

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021752Orig1s030**

**CHEMISTRY REVIEW(S)**

**ONDQA Pre-Marketing Assessment Division II  
Quality Assessment for Efficacy Supplement**

**NDA 21-752 / S-030 (Efficacy Suppl)**

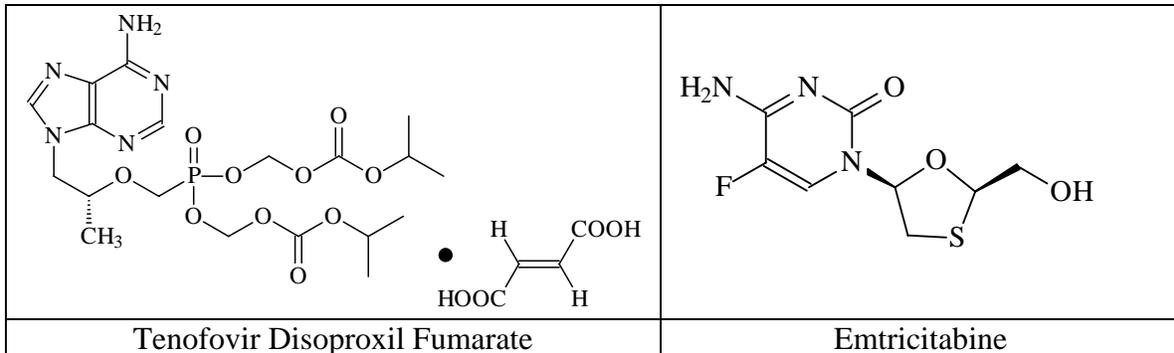
**Gilead**

**Truvada (emtricitabine and tenofovir disoproxil fumarate) Tablets**

**Submission Date: Dec 15, 2011 (EDR-390; SDN-704)**

**PDUFA Date: June 15, 2012**

**GRMP Date: May 22, 2012**



**Summary:**

This efficacy supplement provides for a new indication: Pre-exposure Prophylaxis (PrEP), in which uninfected individuals take Truvada tablets once per day to reduce their risk of acquiring HIV through sexual contact. Evidence for efficacy was obtained from a placebo-controlled study in 2500 HIV-1 uninfected men who have sex with men (MSM) with evidence of high risk behavior, and in a comparison of Truvada (emtricitabine and tenofovir DF) versus tenofovir DF alone to prevent HIV-1 acquisition within HIV-discordant heterosexual couples. HIV acquisition was reduced by Truvada but not totally prevented: 42% risk reduction for MSM at end of treatment (88% estimated risk reduction compared with placebo for subjects with good adherence as demonstrated by measurable drug concentrations); 75% risk reduction in the discordant couple study. As a result, PrEP with Truvada should only be used as part of a prevention strategy which includes other measures (e.g., consistent condom use, reduction of number of sexual partners, regular testing for HIV and other sexually transmitted diseases, etc).

The existing, approved Truvada tablets were used in all studies, and no change in the drug product is proposed for this new indication.

No new facilities are listed on the 356h form, nor is there any info on manufacturing facilities in Section 1.1.2. No CMC information is included in Module 2, and there is no Module 3.

There are no changes to the Description or How Supplied sections of the Prescribing Information when compared to the 2011 Annual Report, and there are no CMC-related edits to the Patient Counseling Information. The Medication Guide appears to be a new addition to labeling, but there are no CMC-related changes and the CMC information in the Medication Guide is correct.

## ONDQA Pre-Marketing Assessment Division II Quality Assessment for Efficacy Supplement

A container label for the bottle of 30 Truvada Tablets is provided. The only change from the bottle label in the 2011 Annual Report is the addition of this statement:

- Dispenser: Each time Truvada is dispensed give the patient the attached medication guide.

This is all consistent with the use of the currently approved products, without any change to the dosage form, container/closure or CMC-related labeling.

Because tenofovir DF is a component of several widely used antiretroviral drugs, the amount manufactured for US use each year exceeds the limit for an Environmental Assessment categorical exclusion. Gilead has updated their 5-year projections for tenofovir DF use to include the anticipated increases from the PrEP indication, and other pending applications. A consult request was sent to the OPS Environmental Assessment Staff requesting review of the environmental effects data that support the increased manufacturing projections. Dr. Raanan Bloom assessed this data and concluded that no significant adverse environmental impacts are expected from approval of the PrEP indication. A Finding of No Significant Impact (FONSI) was therefore issued.

Dr. Bloom's review also concluded that a categorical exclusion is acceptable for emtricitabine, because the expected introduction concentration is expected to remain below 1 ppb in the US aquatic environment.

### **Conclusions:**

This supplement is recommended for approval from the CMC perspective. The only CMC issue was the adequacy of the tenofovir DF data supporting the absence of adverse environmental impact. With the Finding of No Significant Impact, this issue is resolved and the PrEP indication can be approved from the CMC perspective.

Stephen P. Miller, Ph.D.

CMC-Lead

See DARRTS

Date

Thomas F. Oliver, Ph.D.

Branch Chief

See DARRTS

Date

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

/s/  
-----

STEPHEN MILLER  
05/21/2012

THOMAS F OLIVER  
05/21/2012