DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-588

Novartis Pharmaceuticals Corporation
One Health Plaza, Building 105/2W200
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 December 13, 2002, received December 16, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gleevec™ (imatinib mesylate), 100 mg and 400 mg Tablets.

We acknowledge receipt of your submissions dated March 17 and April 2, 2003.

This new drug application provides for the use of Gleevec (imatinib mesylate) Tablets, 100 mg and 400 mg.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. Please note that this approval is considered an accelerated approval (21 CFR 314 subpart H) because all of the indications being approved for Gleevec (imatinib mesylate) Tablets are accelerated approval indications from NDA 21-335 Gleevec (imatinib mesylate) Capsules. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations. Please refer to the below details of the phase 4 accelerated approval commitments and other post-marketing commitments.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and immediate container label). Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. 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. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-588**." 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 commitments from NDA 21-335 that now apply to NDA 21-588. These commitments, along with any completion dates agreed upon, are listed below.

Prior commitment required for accelerated approval of Gleevec for newly diagnosed CML patients:

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 expected January 2004 and annually thereafter until January 2009.

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

1. 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.

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

Prior 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. **Fulfilled:** An updated report of the central pathology review for sNDA trial B2222 should be submitted when review of the 13 pending cases is complete. (released in the September 20, 2002 letter)

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. Data for the EORTC phase 1 study was submitted to the Agency on December 18, 2002 and is under review.

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.

Submit final study reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to these postmarketing study commitments must be clearly designated "Subpart H Postmarketing Study Commitments."

We also remind you of your Phase 4 commitments which are not a condition of accelerated approval.

Prior commitments which are not a condition of accelerated approval of Gleevec for CML patients:

1. 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". The final study report for protocol 103 was submitted to the Agency as NDA 21-335/S-003 and is under review.

2. 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.

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

4. **Fulfilled:** To implement a physician and patient education program regarding the use of concomitant medications with Gleevec. (released in the February 1, 2002 approval letter)

5. 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.

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

7. 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. The final study report for study DMPK (CH) P0100666 was submitted to the Agency on January 24, 2003 and is under review.

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

Prior commitments which are not a condition of accelerated approval of Gleevec for GIST patients:

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) (Estimated submission June 30, 2003).

2. Provide a plan for investigating the incidence and etiology of GI/tumor hemorrhage associated with imatinib therapy. The plan was submitted to the Agency on September 11, 2002 and is under review.

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
(Estimated submission December 31, 2002)

4. **Fulfilled:** 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. (released in the September 20, 2002 letter)

Immediately submit all promotional materials (both promotional labeling and advertisements) to be used within the first 120 days after approval. Send one copy to this division/ the Division of Oncology Drug Products and two copies of the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857

In addition, as required by 21 CFR 314.550, submit all subsequent promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of the promotional materials and the package insert to the address above.

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

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ann Staten, Regulatory Project Manager, at (301) 594-0490.

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

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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