DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-938
NDA 21-968

C.P. Pharmaceuticals International C.V.
c/o Pfizer, Inc.
10646 Science Center Drive
San Diego, CA 92121

Attention: Laurie Strawn, Ph.D.
Associate Director, Worldwide Regulatory Strategy

Dear Dr. Strawn:

Reference is made to your Proposed Pediatric Study Request submitted on July 1, 2005, for Sutent® (sunitinib malate) Capsules to IND 62,382.

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

Background:

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 must 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).

- *Type of studies*:
  Phase 1 and Phase 2

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

  1. **Phase 1:** Pediatric patients with refractory solid tumors

  2. **Phase 2:** Pediatric patients with cKIT positive gastrointestinal stromal tumors (GIST) with disease progression on or intolerance to Gleevec (imatinib mesylate)

3. **Phase 2:** Pediatric patients with anaplastic astrocytoma and glioblastoma multiforme (AA/GBM)

- *Age group in which studies will be performed*:
  Children (2 to 5 years and 6 to 11 years) and adolescents (12 to 17 years)

- *Study endpoints*

  For the Phase 1 study: Safety and tolerability, dose-finding and pharmacokinetics

  For the Phase 2 studies: Primary endpoint: Objective Response Rate; Secondary endpoints: Time to Progression, Progression-Free Survival, Overall Survival, and pharmacokinetics.

  Specific dosing for the Phase 2 studies will depend on the results of the Phase 1 study.

  Pharmacokinetic data should be collected and analyzed in the proposed Phase 1 study and both Phase 2 studies.

  For phase 1 and phase 2 studies, relevant pharmacokinetic endpoints may be derived through approaches such as optimal sparse sampling in all patients with rich sampling in a sub-group. Such data should then be appropriately analyzed using methods such as nonlinear mixed effects modeling.

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

- *Drug information*
  - dosage form: 12.5, 25 and 50 mg capsules or powder in bottle formulation
  - route of administration: oral
  - regimen: once daily for 4 weeks followed by a 14 day rest period.

  - Use an age-appropriate formulation in the studies 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.

If a new commercially-marketable formulation is developed, a relative bioavailability study comparing the commercially-marketable formulation to the age-appropriate formulation used in the clinical studies should be conducted in adults.

- *Drug specific safety concerns*:
  Pancreatic function, hypothyroidism, seizures, venous thromboembolic events, hypertension, hemorrhage, effects on growth of long bones and effects on reproductive organs

  Due to reports of clinically significant congestive heart failure with sunitinib malate in adults, we recommend that monitoring of ejection fraction with either an echocardiogram or a MUGA scan be performed at baseline and every two cycles.

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

  Approximately 30 patients will be evaluated in the Phase I study.

  For the Phase 2 studies in GIST and AA/GBM, the approximate number of patients to be enrolled would be 63 for each study. A modified Simon design would be used with enrollment of 38 patients in the first stage. If objective responses are identified in 2 or more patients, the study would be expanded to enroll a total of 63 patients.

- *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*:
  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 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 on or before January 1, 2013. 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. 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 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.

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 life-threatening. 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/.

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 796-1347.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
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/
Richard Pazdur
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