

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202806Orig1s000

OTHER REVIEW(S)

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: **Cardiac Valve Abnormalities**

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	-
	Study/Clinical trial Completion Date:	_____
	Final Report Submission Date:	<u>10/31/2020</u>
	Other: Final Analysis Plan Submission	<u>06/30/2013</u>
	Other: Interim Report Submission	<u>03/31/2014</u>
	Other: Interim Report Submission	<u>03/31/2016</u>
	Other: Interim Report Submission	<u>10/30/2018</u>

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

Metastatic melanoma is a life threatening condition with historical median survival times of 6 to 9 months and less than 10% of patients surviving beyond five years. Metastatic melanoma accounts for approximately 4% of all newly diagnosed melanoma cases. There are few FDA-approved treatments for metastatic melanoma—vemurafenib, ipilimumab, aldesleukin, and dacarbazine (DTIC).

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.”

In a randomized (3:1) controlled trial in patients with BRAF V600E mutation-positive melanoma, four adverse events related to cardiac valvular abnormalities occurred in three patients (2%) in the dabrafenib treatment group (n=187) compared to none in the DTIC treatment group (n=59). Patients with abnormal cardiac valve morphology (\geq Grade 2) or moderate valvular thickening as documented by echocardiogram were not eligible for this trial based on toxicology findings with dabrafenib. In dogs administered dabrafenib at doses of 50 mg/kg/day (approximately 9 times the human exposure at the recommended dose based on AUC) or greater for up to four weeks, cardiac atrioventricular valve hypertrophy/hemorrhage was observed.

An evaluation of cardiac valves on serial echocardiograms obtained at baseline and periodically while on dabrafenib in a single arm trial of the gelatin capsule formulation of dabrafenib, a formulation with decreased exposure compared to the to-be-marketed hydroxypropyl methylcellulose (HPMC) formulation of dabrafenib, was indeterminate in regard to the risk of cardiac valvular abnormalities with dabrafenib treatment.

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 integrated safety analyses of cardiac valve abnormalities based on centralized, blinded, independent review assessment of all echocardiograms from an adequate number of randomized controlled clinical trials that use Tafinlar (dabrafenib) capsules as monotherapy or in combination with other anti-cancer drugs to inform the label regarding incidence rate and natural history of this safety signal.

Required

- Observational pharmacoepidemiologic study
 Registry studies

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)
Risk of cardiac valvular abnormalities can be assessed in an adequate number of patients from ongoing (or planned) randomized clinical trials intended to support the efficacy dabrafenib in additional oncology indications.

 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)

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

/s/

MARC R THEORET
05/24/2013

JEFFERY L SUMMERS
05/24/2013

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: Secondary Malignancies

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	-
	Study/Clinical trial Completion Date:	-
	Final Report Submission Date:	10/31/2020
	Other: Final Analysis Plan Submission	06/30/2013
	Other: Interim Report Submission	10/31/2013
	Other: Interim Report Submission	10/31/2014
	Other: Interim Report Submission	10/31/2015
	Other: Interim Report Submission	10/31/2016
	Other: Interim Report Submission	10/31/2017
	Other: Interim Report Submission	10/31/2018
Other: Interim Report Submission	10/31/2019	

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

Metastatic melanoma is a life threatening condition with historical median survival times of 6 to 9 months and less than 10% of patients surviving beyond five years. Metastatic melanoma accounts for approximately 4% of all newly diagnosed melanoma cases. There are few FDA-approved treatments for metastatic melanoma—vemurafenib, ipilimumab, aldesleukin, and dacarbazine (DTIC).

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 risk of secondary malignancies is increased in patients taking dabrafenib and appears to be a class effect of inhibitors of BRAF kinases. In a randomized (3:1) controlled trial in patients with BRAF V600E mutation-positive melanoma, cutaneous squamous cell carcinomas and keratoacanthomas (cuSCC) occurred in 7% (14/187) of patients treated with dabrafenib and in none of the patients treated with dacarbazine (n=59). Across clinical trials of dabrafenib (n=586), the incidence of cuSCC was 11%. The incidence of new primary melanomas was also increased in dabrafenib-treated patients compared to dacarbazine treated patients, 2% (3/187) vs. 0, respectively. In trials of vemurafenib, an FDA-approved inhibitor of mutant BRAF kinases, including V600E, the risk of cuSCC was approximately 24% in patients receiving vemurafenib.

CuSCC were managed with excision in the clinical trials of dabrafenib but longer term data are not available to determine the risk of recurrence, either local or distant, from cuSCCs that develop following exposure to dabrafenib.

Also uncertain is the risk of secondary malignancies of non-cutaneous or of non-squamous cell origin. The emerging data from translational studies would suggest that the risk of secondary malignancies will not be limited to tumors of cutaneous origin. Nonclinical studies of BRAF inhibitors demonstrated hyperproliferative lesions in animal models in vivo as well as paradoxical MAPK pathway activation in vitro with increased proliferation of cell lines. Activation of RAS, either through direct mutation or upstream events in the MAPK pathway, with pathophysiologic RAF dimerization and signaling—facilitated by BRAF inhibitors—appears important in the pathobiology of BRAF-inhibitor-induced paradoxical MAPK pathway activation.

Across clinical trials of dabrafenib, predominantly single-arm trials, there were several non-cutaneous, new primary or recurrent malignancies which arose in patients with prolonged durations of exposure to dabrafenib, including two patients with tumors testing positive for mutation in RAS. Comparative data in the development program of dabrafenib are limited to one trial with a control group of 59 patients treated with dacarbazine, a trial which allowed crossover to dabrafenib at the time of disease progression.

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 cumulative safety analyses annually, and for one year after the last patient has completed clinical trial treatment, to identify and characterize the risk of new malignancies, including cutaneous squamous cell carcinoma, in all ongoing and subsequently initiated randomized controlled clinical trials through 2020 that use Tafenlar (dabrafenib) capsules alone or in combination with other anti-cancer drugs. In addition to a cumulative listing of all cases, include the following summary analyses as well as any additional informative analyses of new malignancies in each report:

- Incidence rates, overall and stratified by tumor type, for each arm of the trial(s)
- Timing of onset in regard to exposure to Tafenlar (dabrafenib) capsules (i.e., timing from first and last dose)
- Prognostic features relevant to each tumor type (e.g., clinicopathological features, including pertinent molecular characteristics, as well as disease staging information)
- Treatment(s) administered by tumor type
- Outcome

Required

Observational pharmacoepidemiologic study

Registry studies

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)
Risk of secondary malignancies can be defined and characterized in planned or ongoing randomized clinical trials intended to support the efficacy dabrafenib in oncologic indications.
 - 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)

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/s/

MARC R THEORET
05/24/2013

JEFFERY L SUMMERS
05/24/2013

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: Longer Duration of Exposure Toxicity

PMR/PMC Schedule Milestones: Final protocol Submission Date: _____
Study/Clinical trial Completion Date: _____
Final Report Submission Date: 12/31/2014
Other: _____

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

Metastatic melanoma is a life threatening condition with historical median survival times of 6 to 9 months and less than 10% of patients surviving beyond five years. Metastatic melanoma accounts for approximately 4% of all newly diagnosed melanoma cases. There are few FDA-approved treatments for metastatic melanoma—vemurafenib, ipilimumab, aldesleukin, and dacarbazine (DTIC).

