Traditional approval of Viread and Truvada

On March 8, 2006, FDA granted traditional approval to two tenofovir DF containing products manufactured by Gilead Sciences, VIREAD (tenofovir disoproxil fumarate) and TRUVADA (fixed dose combination of tenofovir DF and emtricitabine). Both products are indicated for the treatment of HIV in combination with other antiretroviral drugs.

VIREAD and TRUVADA had received accelerated approval on Oct. 26, 2001 and August 2, 2004, respectively. Traditional approval is supported by previously submitted studies and the recently submitted Study 934, which compared the antiviral activity of tenofovir DF, emtricitabine, and efavirenz to zidovudine, lamivudine and efavirenz in treatment naïve HIV-infected individuals receiving these regimens through 48 weeks.

The results of Study 934 are included in the updated package inserts of **VIREAD and TRUVADA**. Highlights of the label changes are summarized in the attached pdf file.

Richard Klein
Office of Special Health Issues
Food and Drug Administration

Kimberly Struble
Division of Antiviral Drug Products
Food and Drug Administration

viread-truvada.pdf

An archive of past list serve announcements is available on the FDA web site at
http://www.fda.gov/oashi/aids/listserve/archive.html

VIREAD (tenofovir DF) and TRUVADA (fixed dose combination of tenofovir DF and emtricitabine)

The results of Study 934 are included in the updated package inserts of VIREAD and TRUVADA. Highlights of the label changes are summarized below.

1. The Microbiology section of the label has been revised. Clinical virology data previously presented in the Description of Clinical Studies section has been moved into the Microbiology section and older information has been streamlined. In addition, new information derived from Study 934 is included under the Resistance heading as follows:

> In Study 934 of treatment-naïve patients (VIREAD + EMTRIVA + efavirenz versus zidovudine (AZT)/lamivudine (3TC) + efavirenz), genotypic analysis performed on HIV isolates from all patients with >400 copies/mL of HIV-1 RNA at Week 48 or early discontinuation showed development of efavirenz resistance-associated mutations occurred most frequently and was similar between the two treatment arms. The M184V mutation, associated with resistance to EMTRIVA and lamivudine, was observed in 2/12 (17%) analyzed patient isolates in the VIREAD + EMTRIVA group and in 7/22 (32%) analyzed patient isolates in the zidovudine/lamivudine group. Through 48 weeks of Study 934, no patients have developed a detectable K65R mutation in their HIV as analyzed through standard genotypic analysis. Insufficient data are available to assess the development of the K65R mutation upon prolonged exposure to this regimen.

2. Results of Study 934 have been included in the Description of Clinical Studies section as follows:

> Data through 48 weeks are reported for study 934, a randomized, open-label, active-controlled multicenter study comparing VIREAD + EMTRIVA administered in combination with efavirenz versus zidovudine/lamivudine fixed-dose combination administered in combination with efavirenz in 511 antiretroviral-naïve patients. Patients had a mean age of 38 years (range 18–80), 86% were male, 59% were Caucasian and 23% were Black. The mean baseline CD4 cell count was 245 cells/mm^3 (range 2–1191) and median baseline plasma HIV-1 RNA was 5.01 $\log_{10}$ copies/mL (range 3.56–6.54). Patients were stratified by baseline CD4 count (< or ≥200 cells/mm^3); 41% had CD4 cell counts <200 cells/mm^3 and 51% of patients had baseline viral loads >100,000 copies/mL. Treatment outcomes through 48 weeks for those patients who did not have efavirenz resistance at baseline are presented in Table 7.

Table 7 Outcomes of Randomized Treatment at Week 48 (Study 934)

Outcome at Week 48	VIREAD + FTC + EFV (N=244)	AZT/3TC + EFV (N=243)
	%	%
Responder[1]	84%	73%
Virologic failure[2]	2%	4%
Rebound	1%	3%
Never suppressed	0%	0%
Change in antiretroviral regimen	1%	1%
Death	<1%	1%
Discontinued due to adverse event	4%	9%
Discontinued for other reasons[3]	10%	14%

1. Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48.
2. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48.
3. Includes lost to follow-up, patient withdrawal, noncompliance, protocol violation and other reasons.

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 VIREAD + EMTRIVA group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <50 copies/mL. The mean increase from baseline in CD4 cell count was 190 cells/mm^3 in the VIREAD + EMTRIVA group and 158 cells/mm^3 in the lamivudine/zidovudine group.

Through 48 weeks, 7 patients in the VIREAD + EMTRIVA group and 5 patients in the zidovudine/lamivudine group experienced a new CDC Class C event.

3. Data from Study 934 has also been included in the ADVERSE REACTIONS section of the label as follows:

Study 934 - Treatment Emergent Adverse Events: In Study 934, 511 antiretroviral-naïve patients received either VIREAD + EMTRIVA administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254). Adverse events observed in this study were generally consistent with those seen in previous studies in treatment-experienced or treatment-naïve patients (Table 11).

Table 11 Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥3% in Any Treatment Group in Study 934 (0–48 Weeks)

	VIREAD + FTC + EFV	AZT/3TC + EFV
	N=257	N=254
Gastrointestinal Disorder		
Diarrhea	7%	4%
Nausea	8%	6%
Vomiting	1%	4%
General Disorders and Administration Site Condition		
Fatigue	7%	6%
Infections and Infestations		
Sinusitis	4%	2%
Upper respiratory tract infections	3%	3%
Nasopharyngitis	3%	1%
Nervous System Disorders		
Somnolence	3%	2%
Headache	5%	4%
Dizziness	8%	7%
Psychiatric Disorders		
Depression	4%	7%
Insomnia	4%	5%
Abnormal dreams	4%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	5%	4%

Laboratory Abnormalities: Laboratory abnormalities observed in this study were generally consistent with those seen in previous studies (Table 12).

Table 12 Significant Laboratory Abnormalities Reported in ≥1% of Patients in Any Treatment Group in Study 934 (0–48 Weeks)

	VIREAD + FTC + EFV	AZT/3TC + EFV
	N=257	N=254
Any ≥ Grade 3 Laboratory Abnormality	25%	22%
Fasting Cholesterol (>240 mg/dL)	15%	17%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	7%	6%
Serum Amylase (>175 U/L)	7%	3%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	2%
ALT (M: >215 U/L) (F: >170 U/L)	2%	2%
Hemoglobin (<8.0 mg/dL)	0%	3%
Hyperglycemia (>250 mg/dL)	1%	1%
Hematuria (>75 RBC/HPF)	2%	2%
Neutrophil (<750/mm^3)	3%	4%
Fasting Triglyceride (>750 mg/dL)	4%	2%

4. In the WARNINGS section, a subheading titled “Other” has been included with the following warning language:

> VIREAD should not be used in combination with the fixed-dose combination product TRUVADA since it is a component of that product.