CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203085Orig1s000

OTHER REVIEW(S)

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

/s/

MONICA L HUGHES
09/26/2012

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.

Reference ID: 3194115

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

Reference ID: 3194115

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☒ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☐*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Reference ID: 3194115

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: Drug Interaction

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 or the active metabolites M2 or M5 inhibited CYP2B6, CYP2C9, CYP2C8, CYP2C19, CYP2D6 and/or CYP3A4 in vitro. The R values suggest that a drug interaction trial is warranted with a sensitive substrate of CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2D6, and CYP3A4. A trial to assess the effects of regorafenib on the pharmacokinetics of a substrate of CYP2C8, CYP2C9, CYP2C19, and CYP3A4 is ongoing and the applicant proposes to submit the final study report in November 2012.

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 need to avoid coadministration of sensitive substrates of CYP2C8, CYP2C9, CYP2C19 and CYP3A4 with regorafenib.

Reference ID: 3194115

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 and submit the final study 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.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Reference ID: 3194115

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☐*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Reference ID: 3194115

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: Impaired Renal Function

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	12/31/2012
	Study/Clinical trial Completion Date:	12/31/2013
	Final Report Submission Date:	06/30/2014
	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

   A pooled univariate analysis suggests that exposure of regorafenib increases with worsening renal function. The applicant is requested to conduct a multi-dose pharmacokinetic trial in patients with severe renal impairment.

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 need for a dose reduction or recommend avoidance of regorafenib for patients with severe renal impairment.

Reference ID: 3194115

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.

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.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Reference ID: 3194115

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☒ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☐*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Reference ID: 3194115

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: Population Pharmacokinetic Analyses

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	submitted
	Study/Clinical trial Completion Date:	not applicable
	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

   The applicant proposes to conduct population pharmacokinntic analyses using the data collected in study 11650 and 14387 and submit the report post marketing due to the clinical safety and efficacy trial finished earlier than planned.

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 population pharmacokinetic analyses is to assess the pharamcokinetics of regorafenib and the active M-2 and M-5 metabolites across all clinical trials which included pharmacokientic sampling and use a covariate model to determine the influence of intrinsic and extrinsic factors on the pharmacokinetic parameters. These analyses can support recommendations for dose modifications in specific populations.

Reference ID: 3194115

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.

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.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Reference ID: 3194115

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☒ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☐*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Reference ID: 3194115

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: Exposure-Response Analyses

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	submitted
	Study/Clinical trial Completion Date:	not applicable
	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

   The applicant proposes to conduct an exposure-response analyses using the data collected during the registration trial and submit the report post marketing as the clincial trial trial finished earlier than expected.

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 these analyses is to explore the relationship between exposure of regorafenib and the active M-2 and M-5 metabolites and the safety and efficacy demonstrated in the reigstration trial. This analysis might help support the proposed dose modifications for adverse events listed in the labeling and potential dose modifications for organ impairment or drug interactions in which dose modifications are typically recommended based on identified exposure differences.

Reference ID: 3194115

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.

Submit an exposure-response analysis for regorafenib and its active metabolites M2 and M5 (b) (4) [redacted] using data collected from the CORRECT trial (Study 14387) in patients with metastatic colorectal cancer (mCRC) who have progressed after standard therapy.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Reference ID: 3194115

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
E-R analyses of the data from the registration trial
☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☐*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Reference ID: 3194115

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

/s/

STACY S SHORD
09/25/2012

HONG ZHAO
09/25/2012
I concur.

JEFFERY L SUMMERS
09/26/2012

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

Memorandum

Date: September 25, 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 21, 2012.

Please provide a response by 10:00 am tomorrow, 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

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/s/

MONICA L HUGHES
09/25/2012

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

Memorandum

Date: September 24, 2012

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

Subject: NDA 203085: Proposed PMR/PMC Response

FDA's post-marketing requirement (PMR) and post-marking commitment (PMC) proposals were sent to Bayer as a memorandum on September 18, 2012. Bayer asked for clarifications regarding PMR 3 and also provided a written response to the PMR-PMC proposals to the regulatory project manager via email communications on Tuesday, September 18, 1012; Wednesday, September 19, 2012; and Thursday, September 20, 2012.

Post Marketing Requirements (PMRs)

1. 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.

   Bayer Response: Bayer commits to fulfilling this requirement as proposed by FDA in the September 18, 2012 memo. For Post-Marketing Requirements 1 (QT/QTc study), we wish to clarify that the report submitted in November 2012 will be a final evaluation of the primary variables for these studies, but the report will be titled an "interim" clinical study report. As patients in these studies have the option to remain on drug while receiving therapeutic benefit, the final clinical study report will be generated approximately 12 months following last patient last visit.

   FDA Response: The study report to be submitted in November 2012 as requested in the September 18, 2012, PMR/PMC memorandum as the Final Report Submission date should be a "final" report that adequately addresses the PMR. The clinical trial may be ongoing to address other objectives listed in the protocol. Bayer should identify the report as a final PMR study report.

2. 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.

   Bayer Response: Bayer commits to fulfilling this requirement as proposed by FDA in the September 18, 2012 memo. For Post-Marketing Requirements 2 (probe substrate study), we wish to clarify that the report submitted in November 2012 will be a final evaluation of the primary variables for these studies, but the report will be titled an "interim" clinical study report. As patients in these studies have the option to remain on drug while receiving therapeutic benefit, the final clinical study report will be generated approximately 12 months following last patient last visit.

FDA Response: The study report to be submitted in November 2012 as requested in the September 18, 2012, PMR/PMC memorandum as the Final Report Submission date should be a "final" report that adequately addresses the PMR. The clinical trial may be ongoing to address other objectives listed in the protocol. Bayer should identify the report as a final PMR study report.

3. 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.

Bayer Response: Bayer has evaluated all available data that shows that urinary excretion is not a significant pathway for the elimination of regorafenib. Therefore, Bayer would appreciate further dialogue with the FDA to understand their rationale for conducting a multiple dose study in cancer patients with severe renal impairment.

Background

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[redacted]

As we would like to align on a feasible approach to evaluate this aspect as quickly as possible, we are open to a teleconference anytime during the next days to further discuss the FDA proposal and the PBPK model above.

FDA Response: FDA acknowledges that about 19% of a radiolabeled dose of 120 mg of regorafenib as an oral solution is eliminated in the urine and that 17% of the radiolabeled dose excreted into the urine is eliminated as glucuronides of regorafenib and M-2 as demonstrated in Study 12436.

FDA acknowledges that Bayer submitted an integrative pharmacokinetic (PK) analyses that included a univariate evaluation of the effect of renal function on the exposure to regorafenib using pooled data from five clinical studies. The pooled analysis suggests that the exposure of regorafenib, M-2 and M-5 appear to be increasing with worsening renal function as estimated by the MDRD formula [Table 3-20, Summary of Clinical Pharmacology Studies in the NDA submission]. The FDA notes that the mean $AUC_{0\text{-}24h,ss}$ of regorafenib, M-2 or M-5 in patients with normal renal function and mild renal impairment in this analysis appears lower than that observed in the dose escalation Study 11650.

FDA required this PMR based on the available data listed above. As the FDA draft renal guidance [entitled "*Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling*"] states that renal impairment can adversely affect some pathways of hepatic/gut drug metabolism and has also been associated with other changes, such as changes in absorption, plasma protein binding, transport, and tissue distribution; therefore, the limited renal elimination of regorafenib does not preclude the need to conduct a dedicated clinical study to assess the effect of renal impairment on the pharmacokinetics of regorafenib and its metabolites and recommend an appropriate dose for patients with renal impairment. The guidance also states that for most drugs that are likely to be administered to patients with renal impairment, including drugs that are not primarily excreted by the kidney, pharmacokinetics should be assessed in patients with renal impairment to provide appropriate dosing recommendations.

The analyses proposed by the applicant are considered exploratory and cannot provide definitive conclusions regarding the magnitude of change in the clearance of regorafenib and its metabolites in patients with renal impairment and appropriate dose recommendations for patients with renal impairment. A multiple dose renal impairment study as listed in the September 18, 2012, PMR/PMC memorandum will need to be conducted in accordance with the FDA draft renal guidance.

Post Marketing Commitments (PMCs)

4. 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.

   Bayer Response: Bayer commits to fulfilling this commitment as proposed by FDA in the September 18, 2012 memorandum.

   FDA Response: FDA clarifies that the population PK analyses should incorporate all studies in which sparse or rich PK samples were collected, including the five clinical trials listed in the integrative PK analysis. The FDA acknowledges that the applicant did state that a population PK model would be developed using the data from Study 11650 and incorporate the data from Study 14387 in the Summary of Clinical Pharmacology Studies in the NDA submission.

5. 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.

   Bayer Response: Bayer commits to fulfilling this commitment as proposed by FDA in the September 18, 2012 memorandum.

   FDA Response: FDA has no additional comments.

We are requesting a response to our comments by 4:00 PM ET on September 25, 2012.

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

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/s/

MONICA L HUGHES
09/24/2012

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

Memorandum

Date: September 19, 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 7, 2012.

Please also find our additional comments to your revised carton and container labeling submitted via email communication on September 5, 2012, in response to our August 29, 2012, communication below.

Container Label

1. Bold "40 mg" below the established name on the principal display panel to give it the same prominence as the established name.

2. Relocate "28 tablets" to the bottom of the principal display panel. Post marketing data shows that confusion with the strength and bottle count can occur when they are in close proximity with each other on the principal display panel.

Carton Labeling

3. Revise the storage statement "Keep the bottle tightly closed after first opening" to "Keep the bottle tightly closed".

4. Remove the graphic. Or make the graphic smaller and relocate the graphic away from the trade and established names to avoid distraction from them

Please provide a response to FDA's proposed changes by 2:00 PM on Friday, September 21, 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

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/s/

MONICA L HUGHES
09/19/2012

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

Memorandum

Date: September 18, 2012

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

Subject: NDA 203085; Proposed PMC/PMR Language

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

Mr. Johnson,

Please see FDA's post-marketing requirement and post-marking commitment proposals for the Stivarga (regorafenib) NDA application 203085.

Post Marketing Requirements (PMRs) Under 505(o)

CLINICAL PHARMACOLOGY

QT/QTc Interval Prolongation Assessment:

1. 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.

   Final Protocol Submission: Submitted
   Trial Completion Date: October 2012
   Final Report Submission: November 2012

Drug Interaction Assessment:

2. Complete a clinical trial and submit the final study 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.

   Final Protocol Submission: Submitted
   Trial Completion Date: October 2012
   Final Report Submission: November 2012

Impaired Renal Function Assessment:

3. 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.

   Final Protocol Submission: December 2012
   Trial Completion Date: December 2013
   Final Report Submission: June 2014

Post Marketing Commitments (PMCs) Subject to the Reporting Requirements Under Section 506B

CLINICAL PHARMACOLOGY

Population Pharmacokinetic Analyses Assessment:

4. 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.

   Final Report Submission: November 2012

Exposure-Response Analyses Assessment:

5. Submit an exposure-response analysis for regorafenib and its active metabolites M2 and M5 (b) (4) using data collected from the CORRECT trial (Study 14387) in patients with metastatic colorectal cancer (mCRC) who have progressed after standard therapy.

   Final Report Submission: November 2012

We are requesting that you respond to our proposal by 2:00 PM on Thursday, September 20, 2012.

To assist you in organizing the submission of final study reports, we refer you to the following resources:

- Guidance for Industry entitled, *Structure and Content of Clinical Reports* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf
- Guidance for Industry, entitled, *Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072974.pdf
- Guidance for Industry, entitled, *Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization of 1997* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf.

