DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204114/S-001

ACCELERATED APPROVAL

GlaxoSmithKline, LLC
Attention: Eric Richards, M.S., M.P.H.
Director, Global Regulatory Affairs
1250 South Collegeville Road; UP4400
Collegeville, PA 19426

Dear Mr. Richards:

Please refer to your Supplemental New Drug Application (sNDA) dated July 8, 2013, received July 8, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mekinist (trametinib) tablets, 0.5 mg, 1 mg, and 2 mg.

We acknowledge receipt of your amendment(s) dated October 14, 2013, October 18, 2013, December 13, 2013 (2), January 7, 2014, and January 8, 2014.

This Prior Approval supplemental new drug application proposes to include a new indication for Mekinist (trametinib), in combination with dabrafenib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. This indication is based on the demonstration of durable response rate. Improvement in disease-related symptoms or overall survival has not been demonstrated for MEKINIST in combination with dabrafenib.

APPROVAL & LABELING

We have completed our review of this supplemental 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

Please note that we have previously granted a waiver of 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 text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes, and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If the postmarketing trial described below fails to verify clinical benefit for Mekinist (trametinib) tablets, 0.5 mg, 1 mg, and 2 mg, or is not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval.

Granting of this approval is contingent upon completion of a clinical trial to verify the clinical benefit of Mekinist (trametinib) tablets, 0.5 mg, 1 mg, and 2 mg. This postmarketing trial is subject to the reporting requirements of 21 CFR 314.81.

2117-1 To submit an efficacy supplement containing the final report, including summary analyses, datasets, and revised labeling based on the results of the ongoing MEK115306 trial, "A Phase III, Randomized, Double-Blinded Study, Comparing the Combination of the BRAF inhibitor, Dabrafenib and the MEK inhibitor, Trametinib to Dabrafenib and Placebo as First-Line Therapy in Subjects with unresectable (Stage IIIC) or Metastatic (Stage IV) BRAF V600E/K Mutation-Positive Cutaneous Melanoma." Enrollment of approximately 340 patients is expected. The primary endpoint is progression-free survival. Overall survival is a key secondary endpoint.

The timetable you submitted on December 13, 2013, states that you will conduct this trial according to the following schedule:

Final Report Submission: August, 31, 2014

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

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 COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2117-2 Complete and submit the final report, including datasets, for the ongoing MEK116513 trial, "A Phase III, Randomised, Open-Label Study Comparing the Combination of the BRAF Inhibitor Dabrafenib and the MEK Inhibitor Trametinib to the BRAF Inhibitor Vemurafenib in Subjects with Unresectable (Stage IIIC) or Metastatic (Stage IV) BRAF V600E/K Mutation-Positive Cutaneous Melanoma." Enrollment of approximately 694 patients is expected. The primary endpoint is overall survival.

The timetable you submitted on December 13, 2013, states that you will conduct this trial according to the following schedule:

Final Report Submission: June, 30, 2015

2117-3 Complete and submit a final report, including datasets, for Part C of trial BRF113220 that compares the combination of dabrafenib and trametinib to dabrafenib in patients with unresectable or metastatic BRAF V600E or V600K mutation-positive melanoma.

The timetable you submitted on December 13, 2013, states that you will conduct this trial according to the following schedule:

Final Report Submission: October, 31, 2014

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

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

REPORTING REQUIREMENTS

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

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S): Content of Labeling

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

/s/

PATRICIA KEEGAN
01/08/2014