NDA 21-335

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 new drug application (NDA) dated February 27, 2001, received February 27, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gleevec (imatinib mesylate) 50 mg and 100 mg capsules.

We acknowledge receipt of your submissions dated March 9, 14, 30; April 4, 5, 10, 12, 13, 19, 23, 24; May 1, 4, 8 and 10, 2001.

This new drug application provides for the use of Gleevec (imatinib mesylate) 50 and 100 mg capsules for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. The effectiveness of Gleevec is based on overall hematologic and cytogenetic response rates (see Clinical Studies section). 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 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 mg and 100 mg capsules for use as recommended in the enclosed labeling text. Accordingly, the 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 and bottle label). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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 NDA 21-335." 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 Subpart H postmarketing study commitments specified in your submission dated May 8, 2001. These commitments, along with any completion dates agreed upon, are listed below.

Commitments required for accelerated approval:

To conduct and submit the final study report for Protocol 106 entitled “A phase III study of STI571 versus Interferon- (IFN-) 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.

To provide interval follow-up information on studies 102, 109 and 110. The safety and efficacy update will be provided in July, 2001, with a final analysis report expected in the third quarter, 2001.

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 Postmarketing Commitments."

In addition, we note your following postmarketing study commitments, specified in your submission dated May 8, 2001, that are not a condition of the accelerated approval. These commitments are listed below:

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). The final report is expected at the end of the year or first quarter, 2002.

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.

Protocol Submission: Within 2 months of the date of this letter
Study Start: Within 4 months of the date of this letter
Final Report Submission: expected first quarter, 2002

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

Protocol Submission: Within 4 months of the date of this letter
Study Start: Within 6 months of the date of this letter
Final Report Submission: expected first quarter, 2002

To implement a physician and patient education program regarding the use of concomitant medications with Gleevec within 2 months of the date of this letter.

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.

Protocol Submission: Within 3 months of the date of this letter
Study Start: Within 5 months of the date of this letter
Final Report Submission: expected first quarter, 2002

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

Protocol Submission: Within 3 months of the date of this letter
Study Start: Within 5 months of the date of this letter
Final Report Submission: Within 18 months of the date of this letter

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.

Protocol Submission: Within 2 months of the date of this letter
Study Start: Within 4 months of the date of this letter
Final Report Submission: Within 6 months of the date of this letter

To evaluate the etiology and treatment of the fluid retention syndrome associated with imatinib treatment and to meet with the Division of Oncology Drug Products 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 postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

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.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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}

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

Enclosures