DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-588/S-016

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza, Bldg. 105/Rm. 2W200
East Hanover, NJ 07936-1080

Attention: Joseph Quintavalla
Senior Regulatory Manager Drug Regulatory Affairs

Dear Mr. Quintavalla:

Please refer to your supplemental new drug application dated March 27, 2006, received March 28, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gleevec (imatinib mesylate) Tablets.

We acknowledge receipt of your submissions dated June 6, July 7, and September 25, 2006.

This supplemental new drug application provides for the use of Gleevec for newly diagnosed Philadelphia positive CML in pediatric patients. It also provides a response to our September 12, 2000 Pediatric Written Request (request for Pediatric Exclusivity) and for the fulfillment of two postmarketing commitments.

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) Tablets for use as recommended in the agreed upon 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).

Submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed Please mount individually ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDAs* (January 1999). For administrative purposes, this submission should be designated "**FPL for approved NDA 21-588/S016**." 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 Phase 4 commitments) specified in your submission dated September 25. This commitment, along with any completion dates agreed upon, is listed below.

1. Description of Commitment

   To follow up safety and efficacy information for Study 2108. Updated status reports to be submitted in March 2007 and March 2008. Provision of further long term data will be re-assessed following the submission of the March 2008 study status report and will depend on the number of patients still on study at that time.

Final study reports should be submitted to this NDA as a supplemental application. For administrative purposes, all submissions relating to this Phase 4 commitment must be clearly designated "**Subpart H Phase 4 Commitment**."

We approved NDA 21-588/S001 for the treatment of pediatric patients with Ph+ chronic phase CML whose disease has recurred after stem cell transplant or who are resistant to interferon alpha therapy under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses. Approval of this supplement (S016) fulfills your commitment made under 21 CFR 314.510.

1. To submit a report on available safety, efficacy and PK data from the ongoing NCI/COG Phase 2 Study No. AAML0123 using Gleevec at the 340 mg/m2 dose to treat pediatric patients with: a) Ph+ newly diagnosed CML; b) Ph+ CML in first chronic phase failing any prior treatment including interferon or intolerant of interferon, and; c) Ph+ CML relapsing after transplantation or in second or subsequent chronic phase CML. The data will be based on a data cut-off of 2 years following the first patient's first visit. The study report is estimated to be available in 2Q05.

We also note that this submission provided for fulfillment of the following postmarketing study commitment.

9. 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.

We have reviewed your submission and conclude that the above commitment was fulfilled.

The following commitments acknowledged in our May 8, 2003 letter to NDA 21-335/S-001/S-004 and in our May 20, 2003 letter to NDA 21-588/S-001are open under NDA 21-588.

Prior commitments required for accelerated approval of Gleevec for GIST patients (NDA 21-335/001 submitted October 15, 2001 and approved February 1, 2002):

4. 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.

Prior commitment required for accelerated approval of Gleevec for newly diagnosed CML patients (NDA 21-335/004 submitted June 28, 2002 and approved December 20, 2002):

7. To provide interval follow-up safety and efficacy information on study 106 annually, for three additional years, and survival data and serious adverse event data thereafter for another three years. Timeline: First interval report submitted on December 22, 2003 and to be submitted annually thereafter until January 2009.

We also remind you of your postmarketing commitments which are not a condition of accelerated approval.

Prior commitments which are not a condition of accelerated approval of Gleevec for CML patients (NDA 21-335/000 submitted February 1, 2001 and approved May 10, 2001):

11. 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.

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

    We refer to your submission of September 5, 2006 regarding this commitment. This submission is under review by FDA.

Prior commitment which is not a condition of accelerated approval of Gleevec for GIST patients (NDA 21-335/001 submitted October 15, 2001 and approved February 1, 2002):

15. 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).

Prior commitment which is not a condition of accelerated approval of Gleevec for newly diagnosed CML patients (NDA 21-335/004 submitted June 28, 2002 and approved December 20, 2002):

18. To conduct a prospective study performed in patients receiving both Gleevec and a potent CYP3A4 inducer such as phenytoin, phenobarbital, or carbamazepine and submit a final study report. The purpose of this study is to determine the dose of Gleevec that is necessary to produce similar AUCs in these patients on enzyme inducers to those achieved in adult patients receiving the usual recommended dose (400 mg/day). Timeline: Protocol submission June 2003; study start date December 2003; and final report December 2004.

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. Submit two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

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 Dotti Pease, Regulatory Project Manager, at (301) 796-1434**.**

Sincerely,

{See appended electronic signature page}

Ann Farrell, M.D.
Acting Deputy Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ann Farrell

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