

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-335/S-003**

**Approval Letter(s)**



NDA 21-588/S-001  
NDA 21-335/S-003

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 supplemental new drug application dated April 23, 2003, received April 24, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gleevec™ (imatinib mesylate) Tablets, 100 mg and 400 mg. We note this supplement was originally submitted February 27, 2003 to the Gleevec capsules NDA 21-335/S-003 and that the capsules are being replaced by the tablets.

We acknowledge receipt of your submissions dated May 14 and 20, 2003.

Your submission of February 27, 2003 constituted a complete response to our December 20, 2003 action letter.

This supplemental new drug application provides for the use of for Gleevec™ (imatinib mesylate) Tablets for the treatment of pediatric patients with Ph<sup>+</sup> chronic phase CML whose disease has recurred after stem cell transplant or who are resistant to interferon alpha therapy. 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 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 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).

Please submit the FPL electronically 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, in no case 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

NDA 21-588/S-001

NDA 21-335/S-003

Page 2

should be designated "FPL for approved supplement NDA 21-588/S-001." 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 commitment) specified in your submission dated May 14, 2003. This commitment, along with the completion date agreed upon, is listed below.

To submit report on available safety, efficacy and PK data from the ongoing NCI/COG Phase 2 Study No. AAML0123 using Gleevec at the 340 mg/m<sup>2</sup> 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.

The final study report 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 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.

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, HF-2  
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) 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  
5/20/03 01:19:56 PM

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-335/S-003**

**Approvable Letter (S)**



NDA 21-335/S-003

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 supplemental new drug application dated June 28, 2002, received June 28, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gleevec™ (imatinib mesylate) 100 mg capsules.

We acknowledge receipt of your submissions dated August 26; October 18 and 23, November 13 and 22, 2002.

This supplemental new drug application provides labeling revisions from the results from two dose-escalation, phase 1 studies in children with Ph+ CML and acute leukemias. The data include an evaluation of pharmacokinetics with maximum tolerated doses determined for all appropriate age groups, safety and efficacy. This supplement proposes the addition of the subsection **Pediatric** under **Special Populations** in the **CLINICAL PHARMACOLOGY** section and the addition of **Pediatric Use** section. Additionally, this supplement proposes pediatric dosing information by adding the subsection **Pediatric Patients** under the **DOSAGE AND ADMINISTRATION** section.

We completed our review of this application, and it is approvable. Please note that we have reviewed this application under the provisions of 21 CFR 314 Subpart H (accelerated approval); therefore it will be necessary to reach an agreement on the accelerated approval phase 4 commitment. Before the application may be approved, however, you must address the following deficiencies:

1. Lack of a suitable formulation for children. The planned marketing of a 100 mg scored tablet formulation will remedy this situation.
2. Reach agreement on an accelerated approval phase 4 commitment.
3. Major labeling revisions are required. Please refer to our December 17, 2002 communication that provided proposed labeling changes and submit revised draft labeling.

In addition, all previous revisions, as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application(s) under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes before approval of this supplemental application.

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

**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  
12/20/02 03:28:00 PM