CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203100Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203100

NDA APPROVAL

Gilead Sciences, Inc.
Attention: Christophe Beraud, Ph.D.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Beraud:

Please refer to your New Drug Application (NDA) dated October 26, 2011, received October 27, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Stribild™ (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) fixed dose combination tablets 150 mg/150 mg/200 mg/300 mg.

We acknowledge receipt of your amendments dated

October 26, 2011	January 31, 2012	April 11, 2012	July 2, 2012
October 27, 2011	February 3, 2012	April 11, 2012	July 3, 2012
November 16, 2011	February 9, 2012	April 20, 2012	July 12, 2012
November 21, 2011	February 15, 2012	April 27, 2012	July 18, 2012
November 28, 2011	March 6, 2012	April 27, 2012	July 25, 2012
December 9, 2011	March 9, 2012	May 18, 2012	July 26, 2012
December 13, 2011	March 21, 2012	May 21, 2012	August 1, 2012
December 14, 2011	March 28, 2012	May 23, 2012	August 14, 2012
December 23, 2011	March 29, 2012	May 30, 2012	August 15, 2012
January 10, 2012	March 30, 2012	May 31, 2012	August 17, 2012
January 20, 2012	March 30, 2012	June 1, 2012	August 20, 2012
January 20, 2012	April 2, 2012	June 13, 2012	August 21, 2012
January 21, 2012	April 3, 2012	June 20, 2912	August 24, 2012
January 27, 2012	April 9, 2012	June 27, 2012	

We also acknowledge receipt of information related to Stribild™ (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) fixed dose combination tablets 150 mg/150 mg/200 mg/300 mg for your Gilead Access Program that was included in this application.

This new drug application provides for the use of Stribild™ (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) fixed dose combination tablets 150 mg/150 mg/200

mg/300 mg as a complete regimen for the treatment of HIV-1 infection in treatment-naïve adult patients.

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.

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 package insert and text for the patient package insert). 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed container label that is identical to the enclosed immediate container label, as soon as it is available, but no more than 30 days after it is printed. Please submit the label electronically according to the guidance for industry titled "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 203100**." 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.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Stacey Min, Pharm.D.
Food and Drug Administration

Center for Drug Evaluation and Research
White Oak Building 22, Room: 6315
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

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.

We are waiving the pediatric study requirement for newborn infants to children less than 6 years of age because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group. In addition, achieving the likely needed dose adjustments of the individual components within a single tablet regimen for this age group is not feasible.

We are deferring submission of your pediatric study for ages 6 to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. The required studies are listed below.

1919-1 Conduct a pediatric pharmacokinetic, safety, and antiviral activity trial of Stribild with activity based on the results of HIV-1 RNA virologic response and safety monitoring over at least 48 weeks of dosing in pediatric subjects from 12 to < 18 years of age. Include in the trial safety monitoring assessment of potential renal toxicity (to include serial assessments of serum creatinine, serum phosphate, urine glucose, urine protein, calculated creatinine clearance, glomerular filtration rate (GFR) by cystatin C, and calculated fractional excretion of phosphate) and effects on bone (to include serial DEXA assessment).

Final Protocol Submission:	September 2012
Trial Completion:	March 2016
Final Report Submission:	November 2016

1919-2 Conduct a pediatric pharmacokinetic, safety, and antiviral activity trial of Stribild with activity based on the results of HIV-1 RNA virologic response and safety

monitoring over at least 48 weeks of dosing in pediatric subjects from 6 to < 12 years of age. Dose selection must be based on pharmacokinetic data for component drugs and must be discussed with FDA prior to initiation of trial. Include in the trial safety monitoring assessment of potential renal toxicity (serial assessments of serum creatinine, serum phosphate, urine glucose, urine protein, calculated creatinine clearance, glomerular filtration rate (GFR) by cystatin C, and calculated fractional excretion of phosphate) and effects on bone (to include serial DEXA assessment).

Final Protocol Submission:	April 2016
Trial Completion:	September 2018
Final Report Submission:	December 2018

Submit the protocols to your IND 103093, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the 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 a signal of an increase in the serious risk of renal proximal tubulopathy when tenofovir is given in combination with cobicistat relative to tenofovir without cobicistat. Additional *in vitro* studies of drug transporters are required to elucidate the mechanism of the observed renal toxicity. Also, because cobicistat is structurally similar to the HIV-1 protease inhibitor ritonavir, additional information is required to monitor for and characterize the emergence of protease inhibitor-associated substitutions following treatment failures.

