



TRANSMITTED BY FACSIMILE

Joyce Q. Acbay
Director, Regulatory Affairs
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

RE: NDA # 021752
Truvada® (emtricitabine and tenofovir disoproxil fumarate) Tablets
MACMIS # 18360

Dear Ms. Acbay:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a direct-to-consumer (DTC) print advertisement (Print Ad) (PT0539) for Truvada® (emtricitabine and tenofovir disoproxil fumarate) Tablets (Truvada) submitted by Gilead Sciences, Inc. (Gilead) under cover of Form FDA 2253. The Print Ad is false or misleading because it overstates the efficacy of Truvada, makes unsubstantiated claims, and minimizes the risks associated with the drug. Thus, the Print Ad misbrands Truvada in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(n) & 321(n), and FDA implementing regulations. 21 CFR 202.1(e)(5); (e)(6)(i); & (e)(7)(viii).

Background

According to the Indications & Usage section of its FDA-approved product labeling (PI)¹:

TRUVADA®, a combination of EMTRIVA® and VIREAD®, is indicated in combination with other antiretroviral agents (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infection in adults.

The following points should be considered when initiating therapy with TRUVADA for the treatment of HIV-1 infection:

- It is not recommended that TRUVADA be used as a component of a triple nucleoside regimen.
- TRUVADA should not be coadministered with ATRIPLA®, EMTRIVA, VIREAD or lamivudine-containing products....

¹ The PI submitted with this Print Ad and referred to within this letter is dated November 2008. Although not relevant to the issues raised in this letter, we note that Truvada's PI has since been updated.

- In treatment experienced patients, the use of TRUVADA should be guided by laboratory testing and treatment history....

The Clinical Studies section of the PI for Truvada states (in pertinent part, footnotes not in original):

Clinical Study 934 supports the use of TRUVADA tablets for the treatment of HIV-1 infection. Additional data in support of the use of TRUVADA are derived from Study 903², in which lamivudine and tenofovir disoproxil fumarate (tenofovir DF) were used in combination in treatment-naïve adults, and clinical Study 303³ in which emtricitabine and lamivudine demonstrated comparable efficacy, safety and resistance patterns as part of multidrug regimens. For additional information about these studies, please consult the prescribing information for tenofovir DF and emtricitabine.

The Clinical Studies section of the PI for Truvada also contains the following information regarding the efficacy of Truvada (in pertinent part, emphasis added):

Study 934

Data through 144 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter study comparing emtricitabine + tenofovir DF administered in combination with efavirenz versus zidovudine/lamivudine fixed-dose combination administered in combination with efavirenz in 511 antiretroviral-naïve patients. From Weeks 96 to 144 of the study, patients received TRUVADA with efavirenz in place of emtricitabine + tenofovir DF with efavirenz. Patients had a mean age of 38 years..., 86% were male, 59% were Caucasian and 23% were Black. The mean baseline CD4⁺ cell count was 245 cells/mm³ ... and median baseline plasma HIV-1 RNA was 5.01 log₁₀ copies/mL.... Patients were stratified by baseline CD4⁺ cell count (< or ≥ 200 cells/mm³); 41% had CD4⁺ cell counts <200 cells/mm³ and 51% of patients had baseline viral loads >100,000 copies/mL. Treatment outcomes through 48 and 144 weeks for those patients who did not have efavirenz resistance at baseline are presented in Table 10.

² The Clinical Studies, Clinical Efficacy in Patients with HIV-1 infection, Treatment-Naïve Patients section of the PI for Viread® (tenofovir disoproxil fumarate) includes “data through 144 weeks...for Study 903, a double-blind, active-controlled multicenter study comparing VIREAD (300 mg once daily) administered in combination with lamivudine and efavirenz versus stavudine (d4T), lamivudine, and efavirenz in 600 antiretroviral-naïve patients” (emphasis added).

³ According to the Clinical Studies, Treatment-Experienced Adult Patients section of the Emtriva® (emtricitabine) PI, “Study 303 was a 48-week, open-label, active-controlled multicenter study comparing EMTRIVA (200 mg once daily) to lamivudine, in combination with stavudine or zidovudine and a protease inhibitor or NNRTI in 440 adult patients who were on a lamivudine-containing triple-antiretroviral drug regimen for at least 12 weeks prior to study entry and had HIV-1 RNA ≤ 400 copies/mL” (emphasis added).

