DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-068

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ, 07936-1080

Attention: Robert A. Miranda
Director
Drug Regulatory Affairs

Dear Mr. Miranda:

Please refer to your new drug application (NDA) dated September 29, 2006, received September 29, 2006, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tasigna® (nilotinib) 200 mg. oral capsules.

We acknowledge receipt of your submissions dated November 8, December 19, and December 22, 2006. We also acknowledge receipt of your submissions dated January 3, January 12, January 19, January 26, February 9, February 16, March 2, March 13, May 3, May 10, June 7, June 15, June 22, June 25, July 2, August 17, September 24, September 27, September 28, October 8, and October 24, 2007.

This new drug application provides for the use of Tasigna™ (nilotinib) oral capsules for chronic phase (CP) and accelerated phase (AP) Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to prior therapy that included Gleevec® (imatinib).

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.510), effective on the date of this letter, for use as recommended in the enclosed labeling text and required Medication Guide. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

An expiration dating period of 24 months is granted for the product when stored at room temperature.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format as described at http://www.fda.gov.oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National

Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-068."

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format-Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission **"Final Printed Carton and Container Labels for approved NDA 22-068."** Approval of this submission by FDA is not required before the labeling is used.

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

This application was not taken to the Oncologic Drugs Advisory Committee (ODAC) because, for the following reasons, we determined that the application did not warrant ODAC review. The Office of Oncology Drug Products has previously accepted the endpoint of cytogenetic response as an approval endpoint in the setting of chronic phase CML and the endpoint of hematologic response in the setting of accelerated phase CML. The major toxicities can be managed with dose modifications, dose interruption, attention to concomitant medications, and safety monitoring.

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 specified in your submission dated October 25, 2007. These commitments, along with any completion dates agreed upon, are listed below.

1. To submit the complete study report (with at least 24 months follow-up of all patients) and data from study 2101, a phase 2 multicenter study of nilotinib in patients with imatinib resistant or intolerant chronic myeloid leukemia in chronic and accelerated phases respectively (arms 4 & 3, respectively).

Protocol Submission:	Study 2101 filed to IND 69,764 in April 2004 (SN 000)
Study Start:	May 2004
Final Report Submission:	by August 2010

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

In addition, we note your following postmarketing study commitments, specified in your submission dated October 25, 2007, that are not a condition of the accelerated approval. These commitments are listed below:

2. Submit the completed study report and datasets for the hepatic impairment study.

Protocol Submission:	Study 2116 filed to IND 69,764 on 10/9/06 (SN 326)

Study Start: October 2006
Final Report Submission: by June 2008

3. Conduct a relative bioavailability study (using a liquid formulation as the reference).

Protocol Submission: by August 2009
Study Start: by November 2009
Final Report Submission: by July 2010

4. Conduct a clinical study or studies to evaluate whether multiple doses of nilotinib alter the metabolism of a sensitive CYP2C9 substrate (for example, S-warfarin). If a significant interaction is demonstrated, additional clinical studies may be needed to evaluate whether multiple doses of nilotinib alter the metabolism of a sensitive CYP2C8 substrate (for example, repaglinide) and/or a sensitive CYP3A4 substrate (for example, midazolam).

Protocol Submission: by July 2008
Study Start: by September 2008
Final Report Submission: by June 2009

5. Conduct a clinical study to evaluate if H2 blockers/proton pump inhibitors alter the pharmacokinetics of nilotinib.

Protocol Submission: by July 2008
Study Start: by September 2008
Final Report Submission: by June 2009

6. Submit a supplement containing a revised version of the complete RiskMAP (goals and objectives, tools, implementation plan, evaluation plan and reports to the agency) including all supporting materials. This should incorporate the amendments agreed to in correspondence of October 22 and October 26, 2007.

Submission: by November 30, 2007.

We refer to your correspondence dated October 24, 2007 in which you stated that after launch you will print the Medication Guide statement required under 21 CFR 208.24(d) directly on the front panel of the container.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Commitment Protocol", "Postmarketing Study Commitment Final Report", or "Postmarketing Study Commitment Correspondence."

Immediately submit all promotional materials (both promotional labeling and advertisements) to be used within the first 120 days after approval. Send two copies of the promotional materials and the package insert directly to:

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

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.

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

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). As agreed to in your submission dated October 26, 2007, in addition to the usual postmarketing reporting of adverse drug experiences (21 CFR 314.80(c)), you will initiate a 15-day Alert report and follow-up for each of the following:

1. Medication errors involving dosing outside of the Tasigna (nilotinib) labeled recommendations including, but not limited to:
    - dosing with food
    - dosing outside of the recommended 12 hour frequency
    - taking more tablets than prescribed or recommended by the sponsor
    - or administration with other drug products potentially affecting the absorption or metabolism of nilotinib (e.g. CYP3A4 inhibitor)
2. QTc prolongation. These reports will include information and follow-up as to whether the event was the result of a medication error (e.g., dosing with food, dosing outside of the 12 hr frequency, etc).

Please incorporate this into your revised RiskMAP.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at: www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, please call Janet Jamison, Regulatory Project Manager, at (301) 796-2313.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products

Enclosure: Package Insert containing Medication Guide
Product carton and container proposed labeling

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

10/29/2007 11:02:35 AM