



NDA 21752/S-052

SUPPLEMENT APPROVAL

Gilead Sciences, Inc.
Attention: Kathryn A. Cuca, MA
Regulatory Affairs Manager
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Cuca:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 11, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TRUVADA[®] (emtricitabine/tenofovir disoproxil fumarate) tablets.

This Prior Approval supplemental new drug application proposes modifications to the approved risk evaluation and mitigation strategy (REMS) for TRUVADA to establish a single shared system (SSS) REMS for emtricitabine/tenofovir disoproxil fumarate products.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter. We request that the REMS approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for TRUVADA (emtricitabine/tenofovir disoproxil fumarate) for a Pre-Exposure Prophylaxis (PrEP) indication was originally approved on July 16, 2012, and the most recent modification was approved on April 21, 2017. The REMS consists of elements to assure safe use and a timetable for submission of assessments of the REMS. Your proposed modification to the REMS establishes a SSS REMS for the elements to assure safe use required for the reference listed drug (RLD) Truvada and ANDAs referencing Truvada, called the emtricitabine/tenofovir disoproxil fumarate REMS Program, which will become applicable on the date of full approval of the first ANDA referencing Truvada. The modification being approved results in a two-part REMS consisting of: (1) the requirements previously approved Truvada REMS; and (2) the new single, shared system for emtricitabine/tenofovir disoproxil fumarate products. The requirements of the previously approved Truvada REMS will remain applicable until full approval of the first ANDA, at which time, they will automatically be replaced by the requirements of the single, shared system.

Your proposed modified REMS, submitted on May 22, 2017, amended and appended to this letter, is approved. The modified REMS consists of the two-part REMS document described

above, the REMS supporting documents, all appended materials for the modified REMS, and a timetable for submission of assessments.

The timetable for submission of assessments of the modified REMS is the same as that approved in the Truvada REMS on June 18, 2014, until the full approval of the first ANDA referencing Truvada. Upon full approval of the first ANDA referencing Truvada, you must submit REMS assessments to the FDA 18 months from the effective date of the SSS REMS, and every 18 months thereafter.

1. There are no changes to the Truvada REMS assessment plan described in our February 25, 2016 letter.
2. The SSS REMS assessment plan must include, but is not limited to, the following:
 - 1) Evaluation of an uninfected individual's knowledge of the following:
 - a) Importance of strict adherence to the recommended dosing regimen
 - b) Importance of regular monitoring of HIV-1 serostatus
 - c) Understanding that emtricitabine/tenofovir disoproxil fumarate for a PrEP Indication must be part of a comprehensive prevention strategy that includes safer sex practices
 - 2) Evaluation of prescriber knowledge of the following information:
 - a) Importance of strict adherence to the recommended dosing regimen
 - b) Importance of regular monitoring of HIV-1 serostatus to avoid continuing to take emtricitabine/tenofovir disoproxil fumarate for a PrEP Indication, if seroconversion has occurred, to reduce the risk of development of resistant HIV-1 variants
 - c) Understanding that emtricitabine/tenofovir disoproxil fumarate for a PrEP Indication must be considered as only a part of a comprehensive preventive strategy in order to reduce the risk of HIV-1 infection and that other preventive measures should also be used
 - 3) Number and specialty of prescribers who report completion of the prescriber training materials
 - 4) With respect to the REMS goals, an assessment of the extent to which the elements are meeting the goal or whether the goal or such elements should be modified.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in

the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications, provide a rationale for why the REMS does not need to be modified.*

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 21752 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,

**UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA21752 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 21752/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 21752/S-000 PRIOR APPROVAL
SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 21752/S-000 PRIOR APPROVAL
SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 21752/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 21752

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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 Elizabeth Thompson, MS, Chief, Project Management Staff, at (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

ENCLOSURE:
REMS

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

/s/

POONAM MISHRA

06/08/2017

on behalf of Debra Birnkrant, M.D.