DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204114

NDA APPROVAL

GlaxoSmithKline, LLC
Attention: Eric Richards, M.S., M.P.H.
Director, Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA 19426

Dear Mr. Richards:

Please refer to your New Drug Application (NDA) dated August 2, 2012, received August 3, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mekinist (trametinib) tablets, 0.5 mg, 1 mg, 2 mg.

We acknowledge receipt of your amendments dated July 2, 2012; July 13, 2012; August 7, 2012; August 15, 2012; August 16, 2012; August 17, 2012; August 21, 2012; August 29, 2012; August 31, 2012; September 17, 2012; September 18, 2012; September 21, 2012; September 24, 2012; September 25, 2012;September 27, 2012; September 28, 2012 (2); October 11, 2012; October 26, 2012 (2); October 29, 2012; November 2, 2012; November 6, 2012; November 7, 2012; November 21, 2012 (2), November 28, 2012; November 29, 2012; December 7, 2012; December 14, 2012; January 3, 2013; January 16, 2013 (2); February 6, 2013; February 13, 2013; February 22, 2013; February 27, 2013; February 28, 2013; March 4, 2013; March 5, 2013; March 6, 2013; March 11, 2013; March 12, 2013; March 15, 2013; March 18, 2013; March 20, 2013; March 26, 2013; March 28, 2013 (2); March 29, 2013 (2); April 3, 2013; April 4, 2013; April 5, 2013; April 9, 2013; April 12, 2013; April 22, 2013 (2); May 7, 2013; May 16, 2013, May 22, 2013, May 23, 2013, May 24, 2013, May 28, 2013, and May 29, 2013.

This new drug application provides for the use of trametinib tablets for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. This approval includes the following limitation of use: Mekinist is not indicated for the treatment of patients who have received prior BRAF inhibitor therapy.

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.

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 text for the patient package insert). 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 immediate-container labels submitted on May 7, 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 204114**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) 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 12-month expiration dating period is granted for the 0.5 mg and 2 mg tablets and a 9-month expiration dating period is granted for the 1 mg tablets when stored at 2° to 8°C (36°F to 46°F) and protected from moisture and light.

We acknowledge your commitment provided in the submission dated April 12, 2013 to place all future commercial batches on stability to provide concurrent monitoring at 5°C and to notify FDA of any changes to this protocol. Please note that a prior approval supplement will need to be submitted to revise this commitment. Refer to "Guidance for Industry, Changes to an Approved NDA or ANDA, April 2004."

ADVISORY COMMITTEE

Your application for trametinib was not referred to an FDA advisory committee because the safety profile is acceptable for the indication of metastatic or unresectable melanoma, the clinical study design for the major efficacy trial is acceptable and similar to that used for previously approved products for this indication, the application did not raise significant public health questions on the role of trametinib in the treatment of metastatic melanoma, and outside expertise was not necessary as there were no controversial issues that would benefit from advisory committee discussion.

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 assess an unexpected serious risks of prolongation of the QT/QTc interval with Mekinist (trametinib) tablets, and to assess signals of a serious risk of impaired hepatic function on the pharmacokinetics of Mekinist (trametinib) tablets, ocular toxicity with Mekinist (trametinib) tablets, and cardiomyopathy with Mekinist (trametinib) tablets.

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:

2045-1 **Cardiomyopathy**

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 cardiomyopathy and subsequent sequelae, including safety evaluations adequate to inform labeling of patient populations at highest risk for developing these toxicities and to provide evidence-based dose modification and monitoring recommendations, in all ongoing and subsequently initiated randomized controlled clinical trials through 2020 that use Mekinist (trametinib) alone or in combination with other anti-cancer drugs.

The timetable you submitted on May 22, 2013, states that you will conduct this trial according to the following schedule:

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

2045-2 **Ocular Toxicity**

Submit integrated safety analyses from an adequate number of randomized controlled clinical trial(s) using Mekinist (trametinib) to identify and characterize the risk of retinal pigmented epithelial detachments (RPED), including safety evaluations adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modification and monitoring recommendations in labeling of RPED events.

The timetable you submitted on May 22, 2013, states that you will conduct this trial according to the following schedule:

Final Analysis Plan Submission:	September 2013
Interim Report Submission	September 2014
Final Report Submission:	September 2016

2045-3 **Hepatic Impairment Pharmacokinetic Trial**

Conduct a pharmacokinetic trial to determine the appropriate dose of Mekinist (trametinib) in patients with 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 February 28, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: September 2013
Final Report Submission: December 2015

2045-4 **QT/QTc Interval Prolongation**

Complete a clinical trial to evaluate the potential for Mekinist (trametinib) to prolong the QT/QTc interval in an adequate number of patients administered repeat doses of Mekinist (trametinib) 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.

The timetable you submitted on February 28, 2013, states that you will conduct this trial according to the following schedule:

Final Report Submission: April 2015

Submit the protocol(s) to your IND 102175, 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.

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.

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