



NDA 203085/S-001

**SUPPLEMENT APPROVAL/
FULLFILLMENT OF POST MARKETING REQUIREMENT/
FULLFILLMENT OF POST MARKETING COMMITMENT**

Bayer Healthcare Pharmaceuticals, Inc.
Attention: Philip Johnson, MBA
Deputy Director, Global Regulatory Affairs
P.O. Box 1000, M1/2-1
Montville, NJ 07045-1000

Dear Mr. Johnson:

Please refer to your Supplemental New Drug Application (sNDA) dated November 29, 2012, received November 29, 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 amendment(s) dated April 1, 2013; April 29, 2013; May 13, 2013; and May 23, 2013.

This "Prior Approval" supplemental new drug application proposes to revise the Drug Interaction and Clinical Pharmacology sections of the prescribing information. The changes to the Clinical Pharmacology section include revisions to the drug-drug interactions subsection, addition of an electrophysiology/QT prolongation subsection, and addition of population pharmacokinetic data.

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

We note that your May 23, 2013, submission includes final printed labeling (FPL) for your package insert and patient package insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

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, with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including 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 this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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 a waiver for colorectal cancer (CRC) was granted for Stivarga (regorafenib) in September 2012, with the approval of NDA 203085, none of the criteria apply to your application, and you are exempt from these requirements.

FULFILLMENT OF POSTMARKETING REQUIREMENTS

We received your submissions dated December 5, 2012, and December 14, 2012, containing the final study reports for the following post marketing requirements listed in the September 27, 2012, approval letter.

1925-1 QT/QTc Interval Prolongation Assessment

Complete a clinical trial evaluating the potential for regorafenib to prolong the QT/QTc interval in an adequate number of patients administered repeated doses of 160 mg of regorafenib and submit the final report, along with a thorough review of cardiac safety data.

1925-2 **Drug Interaction Assessment**

Complete a clinical trial and submit the final report to evaluate the effect of repeated doses of 160 mg of regorafenib on the pharmacokinetics of a probe substrate of CYP2C8, CYP2C9, CYP3A4 and CYP2C19.

We have reviewed your submissions and conclude that the above requirements are fulfilled.

FULFILLMENT OF POSTMARKETING COMMITMENTS

We received your submission dated May 17, 2013, containing the final study report for the following post marketing commitment listed in the September 27, 2012, approval letter.

1925-4 **Population Pharmacokinetic Analyses Assessment**

Submit an integrative population pharmacokinetic analysis report to evaluate the effect of intrinsic and extrinsic factors on the pharmacokinetics of regorafenib and its active metabolites M2 and M5.

We received your submission dated December 17, 2012, containing the final study report for the following post marketing commitment listed in the September 27, 2012, approval letter.

1925-5 **Exposure-Response Analyses Assessment**

Submit an exposure-response analysis for regorafenib and its active metabolites M2 and M5 using data collected from the CORRECT trial (Study 14387) in patients with metastatic colorectal cancer (mCRC) who have progressed after standard therapy.

We have reviewed your submissions and conclude that the above commitments are fulfilled.

We remind you that there is a postmarketing requirement listed in the September 27, 2012 approval that is still open.

1925-3 **Impaired Renal Function Assessment**

Conduct a multiple dose trial to determine the appropriate regorafenib dose in patients with severe renal impairment. Submit the final protocol for FDA review before conducting the trial.

The timetable you submitted on September 26, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: March 2013
Trial Completion: December 2014
Final Report Submission: June 2015

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

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

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on 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).

If you have any questions, call Anuja Patel, Regulatory Health Project Manager, at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Jeff Summers, M.D.
Deputy Director for Safety
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S): Content of Labeling

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

/s/

JEFFERY L SUMMERS
05/29/2013