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APPLICATION NUMBER:

203085Orig1s000

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 26, 2012

From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 203085: FDA Labeling Comments

Please find attached FDA's counter proposal to your revised package insert (PI) and patient package insert (PPI) submitted via email communication on September 26, 2012.

Please provide a response by 3:00 PM today, September 26, 2012. In addition to submitting your response to the NDA, please email me a copy of your responses as well as a clean and redlined version of the labeling.

Please let me know if you have any questions.

Regards,

Monica Hughes, M.S.
Lead Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9225, Fax: 301-796-9849

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MONICA L HUGHES
09/26/2012

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Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: QT/QTc Interval Prolongation

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	submitted
Study/Clinical trial Completion Date:	10/31/2012
Final Report Submission Date:	11/30/2012
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Regorafenib inhibited the hERG K+ current with an IC50 value of 12 micromolar, but demonstrated no effect on the cardiac action potential in rabbit Purkinje fibers and no effect on ECG intervals in Beagle dogs after oral and intravenous administration.

In the NDA submission, the applicant included an interim analysis of the QT/QTc intervals completed on 25 patients with advanced solid tumors enrolled in Study 14814. The final study report for the dedicated cardiovascular safety study is to be submitted post marketing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the clinical trial is to assess the risk for regorafenib to potentially prolong the QT/QTc interval.

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3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Complete a clinical trial evaluating the potential for a 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 study report, along with a thorough review of cardiac safety data.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

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