Table 10 Outcomes of Randomized Treatment at Week 48 and 144 (Study 934)

Outcomes	At Week 48		At Week 144	
	FTC + TDF + EFV (N=244)	AZT/3TC + EFV (N=243)	FTC + TDF + EFV (N=227) ^a	AZT/3TC + EFV (N=229) ^a
Responder ^b	84%	73%	71%	58%
Virologic failure ^c	2%	4%	3%	6%
Rebound	1%	3%	2%	5%
Never suppressed	0%	0%	0%	0%
Change in antiretroviral regimen	1%	1%	1%	1%
Death	<1%	1%	1%	1%
Discontinued due to adverse event	4%	9%	5%	12%
Discontinued for other reasons ^d	10%	14%	20%	22%

a. Patients who were responders at Week 48 or Week 96 (HIV-1 RNA <400 copies/mL) but did not consent to continue study after Week 48 or Week 96 were excluded from analysis.

b. Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Weeks 48 and 144.

c. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Weeks 48 and 144.

d. Includes lost to follow-up, patient withdrawal, noncompliance, protocol violation and other reasons.

Through Week 48, 84% and 73% of patients in the emtricitabine + tenofovir DF group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA < 400 copies/mL (71% and 58% through Week 144). The difference in the proportion of patients who achieved and maintained HIV-1 RNA < 400 copies/mL through 48 weeks largely results from the higher number of discontinuations due to adverse events and other reasons in the zidovudine/lamivudine group in this open-label study. In addition, 80% and 70% of patients in the emtricitabine + tenofovir DF group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA < 50 copies/mL through Week 48 (64% and 56% through Week 144). The mean increase from baseline in CD4⁺ cell count was 190 cells/mm³ in the emtricitabine + tenofovir DF group and 158 cell/mm³ in the zidovudine/lamivudine group at Week 48 (312 and 271 cells/mm³ at Week 144).

Through 48 weeks, 7 patients in the emtricitabine + tenofovir DF group and 5 patients in the zidovudine/lamivudine group experienced a new CDC Class C event (10 and 6 patients through 144 weeks).

Truvada is associated with serious and potentially life-threatening risks, including significant drug interactions. For example, the PI lists a number of drugs that are contraindicated,

require dose adjustments, and/or should be used cautiously with Truvada because of potentially life-threatening adverse events. Serious risks associated with Truvada noted in the Boxed Warnings and Warnings & Precautions sections of the PI include lactic acidosis and severe hepatomegaly with steatosis, including fatal cases; new onset or worsening renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia); decreases in bone mineral density, including cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures); fat redistribution; immune reconstitution syndrome; and early virologic failure and high rates of resistance substitutions. In addition, the Boxed Warnings and Warnings & Precautions sections of the PI notes that, “**TRUVADA is not approved for the treatment of chronic Hepatitis B virus (HBV) infection,**” (original emphasis) that, “**severe acute exacerbations of Hepatitis B have been reported in patients coinfecting with HIV-1 and HBV who have discontinued TRUVADA,**” (original emphasis) that, “the safety and efficacy of TRUVADA have not been established in patients coinfecting with HBV and HIV-1,” and that, “in some patients infected with HBV and treated with EMTRIVA, the exacerbations of Hepatitis B were associated with liver decompensation and liver failure.” Furthermore, the most common adverse reactions (incidence \geq 10%, any severity) occurring in Study 934 included diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash.

Overstatement of Efficacy & Unsubstantiated Claims

The Print Ad is false or misleading because it represents or suggests that Truvada is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience. Specifically, the Print Ad presents photographs of a woman who takes Truvada as part of her HIV combination therapy at various stages of her life (e.g., at her graduation, in an office setting reading a document, and as a married woman sitting on a sofa). In each depiction, the woman appears to be happy and in good health. The headline above the images states, “**HIV doesn’t have to change the hopes and dreams I have now.**” (original emphasis). Presentations below the photographs include claims such as, “**With once a day TRUVADA for my HIV, I can plan for long-term success**” (original emphasis), “[p]roven over the long term to reduce viral load to undetectable (< 400 copies/mL) and increase CD4 cell count...,” “Established long-term safety and tolerability,” and “In combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.” The Print Ad also includes the tagline, “**Think long term.* Starting now.**” (original emphasis).