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 development program for dabrafenib used two different formulations, a gelatin capsule and a hydroxypropyl methylcellulose (HPMC) capsule. The to-be-marketed formulation of dabrafenib is the HPMC capsule which results in higher exposures to the drug than the gelatin capsule formulation. The safety database of the to-be-marketed formulation (HPMC capsule) from trials with a control arm consists of 187 patients, including 49 patients who were on treatment for > 6 months. The goal is to identify new potential safety signals or adverse reactions based on longer exposure in the ongoing trial. Longer follow-up of patients enrolled in ongoing randomized controlled trial(s) may identify new adverse reactions based on longer cumulative exposure to the HPMC formulation of dabrafenib.

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)**

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- 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 the final analyses of safety from all ongoing randomized controlled clinical trial(s) using the hydroxypropyl methylcellulose formulation of Tafenlar (dabrafenib) capsules as monotherapy to identify and characterize unexpected serious risks from longer duration of exposure.

Required

- Observational pharmacoepidemiologic study
- Registry studies

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)
Unexpected serious risks with longer duration of dabrafenib exposure can be evaluated in an ongoing randomized controlled trial of dabrafenib.
 - 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
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/s/

MARC R THEORET
05/24/2013

JEFFERY L SUMMERS
05/24/2013

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 202806

Application Type: New NDA

Name of Drug: TAFINLAR, dabrafenib, 50 mg and 75 mg capsules

Applicant: GlaxoSmithKline, LLC

Submission Date: 7/29/2012

Receipt Date: 7/30/2012

1.0 Regulatory History and Applicant's Main Proposals

This is a new NDA for treatment of unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test. The regulatory history includes the following: There was an End of Phase 1/2 meeting held in July 2010. There was an End of Phase 1/PP3 meeting held in February 2011. Orphan Drug Exclusivity was granted January 12, 2011. Fast Track designation issued February 11, 2011. A pre-NDA meeting was held May 9, 2012.

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). The initial review of this PI was conducted during the filing review (10/3/2012).

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.

All SRPI format deficiencies and other labeling issues identified above were conveyed to the applicant in the 74-day, deficiencies identified letter. The Appendix contains the most recent review of the PI which were conveyed in the FDA proposed edits of 4/12/2013.

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.

Selected Requirements of Prescribing Information (SRPI)

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 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:

YES

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

Comment:

YES

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

Comment:

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:

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

Selected Requirements of Prescribing Information (SRPI)

• 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:

YES

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

Comment:

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:

Highlights Limitation Statement

YES

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:

Product Title

YES

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

Comment:

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:

Boxed Warning

N/A

12. All text must be **bolded**.

Comment:

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:

N/A

14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

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.*”)

Selected Requirements of Prescribing Information (SRPI)

Comment:

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

Comment:

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:

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

Comment:

- 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:

- 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:

Indications and Usage

- YES** 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)]."

Comment:

Dosage Forms and Strengths

- YES** 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:

Contraindications

- N/A** 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:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

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**

Selected Requirements of Prescribing Information (SRPI)

(insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch".

Comment:

Patient Counseling Information Statement

- NO** 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: Need to change to add 'Medication Guide' with the addition of new nonREMS Med Guide.

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

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

Comment:

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

Comment:

- 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:

- 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:

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

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

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

Comment:

Selected Requirements of Prescribing Information (SRPI)

- 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:

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:

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

Comment:

- YES** 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
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

Selected Requirements of Prescribing Information (SRPI)

15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 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:

- 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:

- 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:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

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

Comment:

- 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** 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:

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Comment:

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:

- 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:

Selected Requirements of Prescribing Information (SRPI)

“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

- YES** 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)”

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/s/

NORMA S GRIFFIN
05/09/2013

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

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

Memorandum

Date: April 29, 2013

To: Norma Griffin
Regulatory Project Manager
Division of Oncology Products 2 (DOP2)

From: Quynh-Van Tran, PharmD, BCPP
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **TAFINLAR[®] (dabrafenib) capsules, for oral use (Tafinlar)
NDA# 202806
OPDP Review of Prescribing Information (PI), Medication
Guide (MG) and container labeling**

In response to DOP2 September 18, 2012 consult request, OPDP has reviewed the proposed PI (FDA version sent via email to OPDP on April 15, 2013), MG [Division of Medical Policy Programs (DMPP)'s version on April 19, 2013] and container labeling for Tafinlar.

Please see the attached PI with our comments incorporated therein. We agree with DMPP's comments on the MG and offer the following additional comment.

- The MG presents [REDACTED] ^{(b) (4)} as the most common side effects of Tafinlar. However, these adverse reactions do not meet the criterion for common adverse reactions (greater or equal 20%) set by the review division. OPDP recommends revising the list of common adverse reactions in the Medication Guide to be consistent with the list in the PI.

OPDP does not have comments for the container labeling at this time.

Thank you for the opportunity to provide comments on the proposed PI, MG and container labeling for Tafinlar. If you have any questions, please contact Quynh-Van Tran at (301) 796-0185, or quynh-van.tran@fda.hhs.gov.

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

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/s/

QUYNH-VAN TRAN
04/29/2013

**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 - Final

Date: April 23, 2013

Reviewer: James Schlick, RPh, MBA
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Tafinlar (Dabrafenib) Capsules, 50 mg and 75 mg

Application Type/Number: NDA 202806

Applicant: GlaxoSmithKline

OSE RCM #: 2012-1787-1

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

Contents

1	Introduction.....	1
2	Methods and Materials Reviewed.....	1
2.1	Labels and Labeling	1
2.2	Previously Completed Reviews	1
3	Conclusion	1
	Appendices.....	2

1 INTRODUCTION

This review evaluates the proposed container labels and insert labeling for Tafinlar (Dabrafenib), NDA 202806, submitted in response to the Division of Medication Error Prevention and Analysis' comments in the December 7, 2012 OSE Review# 2012-1787.

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted March 27, 2013 (Appendix A)
- Insert Labeling Including Non-REMS Medication Guide submitted March 14, 2013

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously reviewed this product in OSE Review 2012-1787, and we looked at the review to ensure all our recommendations were implemented.

3 CONCLUSION

DMEPA finds the Applicant's revisions to the labels and labeling acceptable. If you have questions or need clarifications, please contact Sue Kang, OSE project manager, at 301-796-4216.

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

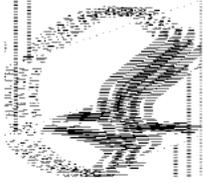
¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JAMES H SCHLICK
04/23/2013

TODD D BRIDGES
04/23/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Maternal Health Team Review

Date: April 19, 2013

From: Tammie Howard, RN, MSN
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

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

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

To: Division of Oncology Products 2 (DOP2)

Drug: Tafinlar (debrafenib) NDA 202806

Subject: Tafinlar (debrafenib) is a new molecular entity (NME) submitted for NDA approval

Applicant: GlaxoSmithKline, LLC (GSK)

Materials Reviewed: Tafinlar product labeling

Consult Question: DOP2 requested that PMHS-MHT attend milestone meetings and provide labeling comments for this new NDA.

INTRODUCTION

GlaxoSmithKline, LLC (GSK) submitted a New Drug Application (NDA) for Tafinlar (debrafenib) capsules on July 30, 2012. Debrafenib is a New Molecular Entity (NME) with a proposed indication for treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test for this use. Tafinlar is not indicated for use in patients with wild-type BRAF melanoma. B-RAF, a Raf kinase, is a protein in a signaling pathway that affects cell division, differentiation and secretion. Mutations in the B-RAF gene can result in stimulation of tumor cell growth, such as in melanomas, colorectal cancers and non-small cell lung cancers.¹ Debrafenib is an inhibitor of some mutated forms of BRAF kinases and human wild type BRAF and CRAF enzymes. The Pediatric and Maternal Health Staff-Maternal Health Team (PMHS-MHT) was consulted by DOP2 on September 18, 2012 to attend milestone meetings during the review cycle and provide labeling comments for this new NDA. This review includes PMHS-MHT comments and recommendations for Tafinlar (debrafenib) labeling.

