DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202806

NDA APPROVAL

GlaxoSmithKline, LLC
Attention: Ellen Cutler
Senior Director, Regulatory Affairs, Oncology
1250 South Collegeville Road
Collegeville, PA 19426

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) dated July 29, 2012, received July 30, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tafinlar (dabrafenib) capsules, 50 mg and 75 mg.

We acknowledge receipt of your amendments dated June 21, 2012, June 29, 2012, July 13, 2012, August 15, 2012, August 17, 2012 (2), August 23, 2012, August 30, 2012, September 6, 2012, September 17, 2012, September 18, 2012 (3), September 24, 2012 (2), September 27, 2012, October 24, 2012, October 31, 2012, November 5, 2012, November 6, 2012, November 14, 2012, November 21, 2012, November 27, 2012 (2), November 30, 2012, December 12, 2012, December 14, 2012, December 18, 2012 (2), December 21, 2012, January 9, 2013 (2), January 11, 2013, January 14, 2013, January 15, 2013, January 23, 2013, January 24, 2013, January 25, 2013, January 30, 2013, February 4, 2013, February 5, 2013, February 6, 2013, March 8, 2013, March 11, 2013, March 12, 2013, March 14, 2013, March 15, 2013, March 19, 2013, March 21, 2013, March 27, 2013, March 29, 2013, April 2, 2013 (2), April 3, 2013, April 4, 2013, April 5, 2013 (2), April 18, 2013 (2), April 22, 2013, April 23, 2013, April 26, 2013, April 30, 2013 (2), May 1, 2013 (2), May 9, 2013 (3), May 17, 2013, May 23, 2013, and May 29, 2013.

This new drug application provides for the use of Tafinlar (dabrafenib) capsules for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. This approval includes the following limitation of use: Taflinar is not indicated for the treatment of patients with wild-type BRAF melanoma.

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

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the enclosed carton and immediate-container labels submitted on March 27, 2013, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 202806**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

CHEMISTRY, CONTROLS AND MANUFACTURING

A 24-month expiration dating period is granted for the 50 mg and 75 mg capsules is granted when stored at 15° to 30°C (59°F to 86°F).

ADVISORY COMMITTEE

Your application for dabrafenib was not referred to an FDA advisory committee because this is not the first drug in its class (BRAF inhibitor), there were no issues related to the clinical trial design or primary endpoint used, and there were no novel issues identified that would benefit from the Advisory Committee's expertise.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of longer duration exposure to Tafinlar (dabrafenib) capsules and prolongation of the QT/QTc interval with Tafinlar (dabrafenib) capsules, and to assess signals of a serious risk of secondary malignancies with Tafinlar (dabrafenib) capsules, cardiac valve abnormalities with Tafinlar (dabrafenib) capsules, impaired hepatic function on the pharmacokinetics of Tafinlar (dabrafenib) capsules, impaired renal function on the pharmacokinetics of Tafinlar (dabrafenib) capsules, and drug-drug interactions of Tafinlar (dabrafenib) capsules with substrates of CYP3A4, CYP2C8, and CYP2C9.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2044-1 **Longer Duration Exposure Toxicity**

Submit the final analyses of safety from all ongoing randomized controlled clinical trial(s) using the (b) (4) formulation of Tafinlar (dabrafenib) capsules as monotherapy to identify and characterize unexpected serious risks from longer duration of exposure.

The timetable you submitted on May 1, 2013, states that you will conduct this trial according to the following schedule:

Final Report Submission: December 2014

2044-2 **Secondary Malignancies**

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 Tafinlar (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 Tafinlar (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

The timetable you submitted on May 1, 2013, states that you will conduct this trial according to the following schedule:

Final Analysis Plan Submission:	June 2013
Interim Report Submission:	October 2013
Interim Report Submission:	October 2014
Interim Report Submission:	October 2015
Interim Report Submission:	October 2016
Interim Report Submission:	October 2017
Interim Report Submission:	October 2018
Interim Report Submission:	October 2019
Final Report Submission:	October 2020

2044-3 **Cardiac Valve Abnormalities**

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.

Submit the first interim report within six months of approval of NDA 202806 and every two years thereafter until the final report submission in 2020.
The timetable you submitted on May 1, 2013, states that you will conduct this trial according to the following schedule:

Final Analysis Plan Submission:	June 2013
Interim Report Submission:	November 2014
Interim Report Submission:	November 2016
Interim Report Submission:	November 2018
Final Report Submission:	November 2020

2044-4 **QT/QTc Interval Prolongation**

Complete a clinical trial evaluating the potential for Tafinlar (dabrafenib) capsules 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 to include central tendency, categorical and concentration-QT analyses, along with a thorough review of cardiac safety data.

The timetable you submitted on April 4, 2013, states that you will conduct this trial according to the following schedule:

Final Report Submission: December 2015

2044-5 **Hepatic Impairment Pharmacokinetic Trial**

Complete a clinical pharmacokinetic trial to determine the appropriate Tafinlar (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*".

The timetable you submitted on April 4, 2013, states that you will conduct this trial according to the following schedule:

Final Report Submission: June 2015

2044-6 **Renal Impairment Pharmacokinetic Trial**

Complete a clinical pharmacokinetic trial to determine the appropriate Tafinlar (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"*.

The timetable you submitted on April 4, 2013, states that you will conduct this trial according to the following schedule:

Final Report Submission: June 2015

2044-7 **Drug-Drug Interaction Trial**

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 Tafinlar (dabrafenib) capsules with regard to concomitant strong CYP3A4 and CYP2C8 inducers.

The timetable you submitted on April 4, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: June 2013
Final Report Submission: June 2015

2044-8 **Drug-Drug Interaction Trial**

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 Tafinlar (dabrafenib) capsules with regard to concomitant strong CYP3A4 inhibitors.

The timetable you submitted on April 4, 2013, states that you will conduct this trial according to the following schedule:

Final Report Submission: May 2013

2044-9 **Drug-Drug Interaction Trial**

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 Tafinlar (dabrafenib) capsules with regard to concomitant strong CYP2C8 inhibitors.

The timetable you submitted on April 4, 2013, states that you will conduct this trial according to the following schedule:

Final Report Submission: May 2013

2044-10 **Drug-Drug Interaction Trial**

Complete a clinical trial evaluating the effects of repeat doses of Tafinlar (dabrafenib) capsules 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 Tafinlar (dabrafenib) capsules with regard to concomitant sensitive CYP2C9 substrates and CYP2C9 substrates with a narrow therapeutic window.

The timetable you submitted on April 4, 2013, states that you will conduct this trial according to the following schedule:

Final Report Submission: May 2013

Submit the protocol(s) to your IND 105032, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to

report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2044-11 **Drug-Drug Interaction Trial**

Conduct a clinical trial to evaluate if proton pump inhibitors, H2 antagonists and antacids alter the bioavailability of Tafinlar (dabrafenib) capsules. The worst case scenario can be assessed first to determine if further trials of other gastric pH elevating agents are necessary. The trial results should allow for a determination on how to dose Tafinlar (dabrafenib) capsules with regard to concomitant gastric pH elevating agents.

The timetable you submitted on March 29, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: June 2013
Final Report Submission: December 2016

Submit clinical protocols to your IND 105032 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

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

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application within two weeks of receipt of this communication.

If you have any questions, call Norma Griffin, Regulatory Health Project Manager, at (301) 796-4255.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Container Labeling

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

/s/

RICHARD PAZDUR
05/29/2013