- Guidance for Industry, entitled, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Food, Drug, and Cosmetic Act* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf >

Please note for any multi-study PMC/PMR, results from each study are to be submitted as an individual clinical study report (CSR) to the NDA or BLA as soon as possible after study completion. The cover letter for these individual CSRs should identify the submission as **PMC/PMR CORRESPONDENCE – PARTIAL RESPONSE** in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the approval letter, as well as the date of the approval letter.

The PMC/PMR final study report (FSR) submission intended to fulfill the PMC/PMR should include submission of the last remaining CSR and all previously submitted individual CSRs. The FSR should also contain an integrated analysis and thoughtful discussion across all studies regarding how these data support the fulfillment of the PMC/PMR. The cover letter should state the contents of the submission.

Furthermore, if a PMC/PMR requests, as a milestone, the submission of individual study reports as interim components of a multi-study PMC/PMR, the cover letter should identify the submission as **PMC/PMR CORRESPONDENCE – INTERIM STUDY REPORT** in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the final action letter, as well as the date of the final action letter.

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

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/s/

MONICA L HUGHES
09/18/2012

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

Memorandum

Date: September 13, 2012

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

Subject: NDA 203085: Internal Labeling Meeting

FDA's proposed revisions as discussed during the September 11, 2012, labeling meeting.

Attendees: Kaushikkumar Shastri, Steven Lemery, Shan Pradhan, Monica Hughes, Patricia Keegan

Sections covered include:

- Continued to review Bayer's September 7, 2012, response to our August 29, 2012, labeling comments. This meeting was a continuation to discuss sections still under review from the September 11, 2012, labeling meeting.
    - Section 2
    - Section 6
    - Highlights

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/s/

MONICA L HUGHES
09/14/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: September 12, 2012

To: Monica Hughes, Lead Regulatory Project Manager
Division of Oncology Products 2 (DOP-2)
Office of Hematology Oncology Drug Products

From: Karen Munoz-Nero, BSN, RN, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
Office of Prescription Drug Promotion (OPDP)

CC: Carole Broadnax, R.Ph., Pharm.D., Regulatory Review Officer
Division of Professional Drug Promotion (DPDP), OPDP

Subject: NDA 203085
Stivarga (regorafenib) tablets, oral
OPDP Comments on proposed patient package insert

In response to the Division of Oncology Products 2 (DOP 2) May 4, 2012, consult request, DCDP has reviewed the proposed patient package insert (PPI) for Stivarga (regorafenib) tablets, oral. Comments for the proposed Package Insert (PI) and carton and container were provided under separate cover by Carole Broadnax on September 11, 2012.

DCDP's comments on the PPI are based on the following documents:

- The completed Division of Medical Policy Programs (DMPP) revised labeling entitled "regorafenib (Stivarga) 203085 DMPP PPI Sep-2012 clean.doc" sent via electronic mail from Karen Dowdy, RN, BSN, Patient Labeling Reviewer on September 11, 2012. It is noted that the DMPP review was based on the PPI version of August 29, 2012.
- The revised PI, dated September 11, 2012, entitled "9-11-12 FDA Proposed Revisions Stivarga - Regorafenib Redline USPI - Bayer Revisions 7 Sep 2012.doc".

DCDP's comments are provided directly in the attached document.

Thank you for the opportunity to comment on this proposed labeling. If you have any questions regarding this consult review, please contact Karen Munoz-Nero at 301-796-3274 or Karen.Munoz@fda.hhs.gov.

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/s/

KAREN MUNOZ-NERO
09/12/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	September 11, 2012
To:	Patricia Keegan, M.D. Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	Stivarga (regorafenib)
Dosage Form and Route:	tablets
Application Type/Number:	NDA 203-085
Applicant:	Bayer HealthCare Pharmaceuticals Inc.

1 INTRODUCTION

On April 27, 2012, Bayer HealthCare Pharmaceuticals Inc. submitted for the Agency's review an Original New Drug Application (NDA) 203-085 for Stivarga (regorafenib) tablets. The proposed indication for Stivarga (regorafenib) tablets is for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with, (b) (4) fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. On May 8, 2012, the Division of Oncology Products 2 (DOP2) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for Stivarga (regorafenib) tablets.

This review is written in response to a request by DOP2 for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for Stivarga (regorafenib) tablets.

2 MATERIAL REVIEWED

- Draft Stivarga (regorafenib) tablets Patient Package Insert (PPI) received on April 27, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on August 29, 2012.
- Draft Stivarga (regorafenib) tablets Prescribing Information (PI) received on April 27, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on August 29, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
09/11/2012

BARBARA A FULLER
09/11/2012

LASHAWN M GRIFFITHS
09/11/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 11, 2012

To: Monica Hughes, Lead Regulatory Project Manager
Division of Oncology Products 2 (DOP-2)
Office of Hematology Oncology Drug Products

From: Carole Broadnax, PharmD, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Cc: Karen Munoz, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP), OPDP

Subject: NDA 203085
Stivarga (regorafenib) tablets
OPDP Labeling Comments

OPDP/DPDP has reviewed the proposed labeling (Package Insert (PI) and carton/container) as requested in your consult dated May 4, 2012. OPDP/DCDP comments for the proposed patient package insert (PPI) will be provided in a separate consult response.

DPDP's comments are based on the substantially complete version of the proposed PI titled, "NDA 203085 Draft USPI FDA proposed revisions Draft AUG 29.doc," sent via electronic mail to OPDP (Carole Broadnax) from DOP 2 (Monica Hughes) on August 29, 2012. OPDP's comments are provided directly in the attached document. Please note that for the PI, OPDP hid DOP 2's deletions and formatting changes so that OPDP comments are easier to read.

DPDP reviewed the proposed revised carton and container labeling sent via electronic mail to OPDP (Carole Broadnax) from DOP 2 (Monica Hughes) on September 7, 2012. OPDP does not have comments on the carton and container labeling at this time.

Thank you for your consult. If you have any questions, please contact Carole Broadnax at (301) 796-0575 or Carole.Broadnax@fda.hhs.gov.

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/s/

CAROLE C BROADNAX
09/11/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 6, 2012

TO: Monica Hughes, Lead Regulatory Health Project Manager
Shan Pradhan, M.D., Medical Officer
Steven Lemery, M.D., Lead Medical Officer

FROM: Janice Pohlman, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203085

APPLICANT: Bayer HealthCare Pharmaceuticals

DRUG: Stivarga (regorafenib)
NME: Yes
THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: Treatment of patients with metastatic colorectal cancer who have been previously treated with, (b) (4) fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and if KRAS wild type, an anti-EGFR therapy.

CONSULTATION REQUEST DATE: May 11, 2012
INSPECTION SUMMARY GOAL DATE: September 5, 2012
DIVISION ACTION GOAL DATE: September 27, 2012
PDUFA DATE: October 27, 2012

I. BACKGROUND:

Regorafenib is a new oral multiple kinase inhibitor that blocks kinases involved in tumor angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, REF, RAF-1, BRAF, BRAFV^{600E}), and the tumor microenvironment (PDGFR, FGFR). It inhibits tumor growth, progression, and metastasis by inhibiting the proliferation of tumor cells, the formation of new tumor vasculature and stromal signaling.

The proposed indication for regorafenib is for treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with, (b) (4) fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and if KRAS wild type, an anti-EGFR therapy.

The Applicant submitted one Phase 3 study in support of this application for NDA 203805.

Study 14387 "A randomized, double-blind, placebo-controlled phase III study of regorafenib plus BSC versus placebo plus BSC in patients with metastatic colorectal cancer (CRC) who have progressed after standard therapy"

The primary study objective was to evaluate the efficacy and safety of regorafenib in patients with metastatic CRC who had progressed after standard therapies.

This was a multi-center, randomized, double-blind phase 3 study. Randomization was stratified by prior treatment with VEGF targeting drugs (yes/no), time from diagnosis of metastatic disease (≥18 months vs < 18 months), and geographical region. Subjects were randomly assigned in a 2:1 ratio to one of the following treatment groups:

- regorafenib 160 mg (four 40 mg tablets) orally once daily for 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks plus best supportive care (BSC)
- placebo plus BSC

Patients continued on treatment until one of the following occurred:

- progressive disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, or clinical progression
- death
- unacceptable toxicity
- patient withdrew consent
- treating physician assessed discontinuation of treatment to be in the subject's best interest
- substantial non-compliance with the protocol.

The primary efficacy endpoint of the study was overall survival defined as the time from randomization to death due to any cause.

The study was conducted at 114 study centers that enrolled subjects in 16 countries. Of these, 105 centers across 15 countries randomized at least one patient. The participating countries,

along with number of sites, were: Japan (19), U.S. (17), Germany (15), Italy (9), France (9), Spain (8), Belgium (6), Australia (5), Israel (5), Canada (5), Czech Republic (2), the Netherlands (2), China (1), Hungary (1), and Switzerland (1). Nine centers enrolled patients who were not randomized.

II. RESULTS (by Site):

Name and location of CI	Protocol # and # of Subjects	Inspection Date	Final Classification*
Site #22004 Alfredo Falcone A.O.U. Pisana Oncologia Medica 2 S.O. Santa Chiara Via Roma, 67 56100 Pisa Italy	Study 14387 29 subjects	July 16 – 18, 2012	Pending (preliminary NAI)
Site #22005 Salvatore Siena A.O. Osp Niguarda Ca' Granda Oncologia Medica Falck Piazza Ospedale Maggiore, 3 20162 Milano Italy	Study 14387 36 subjects	July 9 – 13, 2012	Pending (preliminary NAI)
Site #28001 Eric Van Cutsem UZ Leuven Gasthuisberg Herestraat 49 3000 Leuven Belgium	Study 14387 34 subjects	Aug 21 – 24, 2012	Pending (preliminary NAI)
Site #14001 Axel Grothey Mayo Clinic – Rochester Division of Medical Oncology 200 First St., SW Rochester, MN 55905	Study 14387 22 subjects	June 18 – 21, 2012	Pending (preliminary VAI)
(b) (4)	Study 14387	(b) (4)	Pending (preliminary NAI)

<u>* Key to Classifications</u>
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **Alfredo Falcone**
   A.O.U. Pisana
   Oncologia Medica 2
   S.O. Santa Chiara
   Via Roma, 67
   56100 Pisa
   Italy

   a. **What was inspected**: The inspection was conducted in accordance with Compliance Program 7348.811 from July 16 to July 18, 2012. Thirty six subjects were screened and 29 subjects were enrolled. All 36 subjects' records were reviewed for informed consent documentation. Twenty nine subjects' records were audited for primary efficacy endpoint, adverse events, and drug accountability. The investigator further audited 15 subjects' records for inclusion/exclusion criteria and protocol compliance.

   b. **General observations/commentary**: The primary efficacy endpoint data were verifiable. There was no under-reporting of adverse events.

   c. **Assessment of data integrity**: The study appears to have been conducted adequately and the data generated by this site may be used in support of the pending application.

Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. **Salvatore Siena**
   A.O. Osp Niguarda Ca' Granda
   Oncologia Medica Falck
   Piazza Ospedale Maggiore, 3
   20162 Milano
   Italy

   a. **What was inspected**: The inspection was conducted in accordance with Compliance Program 7348.811 from July 9 to July 13, 2012. Forty eight subjects were screened and 36 subjects were enrolled. All 48 subjects' records were reviewed for informed consent documentation. Thirty six subjects' records were audited for primary efficacy endpoint, adverse events, and drug accountability. The investigator further audited 12 subjects' records for inclusion/exclusion criteria and protocol compliance.

   b. **General observations/commentary**: The primary efficacy endpoint data were verifiable. There were a few mild, nonserious adverse events that were not reported.

   c. **Assessment of data integrity**: The study appears to have been conducted adequately

and the data generated by this site may be used in support of the pending application.

Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

3. **Eric Van Cutsem**
   UZ Leuven Gasthuisberg
   Herestraat 49
   3000 Leuven
   Belgium

   a. **What was inspected**: The inspection was conducted in accordance with Compliance Program 7348.811 from August 21 to August 24, 2012. Forty two subjects were screened and 34 subjects were enrolled. All 42 subjects' records were reviewed for informed consent documentation. Eleven subjects' records were reviewed for inclusion/exclusion criteria, protocol compliance, primary efficacy endpoint, and adverse event reporting. The investigator also reviewed drug accountability, financial disclosures, and training.

   b. **General observations/commentary**: The study was not conducted under IND at this site, so no 1572s were observed on site. Source documents and background information from the NDA was compared and verified. In general, the site followed Good Clinical Practices. There was no Form FDA 483 issued.

   c. **Assessment of data integrity**: The study appears to have been conducted adequately and the data generated by this site may be used in support of the pending application.

Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

4. **Axel Grothey, M.D.**
   Mayo Clinic – Rochester
   Division of Medical Oncology
   200 First St., SW
   Rochester, MN 55905

   a. **What was inspected**: The inspection was conducted in accordance with Compliance Program 7348.811 from June 18 to 21, 2012. Thirty two subjects were screened, 23 subjects enrolled, and 22 subjects received test article. All 36 subjects' records were reviewed for informed consent documentation. Twenty three subjects' records were audited for primary efficacy endpoint, adverse events, and drug accountability. The investigator also audited the records for inclusion/exclusion criteria, protocol compliance, drug accountability, training of site personnel, and correspondence with the IRB and CRO.

b. **General observations/commentary**: The primary efficacy endpoint data were verifiable. There was no under-reporting of adverse events. In general, the study was performed in accordance with Good Clinical Practices. A Form FDA 483 was issued to the site for:

> Investigational drug disposition records were not adequate with respect to quantity and use by subjects. Specifically, there were discrepancies in the records (Patient's Medication Diary or Study Drug Dispensing Diary, Oncology Therapy record, and the Sponsor's Protocol Deviations record) that describe the amount dispensed by the pharmacist, used by subject, and retrieved by the pharmacist. Discrepancies were noted for Subject #s 140010001, 140010005, 140010007, 1400110008, and 140010010.
>
> *OSI Reviewer Comment: The majority of discrepancies involved 1 pill unaccounted for or pill counts off by 4-8 (1 to 2 days of treatment). The study treatment consisted of 4 pills orally per day for 21 days (total 84 pills). The bottle containing study drug or placebo was reported to have 85 pills; this could not be confirmed by site pharmacists since the bottle was to remain closed until distributed to the subject. The site thought that possibly bottles containing less than 85 pills were dispensed. It is unlikely that these infrequent and random discrepancies impacted data reliability.*

c. **Assessment of data integrity:** The study appears to have been conducted adequately and the data generated by this site may be used in support of the pending application.

<u>Note</u>: Observations noted above are based on review of the Form FDA 483 and preliminary review of the EIR; an inspection summary addendum will be generated if conclusions change upon final review of the EIR.

5. (b) (4)

a. **What was inspected**: The inspection was conducted in accordance with Compliance Program 7348.810 from (b) (4). The contract research organization (CRO) was inspected rather than the Sponsor since the trial master file is being maintained by the CRO at the present time. The audit covered review of the following: organization and personnel, selection and monitoring of clinical investigators and clinical monitors, monitoring procedures and activities, safety and adverse event reporting including serious adverse events, quality assurance, contracts with the Applicant, standard operating procedures, financial disclosures and investigator statements (Form 1572), and computer programs used during the study.

Monitoring records were reviewed for the following clinical sites: Drs. Falcone (#22004), Siena (#22005), Van Cutsem (#28001), and Grothey (#14001).

b. **General observations/commentary**: The Sponsor maintained adequate oversight of the clinical trial. In general, monitoring of the investigator sites was considered adequate. There was no evidence of under-reporting of adverse events. No Form FDA 483 was issued at the end of the CRO inspection.

c. **Assessment of data integrity**: The study appears to have been conducted adequately and the data submitted by the Sponsor (Bayer Pharmaceuticals) through the CRO may be used in support of the pending application.

Note: Observations noted above are based on preliminary review of the EIR; an inspection summary addendum will be generated if conclusions change upon final review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The preliminary classification of inspections at the sites of Dr. Falcone, Dr Siena, and Dr. Van Cutsem are NAI (No Action Indicated). This classification is based on communications with the field investigator. Preliminary classification of the inspection at Dr. Grothey's site is VAI (Voluntary Action Indicated) due to infrequent, minor discrepancies in records of pill counts dispensed by the pharmacist, used by the subject, and retrieved by the pharmacist. This classification is based on preliminary review of the EIR. Preliminary classification of the CRO is NAI (No Action Indicated) based on preliminary review of the EIR.

Based on the review of available inspectional findings for these clinical investigators and the CRO, the study data collected appear reliable in support of NDA 203085.

Note: Observations noted above are preliminary and are based on the Form FDA 483 (if issued), communications with the field investigator, and/or preliminary review of the EIR; an inspection summary addendum will be generated if conclusions change upon receipt and/or final review of the EIR.

{See appended electronic signature page}

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/s/

JANICE K POHLMAN
09/06/2012

SUSAN D THOMPSON
09/06/2012

Office of Clinical Pharmacology
Predictive Safety Team
Biological Plausibility Consult

Date: 8/31/2012

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Consult: Predict adverse events and safety concerns for regorafenib

Executive Summary

The Predictive Safety Team (PST) used its new tool called MASE (Molecular Analysis of Side Effects) to predict adverse events for regorafenib that may occur after post market approval. The MASE analysis predicts target related adverse events. These predictions were then compared to the corresponding drug labels of other members in the class and the proposed regorafenib label. The results of the analysis support the potential addition of a number of adverse events (AEs) to the label and recommend modifications to a number of the regorafenib warnings.

Key considerations include the following hypothesized AEs. Arterio- and veno-thrombotic events and congestive heart failure appears to be a class effects for the other VEGF inhibitors and the TKIs. Regorafenib may have the potential to induce arrhythmias including atrial fibrillation. Another TKI AE appears to be renal dysfunction. Edema is not addressed in the proposed label and is seen with other TKIs. Skeletal related events warrant further evaluation, specifically the role of concomitant medications and potential drug-drug interactions as regards osteonecrosis of the jaw and fracture related events. Respiratory AEs have been associated with TKIs and should be added to the label or undergo enhanced surveillance.

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The Computational Toxicology Group used three (Q)SAR analysis tools to predict the human hepatotoxicity profile of regorafenib and eight of its human metabolites based on their chemical structures. The results of the analysis show a strong signal for hepatocellular damage that is consistent across all but one of the metabolites, and is confirmed in two of the three models used. Furthermore, the alerting portion of the structures is substantially conserved across the different (Q)SAR models, and is the same as the alert found in the highly structurally similar drug, sorafenib.

MASE Methodology

A new tool has become available to the FDA to explore mechanisms for adverse events. This tool is called MASE (Molecular Analysis of Side Effects). MASE is currently being evaluated under a Research Collaboration Agreement. MASE integrates the publicly available AERS data with various chemical and biological data sources in a drug-centric manner. The publicly available AERS data is mostly from 2004-2011. Within the data integration process AERS medication synonyms are mapped to drugs and compounds in DrugBank (http://www.drugbank.ca/) and PubChem (http://pubchem.ncbi.nlm.nih.gov/). Based on this medication-drug mapping the link to biomolecules and molecular mechanisms involved in pharmacodynamics and pharmacokinetics is established via UniProt (http://www.uniprot.org/) and the pathway resources NCI Nature (http://pid.nci.nih.gov/), Reactome (http://www.reactome.org) and BioCarta (http://www.biocarta.com/). Literature data is extracted based on co-occurrence of MASE entity names and synonyms in PubMed abstracts (http://www.ncbi.nlm.nih.gov/pubmed/). Drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system (http://www.whocc.no/atc/structure_and_principles/). Indications and reactions are classified using the MedDRA dictionary (http://www.meddramsso.com/). Proportional Reporting Ratios (PRRs) and Relative Odds Ratios (RORs) are calculated using the approach described by van Puijenbroek et al.

Using this software one can analyze for the adverse events associated with a specific molecular target. For this consult lists of adverse events possibly associated with the identified molecular targets for regorafenib were analyzed. These targets included VEGF, PDGFR-β, FGFR-2, TIE-2, c-KIT, and BRAF. The results were then compared to the proposed regorafenib label. For VEGF, bevacizumab was included as the specific comparator inhibitor. For other receptors sunatinib and sorafenib were chosen as multi-kinase inhibitors that bind similar receptors, although with different affinities, as compared with regorafenib. The data results for VEGF, PDGFR-β, and FGFR-2 are presented in the data tables. The analyses for TIE-2, c-KIT, and BRAF did not identify any new adverse events that were not seen in the VEGF, PDGFR-β, and FGFR-2 disproportionality reviews. This result is not surprising as the TKIs bind and inhibit multiple receptors. Therefore, the postmarket analysis of a specific target may reflect the concurrent action of many implicated drugs at other receptors. The comparison of bevacizumab, a specific VEGF inhibitor, to sorafenib might help to mechanistically identify truly VEGF effects from the additional effects of other receptor inhibitions. (This

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analysis was done, but is not presented here.) Beyond VEGF there are no approved drugs that solely inhibit one of the other receptors noted above.

MASE should be considered a hypothesis generating or signal strengthening tool. MASE reflects the post market experience and therefore likely identifies adverse events that clinical trials can not identify. MASE reflects the uncontrolled experience from use outside of the controlled clinical trial. The patient reports may result from drug–drug and drug-disease interactions not seen in clinical trials. Clinical trials are done on a small population and are not designed to detect the more rare or serious adverse events. Clinical trials are often short and some adverse events, e.g. boney pathologies and certain infections may require longer exposure to be seen in a more susceptible subpopulation. Clinical trials often control concomitant medications that may result in drug-drug interactions. Oncology patients, however, take variable chemotherapeutic regimens that include many cytotoxic drugs. This multipharmacy does sometimes make it difficult to clearly identify the primary drug most responsible for a specific adverse event. Therefore, known physiological actions are sometimes highlighted to support a contribution of the receptor inhibition to the potential adverse event.

Further development of MASE is needed to include analysis of the impact of structural differences that result in different binding affinities (inhibition) of receptors and targets. Experience, however, demonstrates that drugs within a similar class often produce similar adverse events, although the frequency and severity may vary.

The data presented in this review has been edited for presentation. The editing process involved deleting the AE if the PRR was less than 1.25 unless it appeared relevant to other AEs that had higher PRR scores.

The above results were then compared to the proposed regorafenib label. If an AE was already being addressed then no further review is provided. For some adverse events, especially some warnings, additional information is provided for consideration in the review of the proposed label. Because of the close structural similarity to sorafenib (the addition of a fluoro-group to one aromatic ring Fig 3), regorafenib will likely have an adverse effect profile similar to sorafenib. In fact a comparison of binding affinities notes that at most receptors, regorafenib is a more potent inhibitor than sorafenib (Strumberg).