BACKGROUND

Debrafenib and Pregnancy

The occurrence of malignancy during pregnancy is uncommon (approximately 1 in 1,000 to 1 in 6,000 pregnancies), with most occurring in breast and cervical cancers, melanoma and lymphoma.^{2,3,4} However, melanoma occurs in a majority male population with a 67% higher incidence in men versus women. The age of fifty-three is the median age of diagnosis, with forty-two percent of cases occurring in those younger than fifty-five.⁵

Debrafenib is a NME and there are no human pregnancy data available. In animal developmental reproductive studies, debrafenib was teratogenic and embryotoxic. Developmental toxicity consisted of embryo-lethality, ventricular septal defects, and variations in thymic shape. There were also delays in skeletal development and reduced fetal body weight. These data are reported in current debrafenib pregnancy labeling.

Debrafenib and Lactation

It is not known if Debrafenib is present in human milk. A search of the Micromedex database resulted in no human or animal data available regarding debrafenib and lactation. In addition, there are no available human lactation data available for other BRAF kinase inhibitors.

¹ Website: http://www.genenames.org/data/hgnc_data.php?hgnc_id=1097, accessed March 27, 2013.

² Website: <http://www.cancer.net/coping/emotional-and-physical-matters/sexual-and-reproductive-health/cancer-during-pregnancy>, accessed March 4, 2013.

³ Esin S, et al., Management of precursor B-lymphoblastic lymphoma/leukaemia of thoracic spine in a pregnancy presenting with acute paraplegia. *Journal of Obstetrics and Gynecology*. 2012;32(5):485-6.

⁴ Perez CA, et al., Primary mediastinal large B-cell lymphoma during pregnancy. *Case Reports in Hematology*. 2012;Article ID 197347, 1-3.

⁵ Website: <http://www.cancernetwork.com/cancer-management/moles-melanomas/article/10165/1802671#> Brady MS, et al. Melanoma and other skin cancers. *Cancer Management: Online Edition*. 2013, accessed April 8, 2013.

REVIEW OF SUBMITTED MATERIALS

Sponsor Proposed Debrafenib Labeling

The PMHS-MHT reviewed the sponsor's proposed debrafenib labeling, submitted July 20, 2012 and participated in several labeling/team meetings during the review period. A summary of PMHS-MHT labeling recommendations appear immediately following Discussion and Conclusions with labeling excerpts provided in **Appendix A**.

DISCUSSION AND CONCLUSIONS

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from 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. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in the label, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

The PMHS-MHT has reviewed the proposed debrafenib labeling, and labeling recommendations are provided below.

MHT Summary of Labeling Comments and Recommendations

Highlights of Prescribing Information

The bullet point (b) (4) under Warnings and Precautions was revised to "Embryo-Fetal Toxicity", to reference the section in the full prescribing information, to comply with requirement of current Safety Endpoints and Labeling Development Team (SEALD) labeling review tool. Language regarding embryo-fetal toxicity was revised to display preferred labeling language.

Under Use in Specific Populations, the language for the bullet, Nursing Mothers, was revised to display preferred labeling language in a more concise format.

5 Warnings and Precautions

The title of section 5.6 was revised to "Embryo-Fetal Toxicity" to comply with requirement of the current SEALD labeling review tool. The summary statement "Dabrafenib was teratogenic and embryotoxic in rats at doses 3 times greater than the human exposure at the recommended clinical dose." was added and the description of animal data was removed, as this data appears in section 8.1.

Language regarding contraception for females of reproductive potential and to indicate when contact with the patient health care provider is needed was revised to appear in active voice. Language regarding effects on male fertility was removed and placed in section 8.6, Females and Males of Reproductive Potential, under Infertility, Males. Appropriate labeling cross references were added. Language was revised to ensure use of appropriate regulatory language.

8 Use in Specific Populations

Pregnancy (8.1)

The Pregnancy section was restructured and the sub-headings Risk Summary and Animal Data were added to provide an organized presentation of data, in the spirit of the proposed rule as described above. Language regarding contraception for females of reproductive potential was removed and placed in section 8.6, Females and Males of Reproductive Potential, under Contraception, Females.

Nursing Mothers (8.3)

The Nursing Mothers section states that it is unknown whether debrafenib is present in human milk, with appropriate regulatory language.

Females and Males of Reproductive Potential (8.6)

Information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in the subsection, Females and Males of Reproductive Potential. The sub-headings Contraception and Infertility were added to provide an organized presentation of data, in the spirit of the proposed rule as described above. Male and Female sub-headings were added under Contraception and Infertility indicating information pertaining to each.

13 Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility (13.1)

This section originally contained information from combined embryo-fetal development and female fertility studies. The information was revised by the non-clinical review team. Infertility information (animal data) remained in this section of labeling, while embryo-fetal toxicity data (animal data) was appropriately relocated to section 8.1 under the “Animal Data” sub-heading. In addition, animal data regarding male fertility studies appears in this section.

Reviewer Comment: In general, available human data should be described under the Females and Males of Reproductive Potential section of labeling. If there are relevant animal data, it is stated and cross referenced to a more detailed description of the studies in section 13.1.

17 Patient Counseling Information

Language regarding pregnancy, lactation, and infertility was revised to describe the potential risk, actions to mitigate the risk and provide instructions for contacting a health care provider.

Appendix A- PMHS-MHT Tafinlar Labeling Recommendation Excerpts

Appendix A-PMHS-MHT Tafinlar Labeling Recommendation Excerpts

Highlights of Prescribing Information

WARNINGS and PRECAUTIONS

- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus. TAFINLAR may render hormonal contraceptives less effective and an alternative method of contraception should be used. (b) (4)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Discontinue drug or nursing. (8.3)

5 Warnings and Precautions

5.4 Embryofetal Toxicity

TAFINLAR can cause fetal harm when administered to a pregnant woman. Dabrafenib was teratogenic and embryotoxic in rats at doses 3 times greater than the human exposure at the recommended clinical dose. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see Use in Specific Populations (8.1)].

Advise female patients of reproductive potential to use a highly effective non-hormonal method of contraception during treatment and for four weeks after treatment, since TAFINLAR can render hormonal contraceptives ineffective. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR [see Drug Interactions (7) and Use in Specific Populations (8.6)].

8 Use in Specific Populations- Pregnancy (8.1), Nursing Mothers (8.3), Females and Males of Reproductive Potential (8.6)

8.1 Pregnancy

Pregnancy Category D

Risk Summary

TAFINLAR can cause fetal harm when administered to a pregnant woman. Dabrafenib was teratogenic and embryotoxic in rats at doses 3 times greater than the human exposure at the recommended clinical dose based on AUC. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see Warnings and Precautions (5.4)].

Animal Data

In a combined female fertility and embryofetal development study in rats, developmental toxicity consisted of embryo-lethality, ventricular septal defects, and variation in thymic shape at a dabrafenib dose of 300 mg/kg/day (approximately 3 times the human exposure at the recommended dose based on AUC). At doses of 20 mg/kg/day or greater, (equivalent to the human exposure at the recommended dose based on AUC) rats demonstrated delays in skeletal development and reduced fetal body weight.

8.3 Nursing Mothers

It is not known whether this drug is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions from TAFINLAR in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.6 Females and Males of Reproductive Potential

Contraception

Females

(b) (4) Advise female patients of reproductive potential to use highly effective contraception during treatment and for four weeks after treatment. Counsel patients to use a non-hormonal method of contraception since TAFINLAR can render hormonal contraceptives ineffective. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR [see Warnings and Precautions (5.4), Interactions (7.1), Use in Specific Populations (8.1)].

