 mg/m^2 intravenously day 1 every 3 weeks
        - Cisplatin 75 mg/m^2 intravenously over 6 hours day 1 every 3 weeks
        - Fluorouracil 750 mg/m^2 intravenously as a continuous infusion days 1-4 every 3 weeks
      - Control Regimen
        - Cisplatin 80 mg/m^2 intravenously over 6 hours day 1 every 3 weeks
        - Fluorouracil 1000 mg/m^2 intravenously as a continuous infusion days 1-4 every 3 weeks

Dose-response should be characterized over an adequate range of doses/dosing regimens, in an adequate number of target patients. A priori knowledge about the drug response rates, if available, should be fully utilized to rationally select the clinical trial design. We recommend consultation with the Agency regarding the choice of the doses/dosing regimens.

- *Use an age-appropriate formulation in the study(ies) described above:*

  If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. 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.

Development of a commercially-marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

If you cannot develop a commercially marketable age-appropriate formulation, 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 label 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 should 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:*

  Neutropenia, leukopenia, thrombocytopenia; skin rashes, mucositis, mild elevations of serum transaminases; neurotoxicity; peripheral edema and weight gain.

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

  Study 1: Descriptive statistics must be submitted. Descriptive statistics for the PK parameters, clearance, half-life, volume of distribution and area under the curve must be included.

  Study 2: Response to Taxotere® will be categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to protocol specified criteria. Preliminary evaluation of efficacy in terms of anti-tumor activity will be carried out in the procedure as follows. Within each category of tumors, 10 patients will be enrolled. If no patients with CR or PR responses, the trial will be terminated for this category because the agent is ineffective. If >=1 patient achieved a CR or PR, then another 10 patients will be enrolled. If <=2 of 20 evaluable patients with CR or PR responses, the trial for this category will be terminated because the agent is ineffective. If >=3 patients achieved a CR or PR, the trial will be terminated for this category because the agent is active. Response rate and overall survival should be described. Toxicity information including type, severity, time of onset, time of resolution, and the probable association should be submitted. Data from this study should be combined with data from Study 1 to develop PK-PD models to explore exposure-response relationships across age groups.

  Study 3: This trial should have 85% probability to correctly select a treatment group with the best complete response rate following the induction treatment. This requires a sample size of 72 patients in a 2:1 ratio of randomization to either the experimental group or the control group.

Descriptive statistics for safety and efficacy of patients at the end of induction chemotherapy of the Phase 2 study must be submitted. Pharmacokinetic parameters should be estimated using a Bayesian estimation method and the existing adult population PK model as prior information.

The analysis should focus on docetaxel plasma clearance and area under the curve as they are well estimated using the Bayesian approach.

- *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 (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. Even if the study fails, we need full study reports with data to support study conclusion. 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(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 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 on or before February 12, 2010. 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.

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 submit the nasopharyngeal protocol for review and comment before you initiate the study 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 your 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.

As a reminder, you are responsible for compliance with section 113 of the Food and Drug Administration Modernization Act of 1997 and section 15 of the Best Pharmaceuticals for Children Act of 2002 by registering certain clinical trials in the Clinical Trials Data Bank (<http://clinicaltrials.gov/>) <<http://prsinfo.clinicaltrials.gov/) >>. If your drug is for the treatment of a serious or life-threatening disease or condition and you are conducting trials to test its effectiveness, then you must register the trials. Although not required, we encourage you to register trials for non-serious diseases.

For additional information on registering your clinical trials, including the required and optional data elements, refer to the Protocol Registration System (PRS) Information Site (<<http://prsinfo.clinicaltrials.gov>>) and FDA's Guidances for Industry entitled *"Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions"* (March 2002; revised draft January 2004).

If you have any questions, please call Frank Cross, Regulatory Project Manager, at 301-796-0876

Sincerely,

{See appended electronic signature page}

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