The totality of these claims and presentations misleadingly suggests that patients taking Truvada as part of an HIV combination therapy will successfully manage their disease by maintaining undetectable HIV-1 RNA levels (“viral load”) and increased CD4 cell count on a long-term basis (i.e., as they achieve key milestones in life) when this has not been demonstrated by substantial evidence or substantial clinical experience. We note that the Print Ad includes contextual information in small, non-prominent font that Truvada was evaluated “through 3 years of a clinical study” and “[p]roven over the long term . . . in 3 years of a clinical study.” However, this contextual information does not mitigate the overwhelming impression created by the prominent images and claims in the Print Ad, which suggest that patients can expect long-term treatment success with Truvada as they achieve their hopes and dreams, such as graduation, a career, and marriage. Any of these goals can easily take more than three years to accomplish.

In addition, the contextual information that Truvada was evaluated through “3 years of a clinical study” is itself misleading because it fails to convey that the three year clinical study only evaluated antiretroviral treatment-naïve subjects. FDA is not aware of substantial evidence or substantial clinical experience that supports efficacy claims through three years of treatment with Truvada in antiretroviral treatment-experienced adults.

Furthermore, claims such as “[p]roven over the long term to reduce viral load to undetectable (< 400 copies/mL) and increase CD4 cell count in 3 years of a clinical study” misleadingly suggest that all patients taking Truvada, in combination with other antiretroviral agents, will experience an undetectable viral load and increased CD4 cell count through three years when this has not been demonstrated by substantial evidence or substantial clinical experience. As stated above, this study did not evaluate antiretroviral treatment-experienced adults. In addition, as described in the Background section, in Study 934 (in antiretroviral treatment-naïve subjects) through Week 144, 71% and 58% of patients in the emtricitabine + tenofovir DF group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA < 400 copies/mL. A portion of subjects experienced virologic failure, died, or discontinued due to adverse events. The FDA-approved patient labeling (PPI) explicitly states that “The long-term effects of TRUVADA are not known at this time. People taking TRUVADA may still get opportunistic infections or other conditions that happen with HIV-1 infection.” Thus, we are not aware of substantial evidence or substantial clinical experience to support the implication conveyed by the totality of the claims and presentations in the Print Ad that all patients will achieve long-term treatment success with Truvada. The inclusion of the disclaimer “Individual results may vary” does not mitigate this misleading impression.

Moreover, the totality of the claims and presentations in the Print Ad misleadingly implies that patients can preserve their “hopes and dreams” and “plan for long-term success” (i.e., preservation of their activities of daily living, academic performance, work productivity, and social and emotional functioning) without interference from HIV infection or from treatment with Truvada. FDA is not aware of substantial evidence or substantial clinical experience to support this implication. Although Truvada has been shown to reduce viral load to undetectable levels and increase CD4 cell count in a portion of treatment-naïve adults, Truvada carries numerous serious, potentially life-threatening risks and adverse reactions (as described in the Background section above) that can have a significant negative impact on a patient’s life. If you have substantial evidence to support these claims and presentations, please submit it to FDA for review.

Minimization of Risk

The Print Ad is false or misleading because it fails to present the risks associated with Truvada with a prominence and readability reasonably comparable with the presentation of information relating to the benefits of the drug. Factors impacting prominence and readability include typography, layout, contrast, headlines, paragraphing, white space, and other techniques apt to achieve emphasis. In the Print Ad, claims pertaining to efficacy and benefits of Truvada are conveyed through headlines, colorful text, illustrations, bullets, and eye-catching graphics and images. In contrast, the risk information is presented in several long, single-spaced paragraphs in small font/text type in a single column along one side of

the Print Ad. This presentation misleadingly minimizes the risks associated with Truvada because it fails to convey this important risk information with a prominence and readability reasonably comparable to the efficacy claims.

Conclusion and Requested Action

For the reasons discussed above, the Print Ad misbrands Truvada in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(n) & 321(n), and FDA implementing regulations. 21 CFR 202.1(e)(5); (e)(6)(i); & (e)(7)(viii).

DDMAC requests that Gilead immediately cease the dissemination of violative promotional materials for Truvada such as those described above. Please submit a written response to this letter on or before April 9, 2010, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Truvada that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Please direct your response to me at the 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, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS # 18360 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Truvada comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Aline M. Moukhtara, RN, MPH
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21752	ORIG-1	GILEAD SCIENCES INC	EMTRICITABINE 200MG/TENOFOVIR DISOPROXIL

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

/s/

ALINE M MOUKHTARA
03/26/2010