Infertility

Males

Effects on spermatogenesis have been observed in animals. Advise male patients of the potential risk for impaired spermatogenesis, and to seek counseling on fertility and family planning options prior to starting treatment with TAFINLAR [see Nonclinical Toxicology (13.1)].

13 Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with dabrafenib have not been conducted. TAFINLAR increased the risk of cutaneous squamous cell carcinomas in patients in clinical trials.

Dabrafenib was not mutagenic *in vitro* in the bacterial reverse mutation assay (Ames test) or the mouse lymphoma assay, and was not clastogenic in an *in vivo* rat bone marrow micronucleus test.

In a combined female fertility and embryofetal development study in rats, a reduction in fertility was noted at doses greater than or equal to 20 mg/kg/day (equivalent to the human exposure at the recommended dose based on AUC). A reduction in the number of ovarian corpora lutea was noted in pregnant females at 300 mg/kg/day which is approximately 3 times the human exposure at the recommended dose based on AUC.

Male fertility studies with dabrafenib have not been conducted; however, in repeat dose studies, testicular degeneration/depletion was seen in rats and dogs at doses equivalent to (b) (4) and (b) (4) times the human exposure at the recommended dose based on AUC, respectively.

17 Patient Counseling Information

- TAFINLAR can cause fetal harm if taken during pregnancy. Instruct female patients to use non-hormonal, highly effective contraception during treatment and for four weeks after treatment. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR [*see Use in Specific Populations (8.1),(8.6)*].
- Nursing infants may experience serious adverse reactions if the mother is taking TAFINLAR. Advise lactating mothers to discontinue nursing while taking TAFINLAR [*see Nursing Mothers (8.3)*].
- Male patients are at an increased risk for impaired spermatogenesis [*see Use in Specific Populations (8.6)*].

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/s/

TAMMIE B BRENT HOWARD
04/19/2013

MELISSA S TASSINARI
04/19/2013

LYNNE P YAO
04/22/2013

**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: April 19, 2013

To: Patricia Keegan, MD
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: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): TAFINLAR (dabrafenib)

Dosage Form and Route: Capsules for oral use

Application Type/Number: NDA 202-806

Applicant: GlaxoSmithKline

1 INTRODUCTION

On July 30, 2012 GlaxoSmithKline submitted for the Agency's review completion of their rolling submission (Part 3 of 3) for original New Drug Application (NDA) 202-806 for TAFINLAR (dabrafenib) capsules. On March 6, 2013 the Agency requested that the Applicant submit a non-Risk Evaluation and Mitigation Strategy (REMS) Medication Guide (MG). On March 14, 2013, the Applicant submitted a non-REMS Medication Guide (MG). The Applicant's proposed indication is for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation as detected by an FDA approved test.

On September 12, 2012, the Division of Oncology Products 2 (DOP2) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for TAFINLAR (dabrafenib) capsules.

This review is written in response to a request by DOP2 for DMPP to review the Applicant's proposed Medication Guide (MG) for TAFINLAR (dabrafenib) capsules.

2 MATERIAL REVIEWED

- Draft TAFINLAR (dabrafenib) capsules Medication Guide (MG) received on March 14, 2013, and received by DMPP on April 15, 2013.
- Draft TAFINLAR (dabrafenib) capsules Prescribing Information (PI) received on July 30, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on April 15, 2013.

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 MG 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 MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

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

4 CONCLUSIONS

The MG 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 MG 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 MG.

Please let us know if you have any questions.

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/s/

LATONIA M FORD
04/19/2013

BARBARA A FULLER
04/19/2013

LASHAWN M GRIFFITHS
04/19/2013

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.

NDA/BLA # NDA 202806, TAFINLAR (dabrafenib)
Product Name: _____

PMR/PMC Description: QT/QTc interval prolongation

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Submitted</u>
	Study/Trial Completion:	<u>March, 2014</u>
	Final Report Submission:	<u>December, 2015</u>
	Other: _____	_____

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

In the NDA submission, there is no adequate data to rule out the QT prolongation potential of dabrafenib.

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 dabrafenib to potentially prolong the QT/QTc interval.

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 dabrafenib to prolong the QT/QTc interval in accordance with the principles of the FDA Guidance for Industry entitled “*E14 Clinical Evaluation of QT/QTc Interval Prolongation*”. Submit the final report that includes central tendency, categorical and concentration-QT analyses, along with a thorough review of cardiac safety data.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- 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)

Continuation of Question 4

- 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 NDAs)

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.

NDA/BLA # NDA 202806, TAFINLAR (dabrafenib)
Product Name: _____

PMR/PMC Description: Hepatic Impairment Pharmacokinetic Trial

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Submitted</u>
	Study/Trial Completion:	<u>September, 2014</u>
	Final Report Submission:	<u>June, 2015</u>
	Other: _____	_____

6. 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 mass balance study suggests that dabrafenib is mainly eliminated through the liver. Fraction of dabrafenib dose excreted 71% in feces. A population PK analysis suggests that mild hepatic impairment has no effect on systemic exposure to dabrafenib and its active metabolites. However, there are no data available for moderate to severe hepatic impairment. Patients with hepatic impairment may have a higher dabrafenib exposure than that of patients with normal hepatic function, which could cause more toxicity.

7. 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 pharmacokinetic trial is to determine appropriate dabrafenib doses in patients with moderate to severe hepatic impairment.

8. 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?

9. 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 pharmacokinetic trial to determine the appropriate dabrafenib dose in patients with moderate to severe hepatic impairment in accordance with the FDA Guidance for Industry entitled “*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*”.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- 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)

Continuation of Question 4

- 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
-

10. 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 NDAs)

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.

NDA/BLA # NDA 202806, TAFINLAR (dabrafenib)
Product Name: _____

PMR/PMC Description: Renal Impairment Pharmacokinetic Trial

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>submitted</u>
	Study/Trial Completion:	<u>September, 2014</u>
	Final Report Submission:	<u>June, 2015</u>
	Other: _____	_____

11. 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 mass balance study suggests that a 23% of dabrafenib dose is excreted in urine. A population PK analysis suggests that mild to moderate renal impairment has no effect on systemic exposure to dabrafenib and its active metabolites. However, no data are available for severe renal impairment. Patients with severe renal impairment may have a higher dabrafenib exposure than that of patients with normal renal function, which could cause more toxicity.

12. 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 pharmacokinetic trial is to determine the appropriate dabrafenib dose in patients with severe renal impairment.

13. 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?

14. 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 pharmacokinetic trial to determine the appropriate dabrafenib dose in patients with severe renal impairment in accordance with the FDA Guidance for Industry entitled “*Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*”.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- 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)

Continuation of Question 4

- 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
-

15. 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 NDAs)

18. 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?

19. 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 drug interaction trial to evaluate the effect of rifampin (a strong CYP3A4 and CYP2C8 inducer) on the repeat dose pharmacokinetics of dabrafenib in accordance with the FDA Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*”. The results of this clinical trial should allow for a determination on how to dose dabrafenib with regard to concomitant strong CYP3A4 and CYP2C8 inducers.

Required

- Observational pharmacoepidemiologic study
- Registry studies

- 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)

Continuation of Question 4

- 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
-

20. 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 NDAs)

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.

NDA/BLA # NDA 202806, TAFINLAR (dabrafenib)
Product Name: _____

PMR/PMC Description: Drug Drug Interaction Trial

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Submitted</u>
	Study/Trial Completion:	<u>Completed</u>
	Final Report Submission:	<u>May 2013</u>
	Other: _____	_____

21. 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

In vitro studies showed that dabrafenib metabolism is mediated by CYP2C8 and CYP3A4 while the two active metabolites, hydroxy- and desmethyl-dabrafenib, are CYP3A4 substrates. A dedicated drug-drug interaction trial with a strong CYP3A4 inhibitor (e.g., ketoconazole) should be conducted and the study results should allow for a determination on how to dose dabrafenib with regard to concomitant strong CYP3A4 inhibitors.

