WR
150

IND 55,666
Page

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health
Service

Food and Drug Administration
Rockville MD

20857

IND 55,666 9-12-2000

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Attention: Ellen Cutler
Associate Director
Drug Regulatory Affairs

Dear Ms. Cutler:

Reference is made to your Proposed Pediatric Study Request submitted on January 21, 2000 for STI571.

To obtain needed pediatric information on **STI 571 (CGP 57148B)**, 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 the following information:

- *Types of studies:*

  Phase 1: A dose finding study, including evaluation of pharmacokinetics, with maximum tolerated doses (MTD) determined for all appropriate age groups. The number of patients entered should be sufficient to achieve Phase 1 objectives.

  Phase 2: Determine STI571 activity in pediatric patients with Philadelphia positive (Ph+) leukemia. Studies should be performed at facilities that have the experience, support, and expertise to care for children with cancer.

- *Indication(s) to be studied:*

Philadelphia positive (Ph+) leukemia in pediatric patients who have recurrent or refractory acute lymphoblastic or myeloblastic leukemia (ALL or AML) or chronic myelogenous leukemia (CML) with demonstrated resistance to interferon-alpha therapy.

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

  Infants > 1 month to adolescents < 16 years. Appropriate representation should be made across this age group for pharmacokinetic and pharmacodynamic characterization.

- *Study endpoints:*

  The Phase 1 study should estimate maximum tolerated dose (MTD) , determine dose-limiting toxicities (DLT), and characterize pharmacokinetics as primary endpoints and preliminarily define the anti-leukemic activity of STI 571 as a secondary endpoint.

  The Phase 2 or pilot study should have a disease-specific surrogate or clinically relevant endpoint, such as complete remission with a pre-specified duration.

  A traditional or sparse sampling technique may be used to estimate the PK parameters and develop pharmacokinetic-pharmacodynamic relationship.

- *Drug information*

  Dosage form: Use age-appropriate formulations in the studies. If no suspension/solution is available, a solid dosage form suspended in food could be used if standardized, palatable, and the bioavailability is known. The plan for drug administration in children that will not be able to ingest the proposed formulation should be specified.

  Route of administration: Oral

  Regimen: To be determined in the Phase 1 study

- *Safety concerns:*

  Complete evaluation of toxicity including nausea/vomiting, myelosuppression, transaminase suppression, gastrointestinal bleeding, and melena.

- *Statistical information:*

Descriptive statistics appropriate to the phase of the study.

- *Labeling that may result from the study:*

  Appropriate sections of the label may be changed to incorporate the dosage, pharmacokinetics, and safety findings of the study.

- *Format of reports to be submitted:*

  Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation of study data should be submitted. In addition to your study report, please submit a summary of your post-marketing experience including safety and efficacy update, if the drug is approved for adult use prior to completion of these pediatric studies.

- *Timeframe for submitting reports of the study:*

  Reports of the above studies must be submitted to the Agency on or before June 2003. This date can only be altered by receipt of an amended Written Request. To obtain an amended Written Request, follow the procedure outlined below. Please remember that pediatric exclusivity extends only existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your reports of the studies in response to this Written Request.

Please submit protocols for the above study 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.

There may be circumstances when it is appropriate to request an exclusivity determination or advisory opinion at the end of Phase 1 or 2 pediatric studies (see i.e., Draft Guidance for Industry *Pediatric Oncology Studies in Response to a Written Request*). Please contact the Agency if you wish to discuss this further.

Reports of the studies should be submitted as a new drug application 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.

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.

If you have any questions, call Ann Staten, Regulatory Project Manager, at (301) 594-5770.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Archival IND 55,666
HFD-150/division file
HFD-150/A.Staten
HFD-150/M.Cohen
/J.Johnson
/L.Kieffer
/A.Rahman
/G.Chen
/S.Kim
/R.Wood
/T.Du
/JLeighton (Act'g PT-TL)
/D.Pease
/S.Hirschfeld
HFD-101/Office Director
HFD-600/Office of Generic Drugs
HFD-2/M.Lumpkin
HFD-104/D.Murphy
HFD-104/T.Crescenzi

Drafted by: D.Spillman/6-13-00/revised by AStaten/8-4-00
Initialed by: D.Pease/6-14-00
G.Chen/6-14-00
L.Kieffer/8-2-00
A.Rahman/8-2-00
S.Hirschfeld/8-7-00/9-8-00
M.Cohen/8-8-00/8-31-00
J.Johnson/8-8-00/8-31-00
R.Pazdur/8-8-00

Discussed @ PdIT: 8-16-00
PdIT edits incorporated by: SHirschfeld/Astaten/8-16-00/8-17-00
Edited by RBerhman 8-30-00
Final: AStaten/8-8-00/8-16-00/8-17-00/9-11-00

filename: c:\...\IND\55,666\letters\WR.doc

PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)