



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-588/S-008

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

Attention: Robert A. Miranda
Director
Drug Regulatory Affairs

Dear Mr. Miranda:

Please refer to your supplemental new drug application dated December 20, 2004, received December 23, 2004, 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 May 13; July 13 and 25; and October 13, 2005.

This supplemental new drug application provides for changes to the package insert for Gleevec (imatinib mesylate) Tablets to reflect additional data accumulated from study B2222 in patients with GIST (postmarketing commitment #3) and data from the completed study 2403, a pharmacokinetic (PK) study in patients with hepatic impairment (postmarketing commitment #12).

We have completed our review of this supplemental application, as amended. This supplemental application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

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

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 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-588/S-008.**" Approval of this submission by FDA is not required before the labeling is used.

We note that this submission also included an update on postmarketing commitment #3.

Commitment #3: Complete the follow-up of sNDA trial B2222 and submit mature response rate, response duration and survival data. The updated overall response rate and response duration was submitted on December 18, 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.

We have reviewed your submissions and you are released from the above commitment. Mature response rate and response duration data has been submitted and reviewed. Although the survival data is not mature at this point, with only 37% of events having occurred, it is not likely that a subsequent survival analysis will be more informative given the limited sample size (147 patients total) and the lack of a placebo or active comparator.

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

Commitment #12: To conduct a pharmacokinetics study with Gleevec in subjects or patients with liver impairment and submit the final study report.

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-001 are open under NDA 21-588.

Open commitments 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):

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.

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.

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.

Prior commitment required for accelerated approval of Gleevec 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 (NDA 21-588/001 submitted April 23, 2003 and approved May 20, 2003).

Open commitment under NDA 21-588/S-001:

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.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Drug Oncology Products and two copies of both 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

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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) 796-1468.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D.
Acting 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/

Robert Justice
10/20/2005 04:01:59 PM