



NDA 21500/S-018
NDA 21896/S-015

SUPPLEMENT APPROVAL

Gilead Sciences, Inc.
Attention: Thomas Haberberger, Ph.D.
Associate Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Haberberger:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received October 13, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Emtriva® (emtricitabine) Capsules (NDA 21500) and Oral Solution (NDA 21896).

We also refer to our letter dated September 15, 2011, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for antiretroviral products. This information pertains to the risk of the autoimmune disorder as syndromes that can occur in the setting of immune reconstitution with the use of antiretroviral products.

In addition, we refer to non-safety labeling changes in our September 15, 2011 letter for all antiretroviral products based on recent studies demonstrating decreased transmission of HIV when HIV-infected patients or their uninfected partners take antiretroviral medication.

These supplemental new drug applications provide for revisions to the labeling for Emtriva® (emtricitabine) Capsules (NDA 21500) and Oral Solution (NDA 21896), consistent with our September 15, 2011, letter as follows (additions are noted by underline and deletion are noted by ~~strikethrough~~).

- 1. The **RECENT MAJOR CHANGES** in the Highlights section of the label has been added as follows:

----- RECENT MAJOR CHANGES -----	
<u>Indications and Usage (1)</u>	<u>11/2011</u>
<u>Warnings and Precautions</u>	
<u>Coadministration with Other Products (5.3)</u>	<u>11/2011</u>
<u>Immune Reconstitution Syndrome (5.6)</u>	<u>11/2011</u>

- 2. The medication, COMPLERA was added in the **WARNINGS AND PRECAUTIONS** in the Highlights section of the labeling.

3. The medication, COMPLERA[™] was added in the first bulleted sentence of the **INDICATIONS AND USAGE**.
4. The **WARNINGS AND PRECAUTIONS/Coadministration with Related Products** sub-section has been revised as follows:

EMTRIVA is a component of ~~TRUVADA (a fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate)~~ and ATRIPLA (a fixed-dose combination of efavirenz, emtricitabine, and tenofovir disoproxil fumarate), COMPLERA (a fixed-dose combination of emtricitabine, rilpivirine, and tenofovir disoproxil fumarate) and TRUVADA (a fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate). EMTRIVA should not be coadministered with ~~TRUVADA or ATRIPLA~~, COMPLERA, or TRUVADA. Due to similarities between emtricitabine and lamivudine, EMTRIVA should not be coadministered with other drugs containing lamivudine, including Combivir (lamivudine/zidovudine), Epivir or Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), or Trizivir (abacavir sulfate/lamivudine/zidovudine).

5. The **WARNINGS AND PRECAUTIONS/Immune Reconstitution Syndrome** sub-section has been revised as follows:

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including EMTRIVA. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

6. The **PATIENT COUNSELING INFORMATION** section has been revised as follows:

Information for Patients/the 9th bulleted sentence in the "Patients should be advised that:"

- EMTRIVA should not be coadministered with ATRIPLA, COMPLERA, or TRUVADA; or with other drugs containing lamivudine, including Combivir (lamivudine/zidovudine), Epivir or Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), or Trizivir (abacavir sulfate/lamivudine/zidovudine) [*See Warnings and Precautions (5.3)*].

7. The medication, COMPLERA[™] was added in the **FDA-Approved Patient Labeling/Who**

should not take EMTRIVA? sub-section.

8. The sections under Rx Only section has been revised as follows:

~~May 2008~~ November 2011

COMPLERA, EMTRIVA, TRUVADA, and VIREAD are trademarks or registered trademarks of Gilead Sciences, Inc., or its related companies. ATRIPLA is a registered trademark of Bristol-Myers Squibb & Gilead Sciences, LLC. All other trademarks referenced herein are the property of their respective owners.

~~21-500-896-DGS-014 23MAY08~~ 07102011

We have completed our review of these supplemental applications. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We note that these supplemental applications do not include the revisions of the non-safety labeling changes in the FDA's September 15, 2011 and we recommend these revisions be made.

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, Medication Guide), 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 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).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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 Kyong Hyon, Safety Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Deputy Director for Safety
Division of Antiviral Products
Office Antimicrobial 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/

KENDALL A MARCUS
11/18/2011