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RESEARCH**

APPLICATION NUMBER:

203094Orig1s000

203094Orig2s000

OTHER ACTION LETTERS



NDA 203094/Original 1

COMPLETE RESPONSE

Gilead Sciences, Inc.
Attention: Naomi Kautz, MSc
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Kautz:

Please refer to your New Drug Application (NDA) dated June 26, 2012, received June 28, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tybost™ (cobicistat) tablet, 150 mg.

We acknowledge receipt of your amendments dated:

June 28, 2012	July 9, 2012	August 21, 2012	September 7, 2012
September 10, 2012	September 11, 2012	October 2, 2012	October 5, 2012
October 19, 2012	October 26, 2012	November 27, 2012	December 4, 2012
December 19, 2012	December 20, 2012	January 21, 2013	January 22, 2013
January 29, 2013	January 31, 2013	February 11, 2013 (2)	February 22, 2013
February 25, 2013	March 4, 2013	March 8, 2013	March 21, 2013
April 9, 2013	April 16, 2013	April 17, 2013	April 23, 2013

We also acknowledge receipt of information related to cobicistat 150 mg tablets for the Gilead Access Program that was included in this application.

NDA 203094 provides for the use of Tybost™ (cobicistat) tablet, 150 mg, for the following indications which, for administrative purposes, we have designated as follows:

- NDA 203094/Original 1 – cobicistat is a CYP3A inhibitor indicated to increase systemic exposure of atazanavir in the treatment of HIV-1 infection in adults.
- NDA 203094/Original 2 – cobicistat is a CYP3A inhibitor indicated to increase systemic exposure of darunavir in the treatment of HIV-1 infection in adults.

The subject of this action letter is NDA 203094/Original 1. A separate action letter will be issued for NDA 203094/Original 2.

All future submissions to NDA 203094/Original 1 should specify the NDA number and the Original number to which each submission pertains.

We have completed our review of NDA 203094/Original 1, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

1. During the current inspection of the Gilead Sciences, (Foster City, CA) facility for this application, FDA field investigators found significant deficiencies and discussed them with firm management. Firm management acknowledged these deficiencies in a letter dated April 23, 2013. Satisfactory resolution of significant deficiencies is required before this application may be approved.

PRODUCT QUALITY

Release and Stability Testing

2. During the Gilead Foster City inspection, FDA field investigators found significant concerns regarding the release and stability data presented in the NDA and in DMF 25188 because of lack of method validation of the test methods used to obtain this data. Before the application can be approved, the integrity of the drug substance and drug product release and stability data need to be assured by submission of a detailed explanation to reconcile the analytical methods submitted in the NDA and the DMF with those used at the Foster City site.

We recommend you submit a proposal outlining how you plan to resolve these deficiencies in a meeting package in preparation for NDA resubmission.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
 7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before NDA 203094/Original 1 may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed for this indication until you have been notified in writing that NDA 203094/Original 1 is approved.

If you have any questions, call Abiola Olagundoye-Alawode, Pharm.D., Regulatory Project Manager, at (301) 796-3982 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

DEBRA B BIRNKRANT
04/26/2013



NDA 203094/Original 2

COMPLETE RESPONSE

Gilead Sciences, Inc.
Attention: Naomi Kautz, MSc
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Kautz:

Please refer to your New Drug Application (NDA) dated June 26, 2012, received June 28, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tybost™ (cobicistat) tablet, 150 mg.

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- NDA 203094/Original 2 – cobicistat is a CYP3A inhibitor indicated to increase systemic exposure of darunavir in the treatment of HIV-1 infection in adults.

The subject of this action letter is NDA 203094/Original 2. A separate action letter will be issued for NDA 203094/Original 1.

All future submissions to NDA 203094/Original 2 should specify the NDA number and the Original number to which each submission pertains.

We have completed our review of NDA 203094/Original 2, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL PHARMACOLOGY

1. During a recent inspection of the [REDACTED] (b) (4) bioanalytical laboratories for this application, our field investigators conveyed form 483 observations to the representatives of the facilities. The form 483 observations that require the submission of additional information have previously been communicated. Satisfactory resolution of these form 483 observations is required before this application may be approved.

FACILITY INSPECTIONS

2. During the current inspection of the Gilead Sciences, (Foster City, CA) facility for this application, FDA field investigators found significant deficiencies and discussed them with firm management. Firm management acknowledged these deficiencies in a letter dated April 23, 2013. Satisfactory resolution of significant deficiencies is required before this application may be approved.

PRODUCT QUALITY

Release and Stability Testing

3. During the Gilead Foster City inspection, FDA field investigators found significant concerns regarding the release and stability data presented in the NDA and in DMF 25188 because of lack of method validation of the test methods used to obtain this data. Before the application can be approved, the integrity of the drug substance and drug product release and stability data need to be assured by submission of a detailed explanation to reconcile the analytical methods submitted in the NDA and the DMF with those used at the Foster City site.

We recommend you submit a proposal outlining how you plan to resolve these deficiencies in a meeting package in preparation for NDA resubmission.

LABELING

4. We reserve comment on the proposed labeling until NDA 203094/Original 2 is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

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8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before NDA 203094/Original 2 may be approved. If you

wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed for this indication until you have been notified in writing that NDA 203094/Original 2 is approved.

If you have any questions, call Abiola Olagundoye-Alawode, Pharm.D., Regulatory Project Manager, at (301) 796-3982 or (301) 796-1500.

Sincerely,

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Debra Birnkrant, M.D.
Director
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