22. 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 determine how to dose dabrafenib with regard to concomitant strong CYP3A4 inhibitors.

23. 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?

24. 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 effects of repeat doses of oral ketoconazole on the repeat dose pharmacokinetics of dabrafenib in accordance with the FDA Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*”. The results of this clinical trial should allow for a determination on how to dose dabrafenib with regard to concomitant strong CYP3A4 inhibitors.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- 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)

Continuation of Question 4

- 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
-

25. 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 NDAs)

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.

NDA/BLA # NDA 202806, TAFINLAR (dabrafenib)
Product Name: _____

PMR/PMC Description: Drug Drug Interaction Trial

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Submitted</u>
	Study/Trial Completion:	<u>Completed</u>
	Final Report Submission:	<u>May 2013</u>
	Other: _____	_____

26. 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

In vitro studies showed that dabrafenib metabolism is mediated by CYP2C8 and CYP3A4. A dedicated drug-drug interaction trial with a strong CYP2C8 inhibitor should be conducted and the study results should allow for a determination on how to dose dabrafenib with regard to concomitant strong CYP2C8 inhibitors.

27. 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 determine how to dose dabrafenib with regard to concomitant strong CYP2C8 inhibitors.

28. 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?

29. 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 effects of repeat doses of oral gemfibrozil on the repeat dose pharmacokinetics of dabrafenib in accordance with the FDA Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*”. The results of this clinical trial should allow for a determination on how to dose dabrafenib with regard to concomitant strong CYP2C8 inhibitors.

Required

- Observational pharmacoepidemiologic study
- Registry studies

- 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)

Continuation of Question 4

- 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
-

30. 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 NDAs)

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.

NDA/BLA # NDA 202806, TAFINLAR (dabrafenib)
Product Name: _____

PMR/PMC Description: Drug Drug Interaction Trial

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Submitted</u>
	Study/Trial Completion:	<u>Completed</u>
	Final Report Submission:	<u>May 2013</u>
	Other: _____	_____

31. 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

In vitro studies showed that dabrafenib is an inducer of CYP2C9. A dedicated drug-drug interaction trial with a CYP2C9 substrate should be conducted and the study results should allow for a determination on how to dose dabrafenib with regard to concomitant sensitive CYP2C9 substrates and CYP2C9 substrates with a narrow therapeutic window.

32. 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 determine how to dose dabrafenib with regard to concomitant sensitive CYP2C9 substrates and CYP2C9 substrates with a narrow therapeutic window.

33. 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?

34. 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 effects of repeat doses of dabrafenib on the single dose pharmacokinetics of warfarin (CYP2C9 substrate) in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations”. The results of this clinical trial should allow for a determination on how to dose dabrafenib with regard to concomitant sensitive CYP2C9 substrates and CYP2C9 substrates with a narrow therapeutic window.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- 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)

Continuation of Question 4

- 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
-

35. 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 NDAs)

38. 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?

39. 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 clinical trial to evaluate if proton pump inhibitors, H₂ antagonists and antacids alter the bioavailability of dabrafenib. You may study the worst case scenario first, and then determine if further studies of other drugs are necessary. The study results should allow for a determination on how to dose dabrafenib with regard to concomitant gastric pH elevating agents.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- 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)

Continuation of Question 4

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

40. 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 NDAs)

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/s/

JIAN WANG
04/10/2013

HONG ZHAO
04/10/2013

JEFFERY L SUMMERS
04/15/2013

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: February 8, 2013

TO: Marc Theoret, M.D.
Suzanne Demko, PA-C, Clinical Team Leader
Norma Griffin, Regulatory Project Manager
Division of Oncology Products II
Office of Hematology and Oncology Products

FROM: Jean Mulinde, M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

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: NDA 202806

APPLICANT: GlaxoSmithKline, LLC

DRUG: Dabrafenib [(b) (4) (proposed)]

NME: Yes

REVIEW PRIORITY: Standard Review

INDICATION: For the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation.

CONSULTATION REQUEST DATE: September 6, 2012
CLINICAL INSPECTION SUMMARY DATE: February 18, 2013
DIVISION ACTION GOAL DATE: April 15, 2013
PDUFA DATE: May 30, 2013

I. BACKGROUND:

(b) (4) (dabrafenib, GSK2118436) is a selective inhibitor of BRAF kinase activity with a mode of action (MOA) consistent with adenosine triphosphate (ATP)-competitive inhibition. Dabrafenib is being developed by GSK as monotherapy (b) (4) (NDA 204114, which was concurrently submitted for review), for the treatment of BRAF V600 mutation positive unresectable or metastatic melanoma. The RAS/RAF/MEK/ERK pathway is a critical proliferation pathway in many human cancers and this pathway can be constitutively activated by alterations in specific proteins, including BRAF. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 40-60% of melanomas. The frequency of this activating mutation, and the pathway to which it leads, thus makes mutated BRAF an attractive target for antineoplastic therapy such as dabrafenib. Dabrafenib is provided as capsules for oral administration (50 mg or 75 mg per capsule). Based on the Applicant's summary of pivotal Phase 2/3 data, the use of dabrafenib in subjects with unresectable or metastatic melanoma has resulted in a significant reduction in risk of disease progression and death.

Of note, as there was no commercially available Food and Drug Administration (FDA)-approved BRAF mutation assay at the time of clinical studies initiation for dabrafenib, an analytically validated "investigational use only" (IUO) allele-specific polymerase chain reaction (PCR) assay was used to screen subjects for eligibility into the GSK-sponsored clinical Study BRF113683. This assay, developed by Response Genetics Institute (RGI), could distinguish BRAF V600E and BRAF V600K mutation subtypes. GSK has partnered with bioMerieux in the co-development of a companion diagnostic (cDx) assay to be available at the time of dabrafenib approval; this diagnostic is undergoing simultaneous review in CDRH.

In support of the efficacy and safety of (b) (4) (dabrafenib, GSK2118436), for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation, the Applicant has submitted data from one pivotal Phase 3 study (BRF113683) and two Phase 2 studies (BRF113710 and BRF113929). A brief description of Study BRF113683 follows.

PROTOCOL BRF113683, ENTITLED "A PHASE III RANDOMIZED, OPEN-LABEL STUDY COMPARING GSK2118436 TO DTIC IN PREVIOUSLY UNTREATED SUBJECTS WITH BRAF MUTATION POSITIVE ADVANCED (STAGE III) OR METASTATIC (STAGE IV) MELANOMA."

Study BRF113683 is a randomized, open-label, multicenter, Phase 3 study comparing intravenous DTIC with the oral single agent GSK2118436 in patients with histologically confirmed advanced (unresectable Stage III) or metastatic melanoma (Stage IV). Key eligibility criteria required subjects: 1) be adults with advanced (unresectable Stage III) or metastatic (Stage IV) BRAF V600E mutant melanoma, 2) be treatment naïve for metastatic

disease, with the exception of IL-2, surgery, and radiotherapy, which were allowed, 3) have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and had an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1 at entry. Once determined to be eligible subjects were randomized 3:1 to GSK2118436 150 mg BID orally or DTIC 1000 mg/m² intravenously every 3 weeks. Subjects remained on treatment until disease progression, death, the occurrence of an unacceptable adverse event (AE), or withdrawal from the study. Subjects randomized to GSK2118436 treatment who experienced investigator reported disease progression but were still benefiting from study treatment with GSK2118436 were permitted to continue receiving GSK2118436. Subjects randomized to DTIC treatment were allowed to receive GSK2118436 after initial progression was confirmed by independent review. Subjects were then followed for response, progression, survival, and further anti-cancer therapy while receiving GSK2118436, and for survival and further anti-cancer therapy after progression while on GSK2118436.