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 this serious risk.

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

1919-3 Evaluate inhibition by the components of Stribild of the hepatic transporters OATP1B1, OATP1B3, OCT1, and BSEP and evaluate transport of the hepatically eliminated components of Stribild (EVG and COBI) by the hepatic transporters

OATP1B1, OATP1B3, and OCT1.

The timetable you submitted on August 14, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	September 2012
Study Completion:	November 2012
Final Report Submission:	December 2012

1919-4 Evaluate inhibition by the components of Stribild of the renal transporters OCT2, MATE1, OAT1, OAT3, MRP2 and MRP4 and evaluate transport of the renally eliminated components of Stribild (FTC and TFV) by renal transporters OCT2, OAT1, OAT3 and MRP2.

The timetable you submitted on August 14, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	September 2012
Study Completion:	November 2012
Final Report Submission:	December 2012

1919-5 Evaluate whether components of Stribild are transported by or inhibit Pgp and Breast Cancer Resistance Protein (BCRP).

The timetable you submitted on August 14, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	September 2012
Study Completion:	November 2012
Final Report Submission:	December 2012

1919-6 Assess possible cobicistat protease inhibitory activity *in vivo* by sequencing the protease in virologic failure subjects' isolates from Studies GS-US-236-0102, GS-US-236-0103, GS-US-236-0121, GS-US-236-0123 and GS-US-236-0128.

The timetable you submitted on August 14, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	December 2012
Study Completion:	October 2016
Final Report Submission:	February 2017

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of an increase in the serious risk of renal proximal tubulopathy when tenofovir, in combination with cobicistat, is administered to women, relative

to men, and to assess the potential for unexpected serious risks of drug interactions with certain important medications used by the intended patient population.

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

1919-7 Perform a clinical trial to better characterize the incidence of and risk factors for renal adverse events in women. Provide adequate renal monitoring in the proposed trial to assess renal safety employing a renal monitoring algorithm similar to that used in GS-US-236-0102 and GS-US-236-0103. The algorithm will include an assessment of serum creatinine, creatinine clearance by Cockcroft-Gault, glomerular filtration rate (GFR) by cystatin C, serum phosphate, renal phosphate threshold (TmP/GFR), urine protein and urine glucose. The trial will enroll approximately 500 women, in order to assess the relative incidence of and risk factors for renal adverse events in women as compared to men enrolled in other Stribild clinical trials.

The timetable you submitted on August 14, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	October 2012
Trial Completion:	July 2016
Final Report Submission:	November 2016

1919-8 Conduct a pharmacokinetic (PK) sub-trial of the renal safety trial in women to evaluate the potential for a drug-drug interaction between Stribild and commonly used oral contraceptives. Intensive pharmacokinetic data on each oral contraceptive, when given alone and when co-administered with Stribild, should be collected in an adequate number of subjects.

The timetable you submitted on August 14, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	October 2012
Trial Completion:	July 2016
Final Report Submission:	November 2016

1919-9 Conduct an *in vivo* drug-drug interaction trial between Stribild and telaprevir.

The timetable you submitted on August 14, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	November 2012
Trial Completion:	September 2013
Final Report Submission:	October 2013

1919-10 Conduct an *in vivo* drug-drug interaction trial of Stribild and buprenorphine/naloxone.

The timetable you submitted on August 14, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	January 2011
Trial Completion:	September 2012
Final Report Submission:	January 2013

1919-11 Conduct an *in vivo* drug-drug interaction trial of Stribild and methadone.

The timetable you submitted on August 14, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	January 2011
Trial Completion:	September 2012
Final Report Submission:	January 2013

Submit the protocol(s) to your IND 103093, with a cross-reference letter to this NDA. Submit all final reports 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, call the Regulatory Project Manager for this application.

If you have any questions, call Stacey Min, Pharm.D., Regulatory Project Manager, at (301) 796-4253.

Sincerely,

{See appended electronic signature page}

Edward Cox, M.D., MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/

EDWARD M COX
08/27/2012