



NDA 022068/S-004
NDA 022068/S-005

**SUPPLEMENT APPROVAL
ACCELERATED APPROVAL**

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

Attention: Darshan Wariabharaj
Senior Associate Director, Drug Regulatory Affairs

Dear Mr. Wariabharaj:

Please refer to your Supplemental New Drug Applications (sNDA) dated December 11 and 21, 2009, received December 11 and 21, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tassigna[®] (nilotinib) Capsules, 150 mg and 200 mg.

We acknowledge receipt of your submissions dated February 9, April 3, 15, and June 16, 2010; and your risk evaluation and mitigation strategy (REMS) modification and assessment dated May 21 (2), amended on June 12, 2010.

“Prior Approval” supplemental new drug application 004 provides for revisions to the package insert based on data from study CAMN107A2121 titled “*A Phase 1, Open-Label, Two Period, Single-Center Study to Assess the Effect of Esomeprazole (proton pump inhibitor) on the Pharmacokinetics of Nilotinib in Healthy Subjects*”. In addition, revisions to the package insert are proposed based on clinical data concerning the impact of total gastrectomy on nilotinib absorption as well as clinical data regarding the pharmacokinetics of midazolam. Finally, this supplemental new drug application proposes modifications to the approved REMS.

We have completed our review of supplemental new drug application 004, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

“Prior Approval” supplemental new drug application 005 provides for a new indication for the treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. In addition, this supplemental new drug application also proposes modifications to the approved REMS.

We have completed our review of supplemental new drug application 005, as amended. According to the regulations for accelerated approval, we have concluded that adequate information has been presented to approve Tasigna[®] (nilotinib) Capsules for use as recommended in the enclosed, agreed-upon labeling text. Accordingly, supplemental new drug application 005 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.

CONTENT OF LABELING

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(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm> that is identical to the enclosed agreed-upon labeling text. 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 022068/S-004 and S-005**”.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

Also within 14 days, amend all pending supplemental applications for this NDA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in these supplemental applications.

CARTON AND IMMEDIATE CONTAINER LABELS

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 022068/S-004/S-005.**” Approval of this submission by FDA is not required before the labeling is used.

POSTMARKETING REQUIREMENTS FOR ACCELERATED APPROVAL UNDER SUBPART H

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies or clinical trials to verify and describe clinical benefit. We remind you of your post marketing trial (Subpart H Postmarketing requirement) specified in your email submission dated June 4, 2010. This requirement, along with any completion dates agreed upon, is listed below.

1651-1 (S-005):

Submit an interim report at 24 months and the completed report (at least 60 months of follow-up) from Trial 2303. Primary data will accompany each report.

The timetable you submitted on June 4, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submitted:	February 2007
Interim Report (at 24 months) Submission Date: (Data Cut-off Date August 31, 2010)	March 2011
Final Report (at least 60 months Follow-Up) Submission Date: (Data Cut-off Date September 30, 2013)	March 2014

Final reports should be submitted to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement.**"

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

Since Tasigna[®] was approved on October 29, 2007, we have become aware from a postapproval study of drug-drug interactions between nilotinib and proton pump inhibitors resulting in a decrease in nilotinib exposure. Due to this finding and the physicochemical properties of nilotinib, co-administration of Tasigna (nilotinib) with H2 blockers or antacids may also cause a decrease in nilotinib exposure. Therefore, we consider this information to be "new safety information" as in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of drug-drug interaction between Tasigna[®] and H2 blockers and drug-drug interaction between Tasigna[®] and antacids.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of drug-drug interaction between Tasigna[®] and H2 blockers, and drug-drug interaction between Tasigna[®] and antacids.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1650-1 (S-004):

A clinical trial to determine dosing regimens with a) H2 blockers and nilotinib, and b) antacids and nilotinib, that minimize alterations of the pharmacokinetics of nilotinib. You should include steps that dose H2 blockers and antacids at a specified period before nilotinib dosing, as well as at specified periods following nilotinib dosing.

The timetable you submitted on June 4, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	June 2011
Trial Completion Date:	January 2012
Final Report Submission:	June 2012

Submit the protocols to your IND 069764, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Tassigna[®] was originally approved on March 15, 2010. The REMS consists of a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of a revised Medication Guide which includes the addition of a new indication and language regarding total gastrectomy and revised educational materials that are part of the communication plan.

Your proposed modified REMS, submitted on May 21, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS and the REMS assessment plan will remain the same as that approved on March 15, 2010.

We remind you that the requirements for assessments of an approved REMS under section 505-1(g)(3)(B) and (C) include requirements for information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessment provisions in 505-1(g) could result in enforcement action.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

Prominently identify submissions containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022068 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 022068
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022068
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

As discussed and agreed during the June 9, 2010, teleconference between the Division of Drug Oncology Products and Novartis, DMEPA recommends educating health care practitioners about the introduction of the new 150 mg strength. In addition to the proposed dosing card that targets prescribers, we suggest communications that target pharmacists which focus on the new strength, the frequency of administration with the new strength and indication, as well as reminding practitioners of the importance of avoiding food two hours before and one hour after taking Tasigna.

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) 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

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

As required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to 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, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

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 Christy Cottrell, Regulatory Project Manager, at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Acting Director
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Carton and Container Labeling
REMS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22068	SUPPL-5	NOVARTIS PHARMACEUTICA LS CORP	TASIGNA (NILETINIB, AMN107)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
06/17/2010