The study was conducted at 70 clinical investigator sites in 12 countries: Australia (4), Canada (5), France (8), Germany (14), Hungary (2), Ireland (2), Italy (7), Netherlands (1), Poland (4), Russia (5), Spain (9), and USA (9). A total of 250 subjects were randomized into the trial. One hundred eighty seven (187) subjects were treated with GSK2118436 and 63 subjects were treated with DTIC. Twenty-eight subjects randomized to DTIC received GSK2118436 in the crossover phase. The first subject was enrolled in the study February 2, 2011. At this time, surviving subjects, who have not had progressive disease, may remain on GSK2118436 at their discretion and the discretion of their physician (this includes option for all surviving subjects that were on DTIC arm to cross over to treatment with GSK2118436). The data cutoff date for the NDA submission was December 19, 2011.

According to the NDA submission five entities provided clinical site monitoring support: GSK, (b) (4) provided central laboratory services and Response Genetics, Inc. provided BRAF screening testing during the study. (b) (4) provided central review of computerized tomography images (CT), electrocardiograms, and echocardiograms (b) (4). (b) (4) was responsible for transfer of CT scans and echocardiograms from sites to (b) (4). (b) (4) was responsible for collection of digital photographs of disease sites. An independent data monitoring committee (IDMC) was utilized for this study to ensure external objective medical and/or statistical review of safety issues. An Independent Review Committee (IRC) was used to assess disease response and progression. Clinical sites were required to submit electronic files with acquired scans and photographs of skin lesions, which were then submitted to the IRC for review. Data was collected by clinical investigators on electronic case report forms (eCRFs), which were transmitted to GSK and combined with data from other sources in a validated data system. According to the NDA, eCRFs (including queries and audit trails) were retained by GSK, and copies of eCRFs were sent to the investigator to maintain as the investigator copy.

The primary endpoint for this study is progression free survival (PFS), which is defined as the time from randomization to the first date of either objective disease progression (confirmed by the IRC) or death due to any cause. A key secondary endpoint for this study is overall survival (OS), which is defined as the time from randomization to death due to any cause.

Safety measurements included assessment of adverse events, physical findings and vital signs, laboratory evaluations, echocardiograms, and ECGs. Protocol defined adverse events of special interest included: cutaneous squamous cell carcinoma, actinic keratosis, keratoacanthoma, other malignancies, pyrexia, abnormal ejection fraction, cardiac valvular abnormalities, uveitis, neutropenia, and renal failure.

The clinical investigator sites were selected for inspection based on enrollment characteristics, patterns of protocol violations reported for the sites, and patterns of serious adverse event reporting. In addition, a sponsor inspection was conducted to evaluate the sponsor's overall conduct of the study.

II. RESULTS (By Site)

Name of CI	Protocol # Site# Subject#	Inspection Dates	Final Classification
Lev Demidov, M.D. Cancer Research Center Kasirskoye Shosse, 24 Moscow, 115478 Russia	Protocol: BRF113683 Site: #86744 Subjects: 9	December 10-14, 2012	Pending (Preliminary Classification VAI)
Jean-Jacques Grob, M.D. CHU - Hôpital de la Timone Service de Dermatologie 264 rue Saint-Pierre Cedex 5 Marseille, 13385 France	Protocol: BRF113683 Site: #87119 Subjects: 10	November 19-22, 2012	NAI
GlaxoSmithKline 1250 South Collegeville Road Collegeville, PA 19426	Protocol: BRF113683	October 24- November 1, 2012	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

Pending = Preliminary classification based on information in 483, if issued, and preliminary communication with the field; the EIR has not been received from the field and complete review of EIR is pending.

1. Lev Demidov, M.D.

Cancer Research Center
Kasirskoye Shosse, 24
Moscow, 115478
Russia
Site #86717

a) What was inspected:

For Study BRF113683, at this site, 19 subjects were screened, 9 subjects were enrolled, and 9 subjects completed the study. Four subjects' records were reviewed during the inspection. The record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, primary efficacy and key secondary endpoint data, concomitant medication usage, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated test article accountability, monitoring and sponsor correspondence with the site, and IRB approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:

Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 202806 were compared. A Form FDA 483, Inspectional Observations, was issued to the CI for:

Failure to ensure that the investigation was conducted according to the signed investigator statement and the investigational plan [21 CFR 312.60].
Specifically for:

- i. Protocol Amendment #4 required that subjects assessed to have unequivocal disease progression by the investigator be discontinued from study drug. Subject #000137 was considered to have unequivocal disease progression by the investigator as of December 22, 2011, but study drug was not stopped until December 30, 2011.
- ii. Protocol Amendment #5 permitted subjects with disease progression whom the investigator considered still benefitting from therapy to remain on study drug. The CI performed study procedures and continued study treatment for four enrolled subjects (Subjects #000129, #000135, #000137, and #000144) with disease progression, but who were considered to still be benefitting from study therapy, prior to receiving Ethics Committee approval of Protocol Amendment #5 on January 19, 2012.
- iii. Pharmacokinetic (PK) samples were either not collected or collected out of protocol specified time frame for one subject. Specifically, for

Subject #000135 the Visit 24 PK sample was not collected and the Visit 12 PK sample was collected >7 days prior to the actual visit date.

OSI Reviewer Comment: In relation to the first two observations, they occurred in close proximity to the approval of Protocol Amendment #5 by the Ethics Committee overseeing the conduct of the study at this site, and there is no evidence that subjects were harmed by continuation of study therapy (Form FDA 483 listed procedures and study drug administration occurred within a 2 day time frame of the EC approval of the amendment). As Subject #000137 was considered by the CI to still have been benefitting from study therapy, despite disease progression, and the subject was eligible to continue study therapy under Protocol Amendment #5 prior to their next scheduled therapy cycle, the issue of failing to discontinue the subject from study therapy at the prior time point becomes a somewhat moot point.

The protocol deviations related to the Visit 12 PK sample collection for Subject #000135 was reported accurately in the NDA clinical study report as a protocol deviation. The missing Visit 24 PK sample occurred after the data cut off point for this submission; therefore, it does not impact NDA analyses presented.

c) Assessment of data integrity:

Notwithstanding the observations above, the data provided by Dr. Demidov's site for Study BRF113683 that were submitted to the Agency in support of NDA 202806 appear to be reliable and acceptable for use in support of the pending application.

Note: The EIR and associated exhibits for this inspection were not available at the time this CIS was written. The general observations described above are based on review of the issued 483 and preliminary summary information provided by the ORA investigator. An inspection summary addendum will be generated if conclusions change upon review of the final EIR.

2. Jean-Jacques Grob, M.D.

CHU - Hôpital de la Timone Service de Dermatologie
264 rue Saint-Pierre Cedex 5
Marseille, 13385
France
Site #87119

a) What was inspected:

For Study BRF113683, at this site, 14 subjects were screened, 10 subjects were enrolled, and all subjects completed the study. All enrolled subjects' records were reviewed during the inspection. The record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to inclusion/exclusion criteria compliance, primary efficacy and key secondary

endpoint data, concomitant medication usage, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated informed consent documentation, randomization procedures, drug compliance and accountability, monitoring logs, and IRB approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:

Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 202806 were compared. The investigator's execution of the protocol was found to be generally adequate and a Form FDA 483, Inspectional Observations was not issued to the clinical investigator.

c) Assessment of data integrity:

The data provided by Dr. Grob's site for Study BRF113683 that were submitted to the Agency in support of NDA 202806 appear to be reliable and acceptable for use in support of the pending application.

