DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204369

**NDA APPROVAL**

Bayer HealthCare Pharmaceuticals, Inc.
Attention: Darshan Wariabharaj
Deputy Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Mr. Wariabharaj:

Please refer to your New Drug Application (NDA) submitted August 30, 2012, received on August 30, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Stivarga (regorafenib) tablets, 40 mg.

We acknowledge receipt of your amendments dated May 31, 2012, July 3, 2012; July 23, 2012; August 13, 2012; September 6, 2012; September 11, 2012; September 14, 2012; September 25, 2012; September 27, 2012; September 28, 2012; October 3, 2012; October 5, 2012; October 9, 2012; October 10, 2012; October 24, 2012; October 29, 2012; October 31, 2012; November 9, 2012; December 13, 2012; January 15, 2013; January 31, 2013; February 6, 2013; February 13, 2013; and February 22, 2013.

This new drug application provides for the use of Stivarga (regorafenib) tablets for the treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.

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

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, and text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

In addition, within 14 days of the date of this letter, amend any pending supplement that includes labeling changes for NDA 203085 with content of labeling in SPL format to include the changes approved in this supplement.

## ADVISORY COMMITTEE

Your application for regorafenib was not referred to an FDA advisory committee because this application did not raise significant safety or efficacy issues that were unexpected for a drug of this class in the intended population.

## 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(s) 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 COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

**2016-1 Overall Survival Assessment**

Submit the results of the protocol-specified final analysis of overall survival, along with datasets and analysis SAS programs, from "Study 14874, A randomized, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care versus placebo plus best supportive care for subjects with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) whose disease has progressed despite prior treatment with at least imatinib and sunitinib."

The timetable you submitted on January 31, 2013, states that you will conduct this trial according to the following schedule:

Trial Completion Date: May 2015
Final Report Submission: March 2016

**2016-2** **Exposure-Response Analyses Assessment**

Submit an exposure-response analysis for regorafenib and its active metabolites M2 and M5 using relevant available data collected in patients with metastatic or unresectable gastrointestinal stromal tumor (GIST).

The timetable you submitted on January 31, 2013, states that you will conduct this trial according to the following schedule:

Final Report Submission: June 2013

## POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your post-marketing commitment:

**2016-3** Submit a Chemistry, Manufacturing, and Controls (CMC) CBE-30 supplement that includes the addition of a microbial purity test as a drug product specification and test each batch prior to release and the addition of X-Ray Powder Diffraction (XRPD) testing methodology & specifications to test any batches that do not meet the dissolution acceptance criterion of NLT (b) (4) dissolved at 45 minutes.

The timetable you submitted on February 6, 2013, states that you will submit this CBE-30 supplement according to the following schedule:

Submission of CMC CBE-30 Supplement: March 2013

Submit clinical protocols to your IND 113896 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to NDA 203085. 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 NDA 203085. 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/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

## PROMOTIONAL MATERIALS

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 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original **NDA 203085** for this drug product, not to this NDA. In the future, do not make submissions to this NDA except for the final printed labeling requested above.

If you have any questions, call Monica Hughes, M.S., Lead Regulatory Project Manager, at 301-796-9225.

Sincerely,

*{See appended electronic signature page}*

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure(s): Content of Labeling

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

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/s/

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PATRICIA KEEGAN
02/25/2013