

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021752Orig1s030

ENVIRONMENTAL ASSESSMENT



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science/Immediate Office

Memorandum

Date: May 1, 2012

From: Raanan A. Bloom, Ph.D.
OPS/IO/SRS

To: Jeannie David, RPM
OPS/ONDQA

Through: Nakissa Sadrieh, Ph.D.
OPS/IO/SRS

Subject: NDA 21-752 / S-030 Truvada® (emtricitabine/tenofovir disoproxil fumarate), PreExposure Prophylaxis (PrEP) Claim of Categorical Exclusion and Environmental Assessment Review

Submission Date: December 15, 2011

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Background

Gilead Sciences, Inc. has filed NDA application 21-752 / S-030, a new indication for Truvada® (emtricitabine/tenofovir disoproxil fumarate), for prevention of acquisition of HIV infection. Gilead Sciences, Inc. has submitted a claim of categorical exclusion for emtricitabine under 21 CFR 25.31(b) and an Environmental Assessment (EA) for tenofovir disoproxil fumarate by cross-reference to the EA in NDA 21-356 / S-038.

Review of the Current Submission

The current submission, NDA application 21-752 / S-030, is for PreExposure Prophylaxis (PrEP) using Truvada® (emtricitabine/tenofovir disoproxil fumarate). Truvada® is a combination product consisting of two active pharmaceutical ingredients, emtricitabine and tenofovir disoproxil fumarate.

The categorical exclusion for emtricitabine is based on an expected introduction concentration (EIC) at the point of entry into the aquatic environment of < 1 part per billion.

The calculated EIC for emtricitabine is (b) (4) ppb based on an estimated annual production of (b) (4) kg/year. Additionally, in compliance with 21 CFR 25.15 (a), Gilead Sciences, Inc. states, "To the best of Gilead's knowledge, no extraordinary circumstances exist with this filing." A categorical exclusion is acceptable for emtricitabine

For the second active ingredient, tenofovir disoproxil fumarate, the applicant cross-references NDA 21-356, Section 1.12.14 Environmental Assessment that was submitted in a Prior Approval Supplement (PAS), SN 0640, dated June 16, 2011. A FONSI, dated November 8, 2011, was issued for this application. Nomenclature, physical-chemical information, environmental fate, and environmental effects data were previously submitted for tenofovir disoproxil fumarate in the cross-referenced EA. No new information, except for a change in estimated predicted sales of tenofovir disoproxil fumarate and the related EIC, is provided. This is basically the same information as was submitted under NDA 21-356 / S-038.

The sponsor estimates that in the first five years of predicted sales of all the applicant's dosage forms and strengths, the highest yearly quantity of tenofovir disoproxil fumarate marketed in the United States will be (b) (4) kg; an increase of (b) (4) kg from the last approval. Using this information and the algorithm described in the FDA EA 'Guidance for Industry' document, the updated EIC of tenofovir disoproxil fumarate is estimated to be (b) (4) µg/L (ppb). This value is an increase from the (b) (4) µg/L value provided in the June 16, 2011, EA.

Environmental effects data (EC₅₀, LC₅₀, and NOEC) include toxicological studies in *Pseudokirchneriella subcapitata*, *Daphnia magna*, *Oncorhynchus mykiss* and *Pimephales promelas*. A respiration inhibition study was also conducted. For all species, the LOEC or EC₅₀/MEEC ratios were greater than 1000. LOEC or EC₅₀/MEEC ratios were recalculated using an EIC of (b) (4) µg/L (ppb) and all ratios were still greater than 1000; greater than the minimum application factor of 100 as specified in the FDA EA guidance document. Additional studies are not required.

Comments and Conclusions

Based on an evaluation of the information provided in this EA and previous EAs, on FDA Guidance, no significant adverse environmental impacts are expected from the approval of this application..

A Finding of No Significant Impact (FONSI) is recommended for this application.

Emtricitabine qualifies for a categorical exclusion under 21 CFR 25.31 (b).

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/s/

RAANAN A BLOOM
05/01/2012

NAKISSA SADRIEH
05/03/2012

**Environmental Assessment
Finding of No Significant Impact**

NDA 21-752/S-030

Truvada® (emtricitabine/tenofovir disoproxil fumarate)

**Food and Drug Administration
Center for Drug Evaluation and Research**

May 1, 2012

FINDING OF NO SIGNIFICANT IMPACT

NDA 21-752/S-030

Truvada® (emtricitabine/tenofovir disoproxil fumarate)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of the regulatory process.

NDA 21-752/S-030 requests approval for Truvada® (emtricitabine/tenofovir disoproxil fumarate). This NDA is intended to expand the use of Truvada® for prevention of acquisition of HIV infection. In support of its application, Gilead Sciences, Inc., submitted an environmental assessment (EA) for tenofovir disoproxil fumarate in accordance with 21 CFR Part 25, and a claim of categorical exclusion for emtricitabine under 21 CFR 25.31(b).

The EA cross references an EA previously submitted and approved for tenofovir disoproxil fumarate (NDA 21-356/S-038). Nomenclature, physical-chemical information, and environmental fate, and environmental effects data were previously submitted for tenofovir disoproxil fumarate in the referenced EA. No new information, except for a change in estimated predicted sales of tenofovir disoproxil fumarate and the related EIC, is provided. A FONSI was issued for NDA 21-356 / S-038 on November 8, 2011.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact due to approval of this application and has concluded that this action is not expected to have a significant impact on the environment. Therefore, an environmental impact statement will not be prepared.

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