3. GlaxoSmithKline

1250 South Collegeville Road
Collegeville, PA 19426

a) What was inspected:

The sponsor, GlaxoSmithKline, was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. Study BRF113683 was conducted globally, and during this sponsor/monitor inspection clinical site records for the CI sites listed in the table above, as well as records for three additional sites (Sites #084791, #084095, and #085130) were focused on. The record review included review of documents associated with the IRB approvals, site and investigator qualifications and site selection, monitor training, delegation of monitoring activities to contractors and actual monitoring activities, Independent Review Committee (IRC) documentation and case review, data collection and handling, drug accountability records, serious adverse events, and the Sponsor's handling of protocol deviations and violations.

b) General observations/commentary:

Consistent with the sponsor compliance program assessments, during the inspection data found in source documents and those measurements reported by the sponsor to the Agency in NDA 202806 were compared and verified. Study BRF113683 was found to be adequately executed by the Sponsor, GlaxoSmithKline. A Form FDA 483 was not issued.

c) Assessment of data integrity:

The data generated, as it pertains to Study BRF113683 were inspected in

accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. Study BRF113683 appears to have been conducted adequately by GlaxoSmithKline and the data submitted by the Applicant for this study may be used in support of the pending Application.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of inspectional findings for the inspections of GlaxoSmithKline, Dr. Demidov, and Dr. Grob, the data submitted by the Applicant for Study BRF113683 appear reliable in support of NDA 202806.

The final classifications for the inspections of Dr. Grob and the Sponsor, GlaxoSmithKline, are No Action Indicated (NAI).

The preliminary classification for the inspection of Dr. Demidov is Voluntary Action Indicated (VAI). The Form FDA 483 observations noted for Dr. Demidov's site are considered minor and unlikely to significantly impact the results of efficacy and safety analyses reported by the Applicant.

Note: All observations noted above related to the inspection of Dr. Demidov are based on preliminary communications with the field investigator who conducted this inspection and the Form FDA 483 issued; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR for this inspection.

{See appended electronic signature page}

Jean Mulinde, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
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Susan D. Thompson, M.D.
Acting Branch Chief, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

JEAN M MULINDE
02/08/2013

JANICE K POHLMAN
02/08/2013

SUSAN D THOMPSON
02/08/2013

**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: December 7, 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 Strengths: (b) (4) (Dabrafenib) Capsules
50 mg and 75 mg

Application Type/Number: NDA 202806

Applicant: GlaxoSmithKline

OSE RCM #: 2012-1787

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

Contents

1	Introduction.....	1
1.1	Product Information.....	1
2	Methods and Materials Reviewed.....	1
3	Results.....	1
4	Recommendations.....	2
	Appendices.....	5
	Appendix A: Container Labels.....	5

1 INTRODUCTION

This review evaluates the proposed container labels and insert labeling for (b) (4) NDA 202806, for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the July 29, 2012 proprietary name submission.

- Established Name: Dabrafenib
- Indication of Use: Treatment of patients with BRAF V600 mutation positive unresectable or metastatic melanoma.
- Route of Administration: Oral
- Dosage Form: Capsules
- Strength: 50 mg and 75 mg
- Dose: Normal starting dose - 150 mg twice daily.
Dose adjustments based on toxicity - 100 mg, 75 mg, and 50 mg twice daily.
- How Supplied: 120 count bottles for both strengths
- Storage: Store at 25°C. Excursions permitted between 15°C to 30°C.
- Container and Closure Systems: Round, white, opaque HDPE bottles packed with silica gel desiccant, and closed with (b) (4) with a (b) (4) induction heat seal liner.

2 METHODS AND MATERIALS REVIEWED

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 Labels submitted on July 29, 2012 (Appendix A)
- Insert Labeling submitted July 29, 2012

3 RESULTS

The proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. DMEPA notes the statement “120 capsules” on the bottle labels should be moved to the bottom of the principal display panel to prevent confusion with the strength. Also,

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

DMEPA recommends changing the label color used to express the 50 mg strength. This will minimize confusion with the brand name, established name, and dosage form on the 75 mg label. For the package insert, DMEPA recommends revising or adding statements that include taking the medication on an empty stomach. Lastly, DMEPA notes that additional statements in the Patient Counseling Information, Section 17, should be added to make the section more comprehensive.

4 RECOMMENDATIONS

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

4.1 COMMENTS TO THE DIVISION

A. General Comment to the Division

1. Consideration should be given to including statements in the label and labeling to help prevent accidental exposure from opening the capsule if the product exposure toxicity profile warrants.

B. Insert Labeling

1. Highlights of Prescribing Information – Dosage and Administration

- a. Revise the statement [REDACTED] (b) (4)
to read [REDACTED] (b) (4)

2. Dosage and Administration, Section 2

- a. Revise the statement [REDACTED] (b) (4)
to read [REDACTED] (b) (4)

- b. Revise the statement [REDACTED] (b) (4)
to read [REDACTED] (b) (4)
Also, relocate the revised statement immediately after the following statement: [REDACTED] (b) (4)

3. Patient Counseling Information, Section 17

- a. Add the following statements:
 - “Females who are able to become pregnant should use birth control during treatment and for 4 weeks after stopping [REDACTED] (b) (4).”
 - “Birth control using hormones (such as the pill, injections, or patches) may not work as well while patients are taking [REDACTED] (b) (4). [REDACTED] (b) (4).”
 - [REDACTED] (b) (4)

(b) (4)

4. Patient Information Leaflet– How should I take (b) (4)?
- a. Revise the statement (b) (4) to read (b) (4)
- b. Revise the statement (b) (4) to (b) (4)

4.2 COMMENTS TO THE APPLICANT

A. Container Labels

1. Relocate "120 Capsules" further to the bottom of the principal display panel and unbold the statement. Additionally, relocate the product strength to just under "(dabrafenib) Capsules". 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.
2. Relocate "Rx only" statement further to the bottom of the principal display panel and unbold.
3. Capitalize the letter 'd' in the established name that is immediately below the proprietary name on the principal display panel.
4. Choose a color (b) (4) to express the strength on the 50 mg label since the color blue is used to express the brand name, established name and dosage form on both labels. When selecting a new color to express the 50 mg strength, ensure that the color is not a color used on the 75 mg label.
5. Include a space between "50" and "mg" on the principal display panel so the strength presentation is easier to read. Do the same for the 75 mg label.
6. Ensure the established name is at least ½ the size of the proprietary name and has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printer features per 21 CFR 201.10(g)(2).

