DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-335/S-001

Novartis Pharmaceuticals Corporation
Route 10
Hanover, New Jersey 07936-1080

Attention: Robert A. Miranda, Associate Director
Drug Regulatory Affairs

Dear Mr. Miranda:

Please refer to your supplemental new drug application dated October 15, 2001, received October 16, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gleevec™ (imatinib mesylate), 50 and 100 mg capsules.

We acknowledge receipt of your submissions dated October 19 and 23, November 7, 21, December 4, 7, 10, 13, and 21, 2001 and January 23, 29, and 30, 2002.

This supplemental new drug application provides for the use of Gleevec (imatinib mesylate) for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). (See CLINICAL STUDIES : Gastrointestinal Stromal Tumors) The effectiveness of Gleevec is based on overall hematologic and cytogenetic response rates in CML and objective response rates in GIST (see CLINICAL STUDIES). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

We have completed the review of this supplemental application, as amended, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to approve Gleevec (imatinib mesylate), 50 and 100 mg for use as recommended in the enclosed labeling text. Accordingly, the supplemental application is approved under 21 CFR 314 subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-335/S-001." Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your post marketing study (Subpart H post marketing commitments) specified in your submission dated January 29, 2002. These commitments, along with any completion dates agreed upon, are listed below.

Commitments required for accelerated approval of Gleevec™ for GIST patients:

1. Complete the follow-up of sNDA trial B2222 and submit mature response rate, response duration and survival data. The suggested timeline for submission of the overall response rate and response duration is December 31, 2002. The suggested timeline for submission of the survival analysis is when either 70% of events have occurred or there has been 5 years follow-up is March 31, 2007.

2. An updated report of the central pathology review for sNDA trial B2222 should be submitted when review of the 13 pending cases is complete (June 2002).

3. Submit data from the two ongoing multicenter trials of imatinib that are testing 400 mg/day versus 800 mg/day in patients with GIST (EORTC and NCI sponsored trials). Response rate, duration of response, safety and survival data should be submitted. The data should be submitted in a timeline consistent with the statistical analysis plan of each respective protocol (est. June 2003).

4. Submit clinical and PK data for the EORTC phase 1 study of imatinib in patients with GIST and other soft-tissue sarcomas. (Submission: July 31, 2002).

5. Assure availability of a validated test kit for detection of CD117 tumor expression by immunohistochemistry.
   Timeline: Pre-Market Application (PMA) filing by 3rd party estimated by December 31, 2002

Final study reports should be submitted to this NDA as a supplemental application. For administrative purposes, all submissions relating to this post marketing commitment must be clearly designated "Subpart H Post Marketing Commitments."

In addition, we note your following post marketing commitments, specified in your submission dated January 29, 2002, that are not a condition of the accelerated approval. These commitments, along with any completion dates agreed upon, include:

1. Submit the PK/PD data from the comparison of 400 mg/day versus 800 mg/day in GIST patients in the two ongoing multicenter trials of imatinib (EORTC and NCI sponsored trials) (Submission June 30, 2003).

2. Provide a plan for investigating the incidence and etiology of GI/tumor hemorrhage associated with imatinib therapy (Submission July 31, 2002).

3. Investigate and submit data regarding:
   a) correlation of c-kit tumor status with clinical outcome
   b) tumor c-kit phosphorylation status at baseline and post-exposure to Gleevec™
   c) correlation between serum VEGF levels and tumor response
   (Submission December 31, 2002)

4. Implement a physician and patient education program for GIST regarding the use of concomitant medications with Gleevec within 2 months of the date of this letter.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these post marketing study commitments must be prominently labeled "**Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

We also remind you of your Phase 4 commitments as stated in the approval letter dated May 10, 2001 as follows:

1. We have completed the review of your submissions to your NDA dated July 2 and 18, 2001, regarding the physician and patient education program regarding the use of concomitant medications with Gleevec and conclude that this commitment has been filled.

2. The following are the remaining studies to be completed:

   Prior commitments required for accelerated approval Gleevec™ for CML patients:

   a. To conduct and submit the final study report for Protocol 106 entitled “A phase III study of STI571 versus Interferon-α (IFN-α) combined with Cytarabine (Ara-C) in patients with newly diagnosed previously untreated Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP)” with Time to Progression (TTP) as the primary surrogate endpoint. TTP is defined as any of the following: loss of complete hematologic response (CHR), loss of cytogenetic response, inability to maintain peripheral blood counts, increasing organomegaly, accelerated phase CML, blast crisis, or death from CML. Protocol 106 interim analysis (one-year hematologic response and QoL) is planned for first quarter, 2002 and the final analysis is expected in the fourth quarter, 2005.

   b. To provide interval follow-up information on studies 102, 109 and 110.

   Prior commitments which are not a condition of accelerated approval:

   a. To conduct and submit the final study report for the pediatric study, Protocol 103 entitled “A

Phase I Study in Children with Refractory/Relapsed Ph+ Leukemias". Protocol 103 is currently ongoing and being conducted by the cooperative group COG (Children's Oncology Group).

b. To conduct and submit the final study report for a phase 2 pediatric efficacy study in an appropriate pediatric population. This will be conducted by a pediatric cooperative group under the NCI.

c. To conduct an appropriate study to assess hepatotoxic drug interactions (e.g., acetaminophen) and submit final reports.

d. To conduct the appropriate study to assess the potential drug interaction between Gleevec and a substrate of CYP2D6 and to submit the final study report.

e. To conduct a pharmacokinetics study with Gleevec in subjects or patients with liver impairment and submit the final study report.

f. To conduct an *in vitro* study to assess the plasma protein binding of the N-demethylated piperazine derivative of Gleevec and submit the final study report.

g. To evaluate the etiology and treatment of the fluid retention syndrome associated with imatinib treatment.

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

{See appended electronic signature page}

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

Enclosure