(Q)SAR Methodology

(Quantitative) structure-activity relationship [(Q)SAR)] models describe the correlation between molecular features and activity at a given endpoint of interest, and are generated using statistical algorithms (QSAR) or by inspection (SAR) of a training set of example structures with known activity. Molecular features are in the form of sub-structural fragments, simple physicochemical properties, or mathematical descriptors, and can be experimentally measured or calculated values. (Q)SAR models can be applied to a test compound structure to prospectively assess activity at the same endpoint for which the training set was constructed.

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MASE Results

1. Thromboembolic events

A broad spectrum of both arteriothrombotic and venothrombotic events are anticipated as a result of VEGF and/or PDGFR inhibition (Tables 1 and 2). In the Warnings and Precautions section proposed for regorafenib myocardial infarction is discussed. The bevacizumab label warns about multiple arteriothrombotic events including CVAs and TIAs. In addition many venothrombotic events (DVTs and intra-abdominal thrombosis) are noted in the clinical trials section. Arterio- and veno-thrombotic events are also seen with sorafenib and sunitinib. These events likely represent a class effect. Mechanistically, nitric oxide is a downstream mediator of VEGF signaling. Nitric oxide signals vasodilatation that VEGF inhibitors may impair.

2.Cardiovascular toxicity
2a. Left Ventricular Dysfunction

The proposed regorafenib label (b) (4) This adverse event is noted from the clinical trials for bevacizumab, while a warning is noted in the sunitinib label and as a common AE for sorafenib. CHF may result from the significant hypertension that is seen with this class of drugs. The mechanism may also be impaired downstream VEGF nitric oxide signaling. CHF should be evaluated further as a possible class effect.

2b. Arrhythmias

The regorafenib label (b) (4) MASE, however, identifies atrial fibrillation as a possible adverse event associated with VEGF inhibition. The sorafenib label notes cases of arrhythmias, although not specifically atrial fibrillation. Although the PRR intervals noted are not that high, atrial fibrillation is a well known complication of left ventricular dysfunction. In addition other drugs that down regulate or impair nitric oxide signaling such as sympathomimetics and some cyclooxygenase inhibitors have been associated with atrial fibrillation. Although the signal is relatively weak there are a number of case reports for bevacizumab (211) and sorafenib (106) in AERS (Empirica run 8/7/12) to warrant a more detailed analysis, (b) (4)

3. Infections

In the clinical trials section of the bevacizumab label many specific infections are addressed. MASE also highlights a variety of infections for the multi-kinase inhibitors. See the Tables. The labels are variable in addressing this issue.

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4. Pain

Specific types of pain, e.g. arthralgia, abdominal, and back are noted in the TKI labels (b) (4) .

5. Renal Dysfunction

The proposed regorafenib label notes proteinuria in the clinical trials section, while the bevacizumab label addresses proteinuria in detail. Renal failure may also be an adverse event associated with TKIs, as MASE notes disproportionality for cases of acute renal failure. Increased creatinine is noted in the sunitinib label. Renal failure is noted as a common AE in the sorafenib label.

6. Vascular Dysfunction (Edema)

The regorafenib label does not report edema. Many presentations of edema have been reported for VEGF inhibitors. Pleural effusion, pulmonary edema, and ascites have specifically been added to TKI labels.

MASE highlights additional edema preferred terms, generalized edema, facial edema, pericardial effusion. A potentially related adverse event is hypoalbuminemia that may possibly result from proteinuria.

7. Skin

In addition to the hand-foot syndrome skin ulcers and discoloration may occur. Skin ulcer is noted in the clinical trials section of the bevacizumab label, although it is not noted on the sunitinib label.

8. Skeletal

A post-marketing AE observed for bevacizumab is osteonecrosis of the jaw. A warning was also recently added for sunitinib. MASE suggests that this AE may mechanistically result from FGFR inhibition. Many of these adverse event reports appear to be complicated by the concomitant use of bisphosphonates, thalidomide and corticosteroids. A synergistic drug-drug interaction may warrant a more detailed review. Concomitant use may increase the risk for osteonecrosis, as well as fractures. FGFR inhibition (Table 3) appears to be associated with other skeletal abnormalities including hip fracture, aseptic necrosis, pathologic fracture, and compression fracture.

9. Biochemical and other laboratory abnormalities

The proposed regorafenib label does warn about many electrolyte and laboratory abnormalities that appear to represent a class effect. Specifically, mentioned are hypophosphatemia, hypocalcemia, hyponatremia, and hypokalemia. Others may be likely

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and include hyperkalemia, and hypercalcemia (Table 3). These were noted in the sunitinib clinical trials along with hypernatremia.

Other laboratory abnormalities proposed for regorafenib include (b) (4) lipase and amylase. Other abnormalities that warrant consideration include hypoglycemia and hyperglycemia that were seen in the sorafenib clinical trials. Increased blood alkaline phosphatase is also noted on other TKI labels. Increased blood cholesterol (Table 1) may warrant further analysis.

10. Neurologic
MASE highlights a number of neurologic preferred terms that may or may not be related to the Reversible Posterior Leukoencephalopathy syndrome (RPLS). These include syncope, peripheral neuropathy, visual acuity reduced, and dysarthria, all included on the bevacizumab label. In addition confusional state and encephalopathy are noted although these could be covered by the mention of altered mental status details of the RPLS warning.

11. Respiratory

Many respiratory AEs are noted by MASE for each of the targets (Tables 1-3). Cough, respiratory failure, hypoxia, and interstitial lung disease have increased PRRs in the MASE analysis. Cough, interstitial lung disease-like events and acute respiratory distress are reported on the sorafenib label and therefore are likely uncommon events that may also occur with regorafenib.

12. Hepatotoxicity. See the QSAR Analysis below

MASE Conclusion

The PST consult identifies a number of adverse events that warrant consideration and further evaluation for addition to the proposed regorafenib label. The PST recommends a broader inclusion of arterio- and veno-thrombotic events beyond myocardial infarction. Congestive heart failure appears to be a class effect for VEGF inhibitors and the TKIs with biological plausibility and therefore is likely to be seen with regorafenib. Arrhythmias including atrial fibrillation warrant additional evaluation, if not specifically addressed in the label enhanced reporting should be considered. The potential for renal dysfunction as seen with sorafenib warrants further consideration. Edema related adverse events are not addressed at all and based upon the experience of other TKIs are likely to occur. Skeletal related events warrant further evaluation, specifically the role of concomitant medications and potential drug-drug interactions in osteonecrosis of the jaw and fracture related events. Respiratory AEs are seen with TKIs in chemotherapeutic regimens and may warrant labeling or enhanced surveillance.

Thanks for requesting this PST consult. Many of the predicted hypothesized AEs for example pain often have other drug or disease associated etiologies. More study and

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evaluation may simply be warranted. The PST looks forward to providing further in-depth analysis of any of the predicted AEs upon request.

QSAR Results

A QSAR analysis of regorafenib and its eight human metabolites (Figure 1) was performed using five human hepatobiliary effect models in two software platforms: Leadscope Model Applier 1.3.3-3 (LMA) and MC4PC 2.4.1.4 (MC). The models used in this evaluation were constructed from post-market data from AERS, SRS, and the published literature, and the model endpoints were defined based on pooling of data for related MedDRA terms (Ursem et al., 2009; Matthews et al., 2009). The nine structures were also analyzed for hepatotoxicity using the SAR software Derek Nexus 2.0.3. (DX), which bases its structural alerts on adverse effect data and mechanistic evidence in the proprietary databases and the published literature (Marchant et al., 2009).

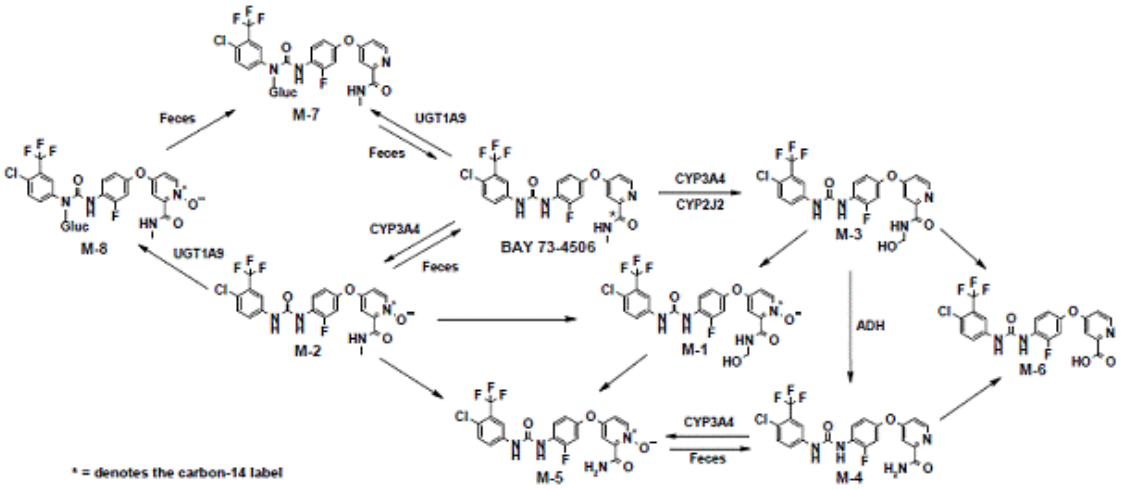

Figure 1. Chemical structures of regorafenib and its eight human metabolites

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(Q)SAR Results

The QSAR analysis showed that regorafenib and seven of its eight human metabolites are predicted to be positive in the liver damage model by both LMA and MC (Table 1).

Table 1. QSAR predictions by LMA and MC for regorafenib and eight human metabolites for hepatobiliary adverse effects

Chem. No.	Chemical Name	Liver Damage		Liver Enzymes		Jaundice		Gall Bladder Disorders		Bile Duct Disorders	
		LMA	MC	LMA	MC	LMA	MC	LMA	MC	LMA	MC
1	Regorafenib	+	+	-	Eqv	Eqv	-	-	Eqv	-	-
2	Metabolite M1	+	+	-	NC	Eqv	NC	-	NC	-	NC
3	Metabolite M2	+	+	-	NC	+	NC	-	NC	-	NC
4	Metabolite M3	+	+	-	Eqv	Eqv	-	-	Eqv	-	-
5	Metabolite M4	+	+	+	Eqv	+	-	-	Eqv	-	-
6	Metabolite M5	+	+	+	NC	+	NC	-	NC	-	NC
7	Metabolite M6	NC	Eqv	NC	Eqv	NC	-	NC	Eqv	NC	-
8	Metabolite M7	+	+	+	Eqv	Eqv	-	Eqv	Eqv	-	-
9	Metabolite M8	+	+	+	NC	Eqv	NC	+	NC	-	NC

Legend: + = positive; − = negative; Eqv = equivocal; NC = test chemical features are not adequately represented in the model training data set, yielding a no call.

The alerting portion of the molecule was found to be the same in all structures predicted positive for liver damage, and the alerts partially overlap across models. The portion of the molecule with the most significant positive contribution in LMA, and the MC4PC structural alert, are shown below in Figure 2 highlighted in red on the regorafenib structure.

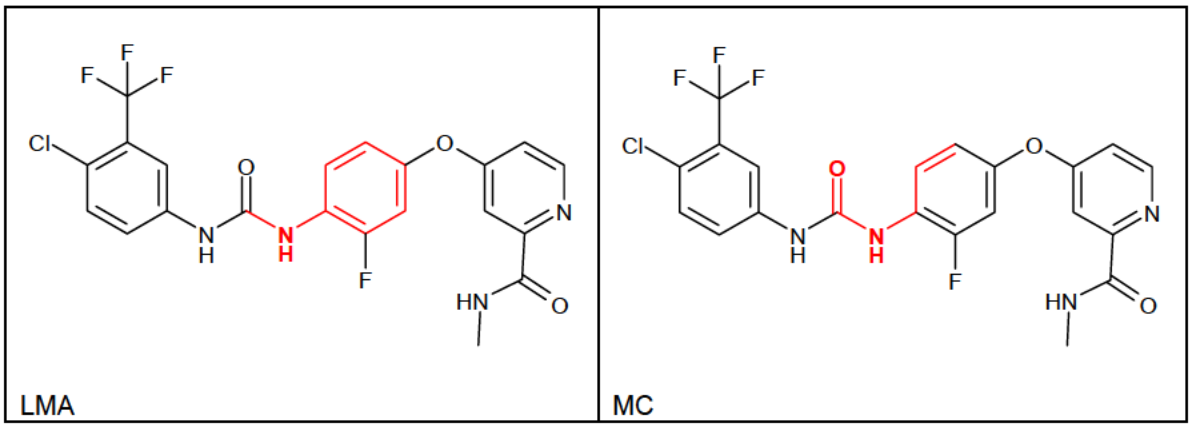

Figure 2. Regorafenib with LMA and MC structural alerts shown in red

Greater confidence in positive predictions can be inferred when different software platforms using different prediction methodologies are positive in consensus, and furthermore when the basis of those positive predictions is the same portion of the molecule. This is the case with regorafenib and its metabolites, which show significant overlap in their structural alerts across models, and since the alerting portion of regorafenib is at the core of the structure, the same alert is present in all 8 metabolites and

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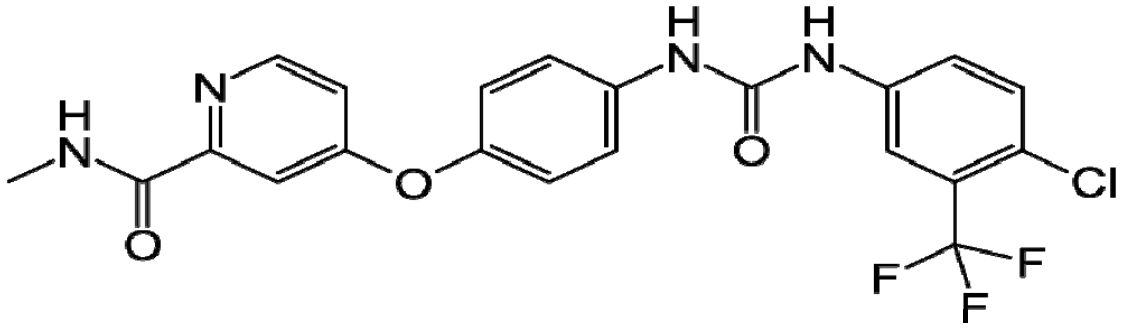
the structural variations across the metabolites offer no significant mitigating effect on predicted activity. Taken together, this evidence supports a strong positive prediction for regorafenib for liver damage.

A SAR analysis was performed on the nine structures using the hepatotoxicity knowledgebase in DX but no structural alerts were found. Since the representation of chemical and toxicological space across the DX knowledgebase is more limited than that of the QSAR models used in this analysis, the lack of a positive prediction should not be interpreted as a negative prediction.

Single model LMA positive predictions were observed for M4, M5, M7 and M8 with the liver enzyme disorders model, for M2, M4, M5 with the jaundice model, and for M9 for the gall bladder disorders models. A single platform positive is sufficient evidence to justify an overall positive call for a compound, but with lower confidence than a two or three platform positive call. Since M2 and M5 are known to be the major circulating metabolites of regorafenib, positive predictions for these metabolites are of greater relevance to a clinical population than those of the other known metabolites. The M8 single platform positive prediction for gall bladder disorders could be discounted on this basis.

A comparison QSAR analysis was also performed on sorafenib, a highly similar structure to regorafenib differing only by an aromatic fluoro group, and it shows the same profile of positive predictions for liver damage in both LMA and MC (data not shown). These positive predictions are confirmed by reported cases of drug-induced liver injury in the published literature (Van Hootegem et al., 2011).

Figure 3. Sorafenib Structure



(Q)SAR Conclusions

The QSAR models predict with high confidence that regorafenib will cause liver damage, and with lower confidence that regorafenib will cause liver enzyme abnormalities and jaundice. The positive prediction for regorafenib for liver damage is further supported by its high structural similarity to sorafenib, since sorafenib is also strongly predicted to be positive for liver damage by (Q)SAR and it has been clinically observed to cause this effect.

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Table 1. Adverse Events potentially associated with VEGF Inhibition

Adverse Event	N	PRR	PRR CI
Myocardial infarction	8052	2.22	2.17 - 2.27
Dyspnoea	7567	1.48	1.45 - 1.52
Diarrhoea	7385	1.79	1.75 - 1.83
Asthenia	6060	1.67	1.63 - 1.72
Dizziness	6036	1.18	1.15 - 1.21
Pyrexia	5551	1.42	1.38 - 1.46
Cerebrovascular accident	5304	1.9	1.85 - 1.96
Headache	4832	0.94	0.92 - 0.97
Pain	4785	1.29	1.26 - 1.33
Hypertension	4703	2.16	2.09 - 2.23
Pneumonia	4337	1.89	1.83 - 1.95
Chest pain	4250	1.57	1.53 - 1.63
Fall	4183	1.51	1.46 - 1.56
Anaemia	4073	2.22	2.14 - 2.29
Oedema peripheral	4043	1.77	1.71 - 1.83
Hypotension	3968	1.83	1.77 - 1.89
Rash	3783	1.18	1.15 - 1.22
Arthralgia	3635	1.41	1.36 - 1.45
Abdominal pain	3487	1.48	1.43 - 1.54
Renal failure acute	3176	1.96	1.89 - 2.03
Cardiac failure congestive	2940	2.65	2.55 - 2.76
Confusional state	2910	1.46	1.40 - 1.52
Thrombocytopenia	2909	2.41	2.31 - 2.50
Constipation	2553	1.66	1.60 - 1.74
Atrial fibrillation	2478	2.6	2.49 - 2.72
Cough	2322	1.33	1.27 - 1.38
Sepsis	2311	1.96	1.88 - 2.05
Pleural effusion	2256	3.03	2.89 - 3.17
Pulmonary embolism	2220	1.65	1.58 - 1.73
Myalgia	2106	1.08	1.04 - 1.13
White blood cell count decreased	1998	2.1	2 - 2.20
Alanine aminotransferase increased	1990	1.42	1.35 - 1.49
Aspartate aminotransferase increased	1972	1.5	1.43 - 1.57
Urinary tract infection	1940	1.79	1.71 - 1.88
Decreased appetite	1878	1.45	1.38 - 1.52
Neutropenia	1857	1.84	1.75 - 1.93

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Adverse Event	N	PRR	PRR CI
Syncope	1833	1.5	1.43 - 1.58
Respiratory failure	1800	1.84	1.75 - 1.93
Deep vein thrombosis	1762	2.04	1.94 - 2.15
Gastrointestinal haemorrhage	1707	2.4	2.28 - 2.53
Infection	1529	1.63	1.54 - 1.72
Pancytopenia	1390	2.18	2.06 - 2.31
Hyponatraemia	1366	1.95	1.84 - 2.06
Bradycardia	1344	1.8	1.70 - 1.91
Dysphagia	1329	1.42	1.34 - 1.51
Transient ischaemic attack	1294	2.26	2.13 - 2.40
Pulmonary oedema	1271	2.22	2.09 - 2.35
Blood cholesterol increased	1216	1.88	1.77 - 2
Osteonecrosis	1214	1.17	1.11 - 1.24
International normalised ratio increased	1198	1.66	1.56 - 1.77
Hypoglycaemia	1187	1.58	1.49 - 1.68
Alopecia	1181	1.24	1.16 - 1.31
Hypokalaemia	1177	2.29	2.15 - 2.44
Blood alkaline phosphatase increased	1167	1.72	1.62 - 1.83
Arrhythmia	1147	1.52	1.43 - 1.61
Palmar-plantar erythrodysaesthesia syndrome	1106	10.92	10.05 - 11.86
Epistaxis	1103	1.9	1.78 - 2.03
Neuropathy peripheral	1089	2.22	2.08 - 2.37
Acute myocardial infarction	1055	2.2	2.06 - 2.35
Cellulitis	994	2.15	2.01 - 2.30
Visual acuity reduced	992	1.63	1.52 - 1.74
Hyperkalaemia	965	2.25	2.10 - 2.41
Joint swelling	958	1.46	1.36 - 1.56
Bronchitis	914	1.66	1.55 - 1.78
Blood bilirubin increased	911	1.55	1.45 - 1.66
Hyperglycaemia	890	1.71	1.59 - 1.84
Ascites	859	2.42	2.25 - 2.61
Staphylococcal infection	855	1.58	1.47 - 1.70
Hypoxia	853	1.98	1.84 - 2.13

Adverse Event	N	PRR	PRR CI
Stomatitis	848	2.23	2.07 - 2.40
Rectal haemorrhage	843	1.79	1.67 - 1.93
Blood sodium decreased	791	2.48	2.30 - 2.68
Speech disorder	784	1.22	1.13 - 1.32
Interstitial lung disease	782	1.56	1.45 - 1.68
Gastritis	776	2.26	2.10 - 2.45
Mitral valve incompetence	755	2.88	2.66 - 3.12
Dysarthria	754	1.41	1.30 - 1.52
Cholelithiasis	745	1.8	1.67 - 1.95
Hepatic failure	728	1.33	1.23 - 1.43

Reference ID: 3184459

Table 2. Adverse Events potentially associated with PDGFR-β Inhibition

Adverse Event	N	PRR	PRR CI
Diarrhoea	2110	2.7	2.59 - 2.81
Pyrexia	1458	2.1	1.99 - 2.20
Dyspnoea	1297	1.36	1.29 - 1.44
Rash	1281	2.26	2.14 - 2.39
Palmar-plantar erythrodysaesthesia syndrome	1206	57.26	53.27 - 61.56
Pleural effusion	1122	8.11	7.64 - 8.61
Asthenia	1088	1.61	1.52 - 1.71
Hypertension	1049	2.57	2.42 - 2.73
Anaemia	1028	2.98	2.80 - 3.17
Thrombocytopenia	940	4.17	3.91 - 4.45
Abdominal pain	840	1.9	1.78 - 2.03
Pneumonia	774	1.71	1.59 - 1.83
Oedema peripheral	722	1.61	1.50 - 1.73
Ascites	528	8.56	7.84 - 9.36
Sepsis	475	2.1	1.92 - 2.30
Neutropenia	466	2.55	2.33 - 2.80
Renal failure acute	445	1.47	1.34 - 1.61
Gastrointestinal haemorrhage	433	3.14	2.86 - 3.46
Pancytopenia	424	3.63	3.29 - 3.99
Stomatitis	422	5.87	5.32 - 6.48
Hepatic failure	364	4.06	3.66 - 4.51
Pulmonary embolism	355	1.36	1.22 - 1.51
Respiratory failure	349	1.92	1.73 - 2.13
Oedema	323	2.89	2.59 - 3.23
Hyponatraemia	306	2.43	2.17 - 2.72
Cerebrovascular accident	303	0.58	0.52 - 0.65
Atrial fibrillation	294	1.53	1.37 - 1.72
Hypothyroidism	280	5.79	5.13 - 6.54
Interstitial lung disease	253	2.82	2.49 - 3.20
Haemorrhage	251	1.5	1.32 - 1.70
Epistaxis	249	2.24	1.98 - 2.54
Cerebral haemorrhage	231	3.37	2.95 - 3.84
Muscular weakness	229	1.08	0.95 - 1.23
Hypokalaemia	218	2.28	1.99 - 2.60
Disseminated intravascular coagulation	210	4.04	3.52 - 4.64
Pericardial effusion	205	4.59	3.99 - 5.28
Pulmonary oedema	200	1.88	1.64 - 2.16
Bone marrow failure	199	4.84	4.19 - 5.58
Dysphonia	199	2.52	2.19 - 2.90
Lipase increased	195	9.7	8.36 - 11.24
Dry skin	181	3.12	2.69 - 3.62
Generalised oedema	174	5.33	4.58 - 6.21

Reference ID: 3184459

Adverse Event	N	PRR	PRR CI
Face oedema	172	3.55	3.05 - 4.13
Periorbital oedema	160	16.34	13.80 - 19.35
Haematuria	159	2.33	1.99 - 2.73
Haematemesis	157	2.42	2.06 - 2.84
Skin ulcer	154	3.5	2.98 - 4.11
Encephalopathy	141	2.6	2.19 - 3.07
Hypocalcaemia	136	4.42	3.72 - 5.25
Hyperkalaemia	128	1.6	1.34 - 1.91
Impaired healing	122	1.81	1.51 - 2.17
Hypophosphataemia	120	11.68	9.65 - 14.14
Skin discolouration	120	1.69	1.41 - 2.03
Osteonecrosis of jaw	116	3.51	2.92 - 4.23
Ileus	115	3.72	3.09 - 4.49
Hypoalbuminaemia	114	6.4	5.29 - 7.74
Lymphadenopathy	114	1.44	1.19 - 1.73

Table 3. Adverse Events potentially associated with FGFR-2 Inhibition

Adverse Event	N	PRR	PRR CI
Pneumonia	889	3.59	3.36 - 3.83
Asthenia	603	1.61	1.48 - 1.74
Fatigue	586	1.2	1.11 - 1.30
Deep vein thrombosis	546	5.66	5.20 - 6.15
Pyrexia	545	1.4	1.29 - 1.52
Osteonecrosis	543	6.54	6.01 - 7.11
Renal failure	536	2.92	2.69 - 3.18
Neuropathy peripheral	526	9.98	9.15 - 10.89
Anaemia	492	2.54	2.33 - 2.78
Pulmonary embolism	454	3.18	2.90 - 3.48
Sepsis	433	3.48	3.17 - 3.82
Oedema peripheral	385	1.55	1.40 - 1.71
Thrombocytopenia	334	2.61	2.34 - 2.91
Infection	331	3.34	3 - 3.72
Respiratory failure	327	3.27	2.93 - 3.64
Neutropenia	319	3.15	2.82 - 3.52
Hypotension	295	1.34	1.20 - 1.51
Cardiac failure congestive	281	2.14	1.90 - 2.40
Pancytopenia	275	4.21	3.74 - 4.75
Renal failure acute	256	1.53	1.35 - 1.73
Syncope	220	1.79	1.57 - 2.04
Febrile neutropenia	217	3.8	3.33 - 4.35
Thrombosis	217	2.17	1.90 - 2.47
White blood cell count decreased	206	2.16	1.88 - 2.48
Atrial fibrillation	195	1.84	1.60 - 2.12
Osteomyelitis	177	7.2	6.19 - 8.36
Neuropathy	172	14.47	12.39 - 16.91
Hypoxia	160	3.74	3.20 - 4.38
Oedema	143	2.29	1.94 - 2.70
Impaired healing	130	3.52	2.96 - 4.19
Blood human chorionic gonadotropin increased	123	158.47	123.16 - 203.90
Mucosal inflammation	121	4.26	3.56 - 5.10
Osteonecrosis of jaw	118	6.51	5.42 - 7.82
Cellulitis	109	2.17	1.80 - 2.62

Reference ID: 3184459

Adverse Event	N	PRR	PRR CI
Septic shock	109	2.49	2.06 - 3
Staphylococcal infection	109	2.07	1.72 - 2.51
Lung infiltration	107	4.33	3.58 - 5.25
Gastrointestinal haemorrhage	106	1.36	1.12 - 1.64
Sinusitis	102	1.49	1.23 - 1.81
Atelectasis	100	4.92	4.03 - 6
Hypercalcaemia	89	6.71	5.43 - 8.29
Hypokalaemia	88	1.64	1.33 - 2.03
Peripheral sensory neuropathy	88	18.37	14.73 - 22.91
Chronic obstructive pulmonary disease	86	1.84	1.48 - 2.27
Herpes zoster	84	2.21	1.78 - 2.74
Neutrophil count decreased	84	2.54	2.05 - 3.15
Hip fracture	82	2.95	2.37 - 3.67
Aseptic necrosis bone	81	12.64	10.08 - 15.85
Pneumonitis	75	3.63	2.89 - 4.57

By PRR < 75 Cases	N	PRR	PRR CI
Renal interstitial fibrosis	10	22.35	11.51 - 43.41
Amyloidosis	36	17.88	12.66 - 25.25
Bone infection	12	17.71	9.74 - 32.19
Myelofibrosis	34	17.52	12.29 - 24.98
Spinal cord compression	65	16.63	12.88 - 21.48
Gastrointestinal inflammation	49	13.95	10.41 - 18.68
Pathological fracture	57	9.61	7.36 - 12.56
Compression fracture	47	9.61	7.16 - 12.90
Staphylococcal bacteraemia	43	8.17	6.01 - 11.10
Bacteraemia	62	5.71	4.44 - 7.36

Reference ID: 3184459

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/s/

KEITH K BURKHART
09/05/2012

DARRELL R ABERNETHY
09/05/2012

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

Memorandum

Date: August 29, 2012

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

Subject: NDA 203085

Shortly after labeling was sent to Bayer on August 29, 2012, the statistical reviewer noted an additional change to be conveyed to Bayer on August 29, 2012.

Table 5: Efficacy Results from Study 1

	Stivarga + BSC (N=505)	**Placebo (160 mg QD) + BSC (N=255)**
Overall Survival		
Number of deaths, n (%)	275 (55%)	157 (62%)
Median Overall Survival (months)	6.4	5.0
95% CI	(5.8, 7.3)	(4.4, 5.8)
HR (95% CI)	0.77 (0.64, 0.94)	
Stratified Log-Rank Test P-value [a,b]	0.0102	
Progression-free Survival		
Number of Death or Progression, n (%)	417 (83%)	231 (91%)
Median Progression-free Survival (months)	2.0	1.7
95% CI	(1.9, 2.3)	(1.7, 1.8)
HR (95% CI)	0.49 (0.42, 0.58)	
Stratified Log-Rank Test P-value [a]	<0.0001	
Overall Response Rate		
Overall response, n(%)	5 (1%)	1 (0.4%)
95% CI	0.3%, 2.3%	0%, 2.2%

[a] Stratified by geographic region and time from diagnosis of metastatic disease.

[b] Crossed the O'Brien-Fleming boundary (p value < 0.018) at second interim analysis.

(b) (4)

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/s/

MONICA L HUGHES
08/29/2012

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

Memorandum

Date: August 29, 2012

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

Subject: NDA 203085

Please find attached FDA's counter proposal to your revised package insert (PI), patient insert, and carton and container labeling as submitted on July 13, 2012, in response to our June 25, 2012, filing communication.

Please provide a response to FDA's proposed changes by 2:00 PM on September 10, 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 note these are our preliminary comments, this labeling is currently being reviewed by our counterparts in Office of Prescription Drug Promotion (OPDP) and the Patient Labeling Team (PLT) and additional comments will follow.

General Comments:

1. Patients may have one carton containing three bottles dispensed to them. Once opened the tablets in a bottle expire after 28 days. To prevent patients from accidentally opening multiple bottles and possibly taking expired drug or wasting medication due to the short expiation, DMEPA recommends including a tamper evident seal on the cap or bottle if there isn't one included already. The seal will assist patients in identifying which bottles have not been opened and serve as a reminder before opening a new bottle.

2. We acknowledge that the established name is at least half as large as the proprietary name, however, in accordance with 21 CFR 201.10(g)(2), the presentation of the established name should also " . . . have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast and other printing features". Therefore, we request you revise the established name (including dosage form) accordingly in each location it is presented.

3. Ensure that the carton and container use command language consistent with the PI.

4. Delete "-40 mg" at the bottom of the principal display panel of the carton and container label as it is redundant.

5. Please note that you need to update the USAN information for Regorafenib to reflect the drug substance as a monohydrate. The update should include structure, chemical name, CAS number and any other relevant information but the USAN name of "Regorafenib" remains unchanged. A commitment to update this should be provided to the NDA.

Carton Labels:

(b) (4)

6. Relocate and decrease the prominence of the graphic above the trade name because it distracts from the trade and established names.

7. Include the following statements on the principal display panel “Store in the original container to protect from moisture. Any remaining tablets should be discarded 28 days after opening the bottle.”

8. Revise “ – oral” to read “ – “for oral administration” to make a complete statement.

9. Remove the statement on the back of the carton “Once opened, the product must be used in 28 days.”

10. Include the statement "Attention Pharmacist: Dispense Stivarga in the original container" on the principal display panel.

11. Include the statement "Swallow tablets whole" on the principal display panel.

12. Ensure the description is consistent with the package insert: " Stivarga tablets are supplied in packages containing three bottles, with each bottle containing 28 tablets, for a total of 84 tablets per package (NDC 50419-407-03). The light pink oval shaped tablets are debossed with "BAYER" on one side and "40" on the other side. Store at 25°C (77°F); excursions are permitted from 15 to 30°C (59 to 86°F) [See USP Controlled Room Temperature].

    Store tablets in the original bottle and do not remove the desiccant. Keep the bottle tightly closed after first opening. Discard any unused tablets 28 days after opening the bottle. Dispose of unused tablets in accordance with local requirements."

Container Label:

(b) (4)

13. Include the statements "Once a bottle is opened, product must be used within 28 days. Bottle Opened: _____" on the principal display panel. Consider deleting the statement "-oral" to make room for this statement.

14. If the statement "-oral" is retained, revise it to read "– "for oral administration" to make a complete statement.

15. Delete the Description statement on the side of the label as it is redundant.

16. Revise the statement on the side of the label "Store in original container" to read "Store in original container to protect from moisture."

17. Revise storage statement to "Store at 25°C (77°F); excursions are permitted from 15 to 30°C (59 to 86°F) [See USP Controlled Room Temperature]."

18. We recommend deleting the circular Bayer logo. We are concerned this may cause confusion with the proposed description of regorafenib tablet.

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

Attachment: FDA proposed revisions to the package insert

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/s/

MONICA L HUGHES
08/29/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
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Pediatric and Maternal Health Staff Review

Date: August 27, 2012 **Date Consulted:** May 2, 2012

From: Carrie Ceresa, Pharm D, MPH
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Melissa Tassinari, PhD, DABT
Acting Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lynne P. Yao, MD
Acting OND Associate Director,
Pediatric and Maternal Health Staff

To: Office of Hematology and Oncology Products (OHOP)
Division of Oncology Products 2 (DOP2)

Drug: Stivarga (regorafenib) tablets/NDA 203085

Subject: Labeling Revisions – Pregnancy, Nursing Mothers

Sponsor: Bayer Healthcare Pharmaceuticals, Inc.

Materials Reviewed:

- Proposed labeling for Stivarga (regorafenib), submitted April 27, 2012.

Consult Question: "Please assign a reviewer to attend milestone meetings and to provide labeling comments for this new NDA."

Reference ID: 3180826

INTRODUCTION

On April 27, 2012, Bayer Healthcare Pharmaceuticals, Inc., Inc. submitted a New Drug Application for Stivarga (regorafenib) tablets (NDA 203085) "for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with, (b) (4) fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, and anti-EGFR therapy."

The Division of Oncology Products 2 (DOP2) consulted the Pediatric and Maternal Health Staff-Maternal Health Team (PMHS-MHT) to review the following:

1. Section 8.1 Pregnancy
2. Section 8.3 Nursing Mothers
3. Section 8.8 Females and Males of Reproductive Potential

This review details the recommendations for revisions and re-ordering of the sponsor's proposed label related to pregnancy, nursing mothers and females and males of reproductive potential in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Regorafenib is a small molecule inhibitor of multiple membrane bound and intracellular kinases (multi-kinase inhibitor) involved in a wide range of normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment.

DISCUSSION AND CONCLUSION

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing Mothers labeling information in the spirit of the Proposed Rule while still complying with current regulations. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

The PMHS-MHT discussed labeling recommendations with the review team during labeling meetings held on August 14 and August 21, 2012. During these labeling meetings, PMHS-MHT recommendations were revised after discussion with the Division.

Reference ID: 3180826

PMHS LABELING RECOMMENDATIONS

PMHS-MHT labeling recommendations (label excerpts) appear below based on the labeling dated August 22, 2012. The animal data section below in 8.1 may undergo additional changes based on recommendations from Pharmacology/toxicology reviewers. **Appendix A** of this review provides a tracked-changes version of labeling that highlights the recommended PMHS-MHT revisions.

(b) (4)

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Reference ID: 3180826

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/s/

TAMMIE B BRENT HOWARD on behalf of CARRIE M CERESA
08/28/2012
Signing for Carrie Ceresa

MELISSA S TASSINARI
08/28/2012

LYNNE P YAO
08/29/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	July 25, 2012
Reviewer:	James Schlick, RPh, MBA Division of Medication Error Prevention and Analysis
Team Leader	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Stivarga (Regorafenib) Tablets 40 mg
Application Type/Number:	NDA 203085
Applicant:	Bayer HealthCare Pharmaceuticals, Inc.
OSE RCM #:	2012-1082

*** This document contains proprietary and confidential information that should not be released to the public.***

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Reference ID: 3163650

1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Stivarga (Regorafenib), NDA 203085, for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the April 30, 2012 proprietary name submission.

- Active Ingredient: Regorafenib
- Indication of Use: For the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with, [redacted] (b) (4) fluoropyrimidine-based chemotherapy, anti-VEGF therapy, and anti-EGFR therapy.
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 40 mg
- Dose and Frequency: The usual starting dose is 160 mg once daily for three weeks, followed by one week off to comprise a four week cycle. The dose can be reduced to 120 mg or 80 mg due to toxicity.
- How Supplied: Package containing three bottles. Each bottle contains 28 tablets. The tablets are light pink oval shaped debossed with "Bayer" on one side and "40" on the other side.
- Storage: Store at 59°F to 86°F in the original package. Close the bottle tightly after each time the bottle is opened.
- Container and Closure Systems: Plastic 45 mL HDPE white opaque bottle with desiccant capsule closed with screw cap (b) (4) white with sealing insert and is child-resistant.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS database for regorafenib medication error reports. We also reviewed the Stivarga labels and labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) database using the strategy listed in Table 1.

Reference ID: 3163650

Table 1: AERS Search Strategy	
Date	No date range
Drug Names	Active Ingredient: Regorafenib Verbatim: Regoraf%
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The AERS database search identified one report, and this report was relevant to the review. The ISR number is 7287965.

2.2 Literature Search

We searched PubMed and the ISMP publications listed below on July 6, 2012, for additional cases and actions concerning Stivarga. The PubMed search consisted of the search terms "regorafenib" and "medication error". The following ISMP newsletters were searched:

- ISMP Acute Care Newsletter
- ISMP Community Edition
- ISMP Nursing Edition
- ISMP Canada Safety Bulletin

Stivarga tablets are required to be dispensed and stored in their original containers with a desiccant. Because of this we included the following search terms when the ISMP publications were searched:

- "Regorafenib"
- "Desiccant"

2.3 Labels and Labeling

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Label submitted April 27, 2012 (Appendix C)
- Carton Labeling submitted April 27, 2012 (Appendix D)
- Desiccant Label submitted July 3, 2012 (Appendix E)
- Insert Labeling submitted June 4, 2012

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Reference ID: 3163650

3 RESULTS

3.1 MEDICATION ERROR CASES

AERS Database (n=1)

The one case identified in AERS included the use of the proposed product for a patient in an investigational study protocol that experienced grade 4 hyperuricemia. The protocol required the patient to stop taking the medication for 7 days. However, the patient continued to take the medication for the next 7 days. The outcome was not reported and it was unclear why the patient continued to take the medication.

ISMP Publications (n=2)

The ISMP search yielded two articles referencing medication errors related to the use of a desiccant and the use of the original container to dispense and store the medication. The references for the articles can be found in Appendix B.

The first ISMP article was about an elderly man with poor eyesight who, intending to take a capsule of his heart medication, nearly asphyxiated when he gagged on a desiccant capsule left in the medication bottle. The article noted a literature search was conducted and confirmed additional cases occurred, some of which required surgery. ISMP recommends that whenever possible, the desiccant should be removed. The information submitted by the Applicant for Stivarga requires the desiccant to remain in the bottle once opened.

The second ISMP article discussed the short expiration date of Pradaxa once the bottle was opened (30 day expiration date for a bottle with a 30 day supply). Some patients who had multiple bottles at home because of insurance requirements (90 day supply) accidentally opened a second bottle before the first one was complete. This caused the patient to throw out expensive medication. This article recommended that a visible message "Any remaining capsules should be discarded 30 days after opening the bottle" be displayed on the bottle or cap. The article also recommended that a tamper evident seal be used on the bottle to assist patients with identifying which bottles have not been opened and as a reminder to check before opening a new bottle.

PubMed Database

The PubMed search did not yield any articles or cases.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

Based on the ISMP cases (see Appendix B for references) discussed in Section 3.1 of this review as well our analysis of the proposed packaging configuration and stability profile for Stivarga, we believe each bottle should include a tamper evident seal on the bottle or cap. The seal will help to accomplish two things. The seal will assist patients in identifying which bottles have not been opened and serve as a reminder before opening a new bottle. This will help prevent the patients from opening more than one bottle at a time; thus, avoiding the risk of using medication beyond the 14 day expiration date or wasting medication. We also believe that the stability profile of the product necessitates warning statements on the principal display panel of the label and labeling to alert healthcare practitioners and patients to keep the medication in the original container and to discard any medication still left in an open bottle after (b) (4)

Reference ID: 3163650

Lastly, since the desiccant should not be removed from the bottle as ISMP suggested, the desiccant should be properly labeled with a warning to help ensure that a patient does not accidentally swallow or eat it. DMEPA reviewed the desiccant label found in Appendix E and determined it is adequate to convey the warning. Additionally, Stivarga tablets are light pink which will help differentiate them from the desiccant.

4 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information to promote the safe use of the product. The most significant recommendations include statements to dispense and store the medication in the original container and statements to use the medication within the appropriate expiration date after opening the container.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. General Comment

1. Patients may have one carton containing three bottles dispensed to them. Once opened the tablets in a bottle expire after (b) (4). To prevent patients from accidentally opening multiple bottles and possibly taking expired drug or wasting medication due to the short expiation, DMEPA recommends including a tamper evident seal on the cap or bottle if there isn't one included already. The seal will assist patients in identifying which bottles have not been opened and serve as a reminder before opening a new bottle.

B. Container Label and Carton Labeling

1. We acknowledge that the established name is at least half as large as the proprietary name, however, in accordance with 21 CFR 201.10(g)(2), the presentation of the established name should also " . . . have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast and other printing features". Therefore, we request you revise the established name (including dosage form) accordingly in each location it is presented.
2. Delete " – 40 mg" at the bottom of the principal display panel as it is redundant.

C. Container Label

1. Include the statements "Once opened, product must be used within (b) (4) Bottle Opened: _____" on the principal display panel. Consider deleting the statement "-oral" to make room for this statement.
2. If the statement "-oral" is retained, revise it to read "– "for oral administration" to make a complete statement.
3. Delete the Description statement on the side of the label as it is redundant.

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4. Revise the statement on the side of the label "Store in original container" to read "Store in original container to protect from moisture."

D. Carton Labeling

1. Include the following statements on the principal display panel "Store in the original container to protect from moisture. Any remaining tablets should be discarded (b) (4) after opening the bottle."
2. Revise " – oral" to read " – "for oral administration" to make a complete statement
3. Remove the statement on the back of the carton "Once opened, the product must be used in (b) (4)."
4. Include the statement "Attention Pharmacist: Dispense Stivarga in the original container" on the principal display panel.
5. Include the statement "Swallow tablets whole" on the principal display panel.

E. Insert Labeling

1. Highlights of Prescribing Information – Dosage and Administration

   Revise this section as indicated below to include the term "low-fat" and describe the duration of therapy. "Low-fat" is the term used in the Patient Information section to describe a light meal. Also, instructions to swallow the tablets whole should also be included.

   a. Revise the statement (b) (4) to read
      - (b) (4)
      -
2. Full Prescribing Information

   a. 2.1 Recommended Dose

      1. (b) (4)

   b. 16.2 Storage and Handling

      1. Revise the statement (b) (4) to

         "Store Stivarga at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)."

         "Store the tablets in the original bottle."

      Placing the second sentence on a separate line will help it stand out.

   c. 17 Patient Counseling Information

      1. Consider including information on Reversible Posterior Leukoencephalopathy Syndrome (RPLS) and wound healing in this

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section. These are noted in section 5 with the other warnings and precautions, but not mentioned in section 17.

2. Add a section that contains the following statements:

   "Store medicine in the original container. Do not place medication in daily or weekly pill boxes. Any remaining tablets should be discarded (b) (4) after opening the bottle. Tightly close bottle after each opening and keep the desiccant in the bottle."

d. Patient Information

1. How do I store Stivarga?

   a. Add the word "temperature" after the word "room" in the first bullet point. Include the statement "Do not place medication in daily or weekly pill boxes" at the end of the first statement.

   b. Add the following statement:

      Any remaining tablets should be discarded (b) (4) after opening the bottle.

If you have further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

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APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

APPENDIX B: ISMP REFERENCE ARTICLES

1. ISMP Medication Safety Alert. Volume 5, Issue 24. November 29, 2000. Pg. 1.

2. ISMP Medication Safety Alert. Acute Care Edition. Volume 16, Issue 4. February 24, 2011. Pg. 3.

APPENDIX C: CONTAINER LABELS

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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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.

/s/

JAMES H SCHLICK
07/24/2012

TODD D BRIDGES
07/24/2012

CAROL A HOLQUIST
07/25/2012

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 203085

Application Type: New NDA

Name of Drug: PROPRIETARY NAME under review, regorafenib 40 mg tablets

Applicant: Bayer HealthCare Pharmaceuticals Inc.