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

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/s/

JAMES H SCHLICK
12/07/2012

TODD D BRIDGES
12/07/2012

CAROL A HOLQUIST
12/07/2012

RPM FILING REVIEW
Including Memo of Filing Meeting and Filing Meeting Minutes

Application Information		
NDA # 202806	NDA Supplement #: S- Not Applicable	Efficacy Supplement Type SE- Not Applicable
Proprietary Name: (b) (4) Established/Proper Name: dabrafenib Dosage Form: Capsules Strengths: 50 mg and 75 mg		
Applicant: GlaxoSmithKline Agent for Applicant (if applicable): Not Applicable		
Date of Application: July 29, 2012 Date of Receipt: July 30, 2012 Date clock started after UN: Not Applicable		
PDUFA Goal Date: May 30, 2013	Action Goal Date (if different):	
Filing Date: September 28, 2012	Date of Filing Meeting: August 31, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1		
Proposed indication(s)/Proposed change(s): For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>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.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>): Not Applicable				
List referenced IND Number(s): IND 105032				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	Yes			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>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.</i>	Yes			
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)? <i>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</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	Yes			Changed from 'priority' to standard per decision in Team Meeting 1 of 9.18.2012. Sponsor withdrew their priority designation request on 9.28.2012.
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		No		
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?	Yes			

<p><u>User Fee Status</u></p> <p><i>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.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>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.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>NA</p>																	
<p>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)].</p>			<p>NA</p>																	
<p>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)]?</p> <p><i>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 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>NA</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1449 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>NA</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>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.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>No</p>																		

<p>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)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			NA	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	Yes			5-year New Chemical Entity Exclusivity
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		No		
<p>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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			NA	

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

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			NA	
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			NA	
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 			NA	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			NA	Information is included, however this application does not fall under PDUFA V.
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			NA	Information is included, however this application does not fall under PDUFA V.
Forms and Certifications				
<i>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.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	Yes			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	Yes			
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)?	Yes			
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	Yes			

(3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	Yes			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>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..."</i>	Yes			
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? <i>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)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			NA	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			NA	

Pediatrics	YES	NO	NA	Comment
<p>PREA</p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>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.</i></p>	No			Orphan Drug Exclusivity issued January 12, 2011
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			NA	
<p>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?</p> <p><i>If no, request in 74-day letter</i></p>			NA	
<p>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)?</p> <p><i>If no, request in 74-day letter</i></p>			NA	
<p>BPCA (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>		No		
Proprietary Name	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	Yes			
REMS	YES	NO	NA	Comment
<p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>		No		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	Yes			
Is the PI submitted in PLR format? ⁴	Yes			
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? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			NA	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	Yes			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	Yes			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	Yes			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
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 study report to QT Interdisciplinary Review Team)	Yes			CDRH – 7.30.2012; QT-IRT – 8.3.2012
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		No		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 5/9/2012	Yes			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		No		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 31, 2012

BLA/NDA/Supp #: NDA 202806

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: dabrafenib

DOSAGE FORM/STRENGTH: Capsules / 50 mg and 75 mg

APPLICANT: GlaxoSmithKline

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation

BACKGROUND: New NME NDA submission.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Norma Griffin	Yes
	CPMS/TL:	Karen Jones	No
Cross-Discipline Team Leader (CDTL)	Suzanne Demko		Yes
Clinical	Reviewer:	Marc Theoret	Yes
	TL:	Suzanne Demko	Yes
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	NA	NA
	TL:	NA	NA
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	NA	NA
	TL:	NA	NA
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	NA	NA
	TL:	NA	NA

Clinical Pharmacology	Reviewer:	Jian Wang	Yes
	TL:	Hong Zhao	Yes
Biostatistics	Reviewer:	Vivian Yuan	Yes
	TL:	Kun He	Yes
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Alexander Putman	Yes
	TL:	Whitney Helms	Yes
Statistics (carcinogenicity)	Reviewer:	NA	NA
	TL:	NA	NA
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	NA	NA
	TL:	NA	NA
Product Quality (CMC)	Reviewer:	Amit Mitra and Gaetan Ladouceru	Yes
	TL:	Liang Zhou	Yes
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Bryan Riley	No
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Mahesh Ramanadham	Yes
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	James Schlick	No
	TL:		
OSE/DRISK (REMS)	Reviewer:	Cynthia LaCivita	No
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NA	NA
	TL:	NA	NA

Bioresearch Monitoring (OSI)	Reviewer:	Jean Mulinde	Yes
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	NA	NA
	TL:	NA	NA
Other reviewers	Rosane Charlab-Orbach, Genomics Debasis Ghosh, QbD Liason Akm Khairuzzaman, Biopharmaceutics Jeff Summers, DOP2 Dep. Dir of Safety Cathryn Lee, DOP 2 Safety RPM Sue Kang, OSE RPM Derek Smith, OC (facilities) Donna Roscoe, CDRH Consultant Amarylis Vega, DRISK		Yes
Other attendees	Jewell Martin, ONDQA RPM		Yes

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>Comments:</p> <ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? 	<input type="checkbox"/> YES

<p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <p><input checked="" type="checkbox"/> this drug/biologic is not the first in its class</p> <ul style="list-style-type: none"> <input type="checkbox"/> <i>the clinical study design was acceptable</i> <input type="checkbox"/> <i>the application did not raise significant safety or efficacy issues</i> <input type="checkbox"/> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p>Date if known:</p> <p><input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> To be determined</p> <p>Reason:</p>
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • 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? <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p>BIOSTATISTICS</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Richard Pazdur, M.D.	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): Originally scheduled for October 30, 2012 and later re-scheduled to December 7, 2012, based on Sponsor’s request to withdraw ‘priority review’.	
Comments - The Review Team discussed the following during the Filing Meeting:	
<ol style="list-style-type: none"> 1. The review team agreed to review this submission as a standard review. 2. A mid-cycle meeting was scheduled for October 30, 2012 (based on a 6-month review clock). Mid-cycle slides are due to CDTL by October 22, 2012 3. Standing monthly meetings were set up from September 2012 – January 2013. 4. Labeling meetings are to be scheduled. 5. Clinical sites have been selected for inspections, inspections are being scheduled. 6. Facility manufacturing site inspections are being scheduled. 7. Possible PMRs: disciplines will determine and may go in the 74-day letter. 8. Disciplines determined application is fileable, however Division Director and CDTL requested that all deficiencies be identified and included in the 74-day letter. 	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

ACTIONS ITEMS	
<input checked="" type="checkbox"/>	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).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	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.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • 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)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	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]
<input type="checkbox"/>	Other

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

/s/

NORMA S GRIFFIN
10/02/2012

MONICA L HUGHES
10/02/2012

10/2/2012

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 202806

Application Type: New NDA

Name of Drug: (b) (4) (dabrafenib) Capsules; 50 mg and 75 mg

Applicant: GlaxoSmithKline

Submission Date: July 30, 2012

Receipt Date: July 30, 2012

This version was
done as part of filing
review.

1.0 Regulatory History and Applicant's Main Proposal

This is a new NME 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. See the following:

1. White space must be present before each major heading in Highlights.
2. In general in the Full Prescribing Information, there needs to be white space between Sections, subsections, and paragraph text.
3. In general in the Full Prescribing Information, the left margin of wrapped text should align with the first indented line of the paragraph.
4. Consistency in font (?)

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by October 29, 2012. The resubmitted PI will be used for further labeling review.

5.0 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 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:

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

Comment:

- NO** 4. White space must be present before each major heading in HL.

Comment: Will note this as a comment in 74-day letter

- 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:

Selected Requirements of Prescribing Information (SRPI)

- S 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:

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

Comment:

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:

Highlights Limitation Statement

- YES 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:

Product Title

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

Comment:

Initial U.S. Approval

- N/A 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: *Not yet approved and sponsor indicated '0000'.*

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

12. All text must be **bolded**.

Comment:

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:

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

Comment:

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:

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

Comment:

Recent Major Changes (RMC)

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:

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

Comment:

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:

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:

Indications and Usage

YES 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)].”

Comment:

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

- YES 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: *Does not have multiple dosage forms.*

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:

- N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

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:

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:

Revision Date

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

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

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

Comment:

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

Comment:

YES

Selected Requirements of Prescribing Information (SRPI)

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:
- 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:
- YES 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- 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:

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:
- YES 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES 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
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

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:

- YES** 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:**
- 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:**
- YES** 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:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.
- Comment:**
- 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** 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:

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Selected Requirements of Prescribing Information (SRPI)

Comment:

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:

- 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

- YES** 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:
