



NDA 203085/S-006

**SUPPLEMENT APPROVAL/  
FULLFILLMENT OF POSTMARKETING REQUIREMENTS**

Bayer HealthCare Pharmaceuticals, Inc.  
Attention: Lisa Chao, Ph. D.  
Deputy Director, Global Regulatory Affairs, Specialty Medicine  
100 Bayer Boulevard, P.O. Box 915  
Whippany, NJ 07981-0915

Dear Dr. Chao:

Please refer to your Supplemental New Drug Application (sNDA) dated February 26, 2016, received February 26, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Stivarga (regorafenib) tablets, 40 mg.

This Prior Approval supplemental new drug application is based on data from a trial to determine the appropriate regorafenib dose in patients with renal impairment and data from a drug interaction study of transport proteins P-gp and BCRP and provides for the following updates to the labeling:

- Addition of a new subsection under Section 7 DRUG INTERACTIONS, Effect of Regorafenib on Breast Cancer Resistance Protein (BCRP) substrates;
- Revised Section 8, Hepatic Impairment subsection to state that no dose adjustment is needed for patients with mild or moderate hepatic impairment;
- Revised Section 8, Renal Impairment subsection to state that no dose adjustment is needed for patients with mild, moderate, or severe renal impairment; and,
- Addition of a new subsection under Section 12 CLINICAL PHARMACOLOGY to include effects of BCRP substrates.

**APPROVAL & LABELING**

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.

## **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, with the addition of any labeling changes in pending “Changes Being Effectuated” (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 include 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 none of these criteria apply to your application, you are exempt from this requirement.

## **FULFILLMENT OF POSTMARKETING REQUIREMENT(S)**

We have received your submission dated February 26, 2016, containing the final report for the following postmarketing requirement listed in the September 27, 2012, approval letter.

### **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.

We have reviewed your submission and conclude that the above requirement is fulfilled.

This completes all of your postmarketing requirements and postmarketing commitments in our September 27, 2012, letter for metastatic colorectal cancer (CRC).

We remind you that there is a postmarketing commitment listed in the February 25, 2013, approval letter for locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate that is still open.

### **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:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

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/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. 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, Senior Regulatory Health Project Manager, at (301) 796-9022.

Sincerely,

*{See appended electronic signature page}*

Jeffrey Summers, M.D.  
Deputy Director for Safety  
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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JEFFERY L SUMMERS  
08/26/2016