Submission Date: 4/27/12

Receipt Date: 4/27/12

1.0 Regulatory History and Applicant's Main Proposals

This is a new NDA for mCRC. The regulatory history includes the following: There was an End of Phase 2 meeting held in September 2009. A Special Protocol Assessment – No Agreement Letter issued in January 2010. A letter containing advice for the pivotal Phase 3 study design in response to Bayer's Type A meeting questions issued in April 2010. An Advice letter for the pivotal Phase 3 study design, granting Fast Track designation issued June 2011. A Pre-NDA meeting was held in August 2011. A pre-submission guidance teleconference was held April 3, 2012 to reach agreement on format and content of the NDA, Clinical Pharmacology section of the application and to discuss proposed PMRs for information not contained in the original NDA submission.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

Selected Requirements of Prescribing Information (SRPI) format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

Additional labeling issues were also identified in consultation with CDER/SEALD. The attached PI contains our additional labeling comments and proposed revisions.

All SRPI format deficiencies and other labeling issues identified above will be conveyed to the applicant in the filing or 74-day, deficiencies identified letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by July 13, 2012. The resubmitted PI will be used for further labeling review.

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4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *No comments.*

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *No comments.*

YES 4. White space must be present before each major heading in HL.

Comment: *No comments.*

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *No comments.*

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YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment: *No comments.*

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment: *No comments.*

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment: *No comments.*

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: There is a space present that needs to be deleted.

Product Title

YES 10. Product title in HL must be **bolded.**

Comment: *No comments.*

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *No comments.*

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Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

N/A 12. All text must be **bolded**.

Comment: *Not applicable, no boxed warning.*

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment: *Not applicable, no boxed warning.*

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment: *Not applicable, no boxed warning.*

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment: *Not applicable, no boxed warning.*

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment: *Not applicable, no boxed warning.*

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment: *No comments, this is the original approval therefore there are no recent changes.*

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment: *No comments, this is the original approval therefore there are no recent changes*

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment: *No comments, this is the original approval therefore there are no recent changes*

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment: *No comments, this is the original approval therefore there are no recent changes*

Indications and Usage

NO 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

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Comment: Please revise this statement to read as follows "[PTN] is a kinase inhibitor indicated for mCRC"

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment: *No comments, only one dosage form.*

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.
Comment: *No comments.*

N/A 24. Each contraindication is bulleted when there is more than one contraindication.
Comment: *No comments.*

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment: *No comments.*

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment: *No comments.*

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment: *No comments.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment: *No comments*

.

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Selected Requirements of Prescribing Information (SRPI)

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment: *No comments.*

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *No comments.*

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment: *No comments.*

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment: *No comments.*

NO 33. All subsection headings must be indented, not bolded, and in title case.

Comment: Please use title case for all subsection headings.

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment: *No comments.*

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment: *No comments.*

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment: *No comments.*

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment: *No comments.*

NO 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

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8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: Section 12.4 is reserved for Microbiology. It is listed incorrectly listed as 12.4 (b) (4) and needs to be deleted, please see the attached package insert for additional comments. In addition, Section 17.8 is incorrect, no patient labeling subheading should be listed.

NO 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: Labeled incorrectly.

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment: *No comments.*

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: *N/A*

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment: *N/A*

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N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment: *N/A*

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment: *N/A*

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment: *No comments.*

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment: *No comments.*

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: The package insert currently states*" See 17.8 for FDA Approved Patient Labeling"*,please revise to state "See FDA-approved patient labeling (Patient Information)"

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

Reference ID: 3150098

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/s/

MONICA L HUGHES
06/25/2012

RPM FILING REVIEW

Including Memo of Filing Meeting and Filing Meeting Minutes

Application Information		
NDA # 203085		
Proprietary Name: Under Review Established/Proper Name: regorafenib Dosage Form: tablet Strengths: 40mg		
Applicant: Bayer HealthCare Pharmaceuticals Inc. Agent for Applicant (if applicable): N/A		
Date of Application: April 27, 2012 Date of Receipt: April 27, 2012 Date clock started after UN: N/A		
PDUFA Goal Date: October 27, 2012	Action Goal Date (if different): September 27, 2012	
Filing Date: June 26, 2012	Date of Filing Meeting: May 29, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1 NME		
Proposed indication(s): For the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with, [redacted] (b) (4) fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.		
Type of Original NDA: AND (if applicable)	☒ 505(b)(1) ☐ 505(b)(2)	
Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

Reference ID: 3144643

☒ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

Reference ID: 3144643

User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***			X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

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If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

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☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

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Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	X			

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			Request for full waiver included, justification document was

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

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				ambiguous referring to both a deferral and a waiver, Bayer confirmed they were requesting a full waiver and submitted a revised justification document to clearly state their request for a full waiver on June 4, 2012.
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			OSE is currently reviewing the proposed proprietary name "Stivarga."
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL	X			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

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format? ***If no, request applicant to submit SPL before the filing date.***				
Is the PI submitted in PLR format?[4]	X			

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***			X	
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			X	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT		X		QT will be consulted

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

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study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***				when final study report is submitted as PMR in November 2012 (post approval)
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** September 3, 2009 ***If yes, distribute minutes before filing meeting***	X			Issued on 10/2/09

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** August 23, 2011 ***If yes, distribute minutes before filing meeting***	X			Issued 9/19/11
Any Special Protocol Assessments (SPAs)? **Date(s):** No Agreement Letter issued on January 22, 2010 ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

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ATTACHMENT

MEMO OF FILING MEETING

DATE: May 29, 2012

NDA#: 203085

PROPRIETARY NAME: Under Review

ESTABLISHED/PROPER NAME: regorafenib

DOSAGE FORM/STRENGTH: tablet/40mg

APPLICANT: Bayer HealthCare Pharmaceuticals Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): mCRC

BACKGROUND: This is a new NDA for mCRC. The regulatory history includes the following: There was an End of Phase 2 meeting held in September 2009. A Special Protocol Assessment – No Agreement Letter issued in January 2010. A letter containing advice for the pivotal Phase 3 study design in response to Bayer's Type A meeting questions issued in April 2010. An Advice letter for the pivotal Phase 3 study design, granting Fast Track designation issued June 2011. A Pre-NDA meeting was held in August 2011. A pre-submission guidance teleconference was held April 3, 2012 to reach agreement on format and content of the NDA, Clinical Pharmacology section of the application and to discuss proposed PMRs for information not contained in the original NDA submission.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Monica Hughes, M.S.	Y
	CPMS/TL:	Karen Jones	Y
Cross-Discipline Team Leader (CDTL)	Steven Lemery, M.D.		Y
Clinical	Reviewer:	Shan Pradhan, M.D., Medical Officer (Efficacy Review) Kaushik Shastri, M.D., Medical Officer (Safety Review)	Y
	TL:	Steven Lemery, M.D. Suzanne Demko	Y
Clinical Pharmacology	Reviewer:	Stacy Shord, Ph.D.	Y

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	TL:	Hong Zhao, Ph.D.	Y
Biostatistics	Reviewer:	Huanyu (Jade) Chen, Ph.D.	Y
	TL:	Kun He, Ph.D.	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Anwar Goheer, Ph.D.	Y
	TL:	Whitney Helms, Ph.D. (Andrew McDougal, current acting TL attended this meeting)	Y
Product Quality (CMC)	Reviewer:	Josephine Jee, Ph.D., Drug Product (Liang Zhao, CMC lead attended) Robert (Donghao) Lu, Drug Substance Elsbeth Chikhale, Ph.D., Biopharmaceutics Reviewer	N N Y
	TL:	Liang Zhou, Ph.D. Janice Brown, Ph.D., Acting Product TL	Y Y
CMC Labeling Review	Reviewer:	Josephine Jee Robert Lu	N N
	TL:	Janice Brown	Y
Facility Review/Inspection	Reviewer:	Mahesh Ramandhan, OMPQ TL	Y
OSE/DMEPA (proprietary name)	Reviewer:	James Schlick	Y
	TL:	Todd Bridges	N
OSE/DRISK/DPV/DEPI	Reviewer:	Amarilys Vega/DRISK	Y
	TL:	Cynthia LaCivita/DRISK	N
		Bob Pratt, OSE/DPV Cunlin Wang, OSE/DEPI	N N

Bioresearch Monitoring (OSI)	Reviewer:	Janice Pohlman	Y

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Other reviewers and attendees	Jewell Martin, Product (ONDQA RPM) Sue Kang, (OSE RPM) Karen Munoz, OPDP, Consumer Reviewer Karen Dowdy, PLT Sharon Mills, PLT (TL) Carrie Ceresa, PMHT	

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues: Not applicable.	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation?	☒ YES ☐ NO
• Electronic Submission comments **List comments**: No Comments	☐ Not Applicable
CLINICAL **Comments**: No issues identified. Requested that Bayer submit a clarification to their justification document for their request for a full pediatric waiver (current document uses the terms waiver and deferral interchangeably when they have different regulatory meanings). Bayer provided a revised waiver on June 4, 2012.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? Site selection has been completed; clinical site inspections are being scheduled.	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: AC is not needed. **Reason**: The application does not raise significant safety or efficacy issues.	☐ YES Date if known: ☒ NO ☐ To be determined

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• Abuse Liability/Potential	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: No filing issues identified, Bayer did not propose a PMR for organ dysfunction, and we will need to discuss this issue with Bayer as the review progresses.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: No filing review issues identified, a few information requests have been sent to Bayer and they are responding in a timely manner.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: No filing issues were identified, and we will have an information request to send to Bayer regarding the nonclinical micronucleus study (Study No. T 3074309, Report No. PH-33682), submit the clinical observation and body weight data for each animal in the study. If any other data are available regarding exposure or toxicity (e.g. plasma concentrations) that was not provided in the original study report, provide these data as well.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

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IMMUNOGENICITY (BLAs/BLA efficacy supplements only)	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: No filing issues identified.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: No comments.	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**: Drug Product site inspection will be scheduled.	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only)	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

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CMC Labeling Review **Comments**: Comments regarding the bottle and desiccant were conveyed to Bayer on June 8, 2012. The proprietary name "Stivarga" is still under review, therefore, there are no additional CMC comments at this time.	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Richard Pazdur, M.D.

21st Century Review Milestones: Filing Action: June 26, 2012, 74 day letter: July 10, 2012

Comments: The review team discussed the following during the filing meeting:

1. The review team agreed to review this submission as a priority review.
2. A mid-cycle meeting was scheduled for July 26, 2012.
3. The PeRC meeting to discuss the full pediatric waiver was scheduled for July 25, 2012.
4. Standing monthly meetings were set up from June-September 2012.
5. Labeling meetings have been scheduled for July and August 2012.
6. Clinical sites have been selected for inspections, inspections are being scheduled.
7. DP manufacturing site will be inspected.
8. Clinical Pharmacology PMRs: update, organ dysfunction was not included as a proposed PMR; the team will discuss the need for this PMR at upcoming meetings.

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Labeling issues identified. Review Classification: ☐ Standard Review ☒ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).

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☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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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.

/s/

MONICA L HUGHES
06/13/2012

KAREN D JONES
06/13/2012

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

Memorandum

DATE: May 15, 2012

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

SUBJECT: Designation of NDA application review status
Sponsor: Bayer Healthcare Pharmaceuticals, Inc.
Product: regorafenib
Proposed Indication: For the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with, (b) (4) fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.

TO: NDA 203085

The review status of this file submitted as an original NDA is designated to be:

☐ Standard (10 Months) ☒ Priority (6 Months)

{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

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

/s/

MONICA L HUGHES
05/15/2012

PATRICIA KEEGAN
05/15/2012