



NDA 21-588/S-002, S-003

Novartis Pharmaceuticals Corporation
One Health Plaza, Building 105/2W200
Hanover, New Jersey 07936-1080

Attention: Robert A. Miranda, Director
Drug Regulatory Affairs

Dear Mr. Miranda:

We acknowledge receipt of your February 4, 2004 submission containing final printed labeling in response to our December 8, 2003 letter approving your supplemental new drug application (S-002) for Gleevec™ (imatinib mesylate) Tablets.

We have reviewed the labeling that you submitted in accordance with our December 8, 2003 letter and we find it acceptable.

Please also refer to your supplemental new drug application (S-003) dated February 4, 2004, received February 9, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

This “Changes Being Effected” supplemental new drug application provides for revised labeling text to reflect safety data reported to Novartis in post-marketing experience and to harmonize global safety information.

We completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on February 4, 2004.

Additionally, we have received your postmarketing study commitments submissions identified below.

Commitment #8: 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”.

Submitted on February 27, 2003 to NDA 21-335/S-003 and resubmitted April 23, 2003 to NDA 21-588/S-001.

Commitment # 10: To conduct an appropriate study to assess hepatotoxic drug interactions (e.g., acetaminophen) and submit final reports.

Submitted on August 12, 2003 to NDA 21-588.

Commitment #13: 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.

Submitted on January 24, 2003 to NDA 21-335.

Commitment #16: Provide a plan for investigating the incidence and etiology of GI/tumor hemorrhage associated with imatinib therapy.

Submitted on September 11, 2002 to IND 55,666, serial number 538.

Commitment # 17: 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

Submitted on May 30, 2003 to NDA 21-588.

We have reviewed your submissions and conclude that the above commitments have been fulfilled and that the labeling of your product should be updated. We request that you submit a “Changes Being Effected” (CBE) labeling supplement for the following changes to which you agreed in your May 11, 2004 and correspondence:

For Commitment #10:

Please incorporate the following statement under PRECAUTIONS /Drug Interactions/*Drugs that may have their plasma concentration altered by Gleevec* in the current package insert for GLEEVEC:

In vitro, GLEEVEC inhibits acetaminophen O-glucuronidation (K_i value of 58.5 μM) at therapeutic levels. Systemic exposure to acetaminophen is expected to be increased when co-administered with GLEEVEC. No specific studies in humans have been performed and caution is recommended.

For Commitment #13:

A statement should be added to the package insert, Clinical Pharmacology Section, Metabolism and Elimination, following the sentence “The plasma AUC for this metabolite is about 15% of the AUC for imatinib.”, to the effect that “The plasma protein binding of the N-demethylated metabolite CGP71588 is similar to that of the parent compound.”

Miscellaneous Change:

Under the **Precautions** section to reflect the added cardiac tamponade language as follows:

Fluid Retention and Edema: Gleevec[®] (imatinib mesylate) is often associated with edema and occasionally serious fluid retention (see ADVERSE REACTIONS). Patients should be weighed and monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided. The probability of edema was increased with higher Gleevec dose and age >65 years in the CML studies.

Severe superficial edema was reported in 0.9% of newly diagnosed CML patients taking Gleevec, and in 2%-6% of other adult CML patients taking Gleevec. In addition, other severe fluid retention (e.g., pleural effusion, pericardial effusion, pulmonary edema, and ascites) events were reported in 2%-6% of other adult CML patients taking Gleevec. Severe superficial edema and severe fluid retention (pleural effusion, pulmonary edema and ascites) were reported in 1%-6% of patients taking Gleevec for GIST.

There have been post-marketing reports, including fatalities, of cardiac tamponade, cerebral edema, increased intracranial pressure, and papilledema in patients treated with Gleevec.

We have the following comment regarding commitment #10:

Your *in vitro* human liver microsomes studies demonstrated that GLEEVEC is a potent inhibitor of acetaminophen O-glucuronidation but has no effect on the formation of the intermediate hepatotoxic metabolite, NAPQI. However, because the glucuronidation pathway represents about 50% of acetaminophen metabolism, the inhibition of acetaminophen glucuronidation by GLEEVEC may result in shunting acetaminophen metabolism to other pathways and the more hepatotoxic intermediate metabolite (NAPQI) may be formed in the body as a consequence of this inhibition. Therefore, we recommend that you conduct a formal drug-drug interaction study in cancer patients to examine the effect of GLEEVEC on the pharmacokinetics of acetaminophen in order to properly adjust acetaminophen dose when it is concomitantly administered with GLEEVEC.

We have also received your submissions dated July 24, 2003 (submitted to NDA 21-335) and August 29, 2003 (submitted to NDA 21-588) reporting on the following postmarketing study commitments:

Commitment #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.

Commitment #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).

We have reviewed your submissions and conclude that the terms of the commitments were not met.

Commitment #4:

In the case of the NCI sponsored study, interim results were presented only. Therefore, further follow-up is needed. In the case of the EORTC sponsored study, although the number of events required for an evaluation of PFS had been reached, further follow-up is needed to evaluate survival.

In both cases, only posters and abstracts were submitted. Complete evaluation of the data requires submission and review of complete study reports.

Due to the interim nature of the results presented and the lack of complete study reports, we have determined that you have not completed this commitment under subpart H.

Commitment #18:

If the trial is conducted in patients, doses consistent with the package insert can and should be used to reduce the risk of subtherapeutic dosing. That is, the minimum dose administered should be as the package insert currently recommends: at least 50% greater than that administered in the absence of an inducer.

The large inter-subject variability observed in the St. John's Wort study makes it all the more important to perform a study to learn how to dose patients receiving a potent inducer. To rephrase, the St. John's Wort results do not compromise our conclusion that a study is needed, but reinforce it.

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):

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.
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 (first submitted July 24, 2003; next submission under negotiation).

6. Assure availability of a validated test kit for detection of CD117 tumor expression by immunohistochemistry.

(
b)(4)----- -- -----

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 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 (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.
12. 11To conduct a pharmacokinetics study with Gleevec in subjects or patients with liver impairment and 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.

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 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) 594-0490.

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
6/23/04 03:49:58 PM