CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-356

APPROVED DRAFT LABELING

PROPOSED PACKAGE INSERT FOR VIREAD TABLETS – Version 13– FINAL

VIREAD™

(tenofovir disoproxil fumarate) Tablets

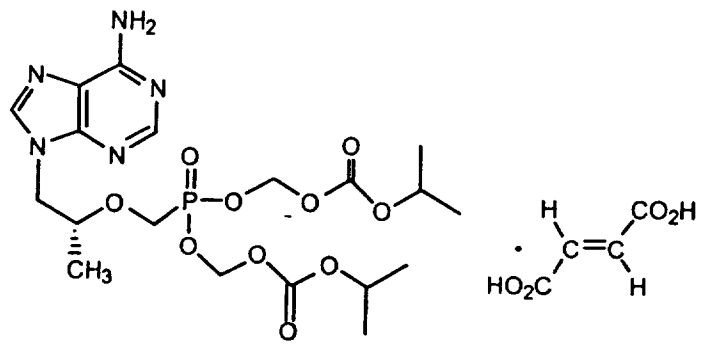
]Only

> WARNING
> **LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGS ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS).**

DESCRIPTION

VIREAD is the brand name for tenofovir disoproxil fumarate (a prodrug of tenofovir) which is a fumaric acid salt of *bis*-isopropoxycarbonyloxymethyl ester derivative of tenofovir. *In vivo* tenofovir disoproxil fumarate is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir exhibits activity against HIV reverse transcriptase.

The chemical name of tenofovir disoproxil fumarate is 9-[(*R*)-2-[[bis[[(isopropoxycarbonyl) oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula:



Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in distilled water at 25°C. It has an octanol/phosphate buffer (pH 6.5) partition coefficient (*log p*) of 1.25 at 25°C.

VIREAD tablets are for oral administration. Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil, and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The tablets are coated with a blue colored film (Opadry II Y-30-10671-A) that is made of FD&C blue #2 aluminum lake, hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide, and triacetin.

In this insert, all dosages are expressed in terms of tenofovir disoproxil fumarate except where otherwise noted.

CLINICAL PHARMACOLOGY

Microbiology

Mechanism of Action: Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerasesα, β, and mitochondrial DNA polymeraseγ.

Antiviral Activity In Vitro: The in vitro antiviral activity of tenofovir against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, primary monocyte/ macrophage cells and peripheral blood lymphocytes. The IC_{50}(50% inhibitory concentrations) for tenofovir was in the range of 0.04 µM to 8.5 µM. In drug combination studies of tenofovir with nucleoside and non-nucleoside analog inhibitors of HIV reverse transcriptase, and protease inhibitors, additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans.

In Vitro Resistance: HIV isolates with reduced susceptibility to tenofovir have been selected in vitro. These viruses expressed a K65R mutation in reverse transcriptase and showed a 3-4 fold reduction in susceptibility to tenofovir.

Cross-resistance: Cross-resistance among certain reverse transcriptase inhibitors has been recognized. The in vitro activity of tenofovir against HIV-1 strains with zidovudine-associated reverse transcriptase mutations (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N) was evaluated. Zidovudine-associated mutations may also confer reductions in susceptibility to other NRTIs and these mutations have been reported to emerge during combination therapy with stavudine and didanosine. In 20 samples that had multiple zidovudine-associated mutations (mean 3), a mean 3.1-fold increase of the IC_{50} of tenofovir was observed (range 0.8 to 8.4). The K65R mutation is selected both in vitro and in some HIV-infected subjects treated with didanosine, zalcitabine, or abacavir; therefore, some cross-resistance may occur in patients who develop this mutation following treatment with these drugs. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir.

Genotypic and Phenotypic Analyses of VIREAD in Patients with Previous Antiretroviral Therapy (Studies 902 and 907): See Description of Clinical Studies

In Vivo Resistance:

Post baseline genotyping in Studies 902 and 907 showed that seven of 237 VIREAD-treated patients' HIV (3%) developed the K65R mutation, a mutation selected by VIREAD and other NRTIs in vitro. Among VIREAD-treated patients whose HIV developed NRTI-associated mutations, there was continued HIV RNA suppression through 24 weeks. The rate and extent of tenofovir-associated resistance mutations has not been characterized in antiretroviral naïve patients initiating VIREAD treatment.

Phenotypic analyses of HIV isolates after 48 weeks (Study 902, n=30) or 24 weeks (Study 907, n=35) of VIREAD therapy showed no significant changes in VIREAD susceptibility unless the K65R mutation had developed.

Pharmacokinetics

The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption: VIREAD is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from VIREAD in fasted patients is approximately 25%. Following oral administration of a single dose of VIREAD 300 mg to HIV-infected patients in the fasted state, maximum serum concentrations (C_{max}) are achieved in 1.0± 0.4 hours. C_{max} and AUC values are 296± 90 ng/mL and 2287± 685 ng*h/mL, respectively.

The pharmacokinetics of tenofovir are dose proportional over a VIREAD dose range of 75 to 600 mg and are not affected by repeated dosing.

Effects of Food on Oral Absorption: Administration of VIREAD following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40% and an increase in C_{max} of approximately 14%. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 326± 119 ng/mL and 3324± 1370 ng*h/mL following multiple doses of VIREAD 300 mg once daily in the fed state. VIREAD should be taken with a meal to enhance the bioavailability of tenofovir.

Distribution: In vitro binding of tenofovir to human plasma or serum proteins is less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25μg/mL. The volume of distribution at steady-state is 1.3± 0.6 L/kg and 1.2± 0.4 L/kg, following intravenous administration of tenofovir 1.0 mg/kg and 3.0 mg/kg.

Metabolism and Elimination: In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP450 enzymes.

Following IV administration of tenofovir, approximately 70-80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. After multiple oral doses of VIREAD 300 mg once daily (under fed conditions), 32± 10% of the administered dose is recovered in urine over 24 hours.

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Special Populations:

There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations.

Tenofovir pharmacokinetics are similar in male and female patients.

Pharmacokinetic studies have not been performed in children or in the elderly.

The pharmacokinetics of tenofovir have not been studied in patients with hepatic impairment; however, tenofovir and tenofovir disoproxil are not metabolized by liver enzymes, so the impact of liver impairment should be limited. (See PRECAUTIONS, Hepatic Impairment)

The pharmacokinetics of tenofovir have not been evaluated in patients with renal impairment (creatinine clearance < 60 mL/min). Because tenofovir is primarily renally eliminated,

tenofovir pharmacokinetics are likely to be affected by renal impairment. (See WARNINGS, Renal Insufficiency)

Drug Interactions:

At concentrations substantially higher (~ 300-fold) than those observed in vivo, tenofovir did not inhibit in vitro drug metabolism mediated by any of the following human CYP450 isoforms: CYP3A4, CYP2D6, CYP2C9 or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on the results of in vitro experiments and the known elimination pathway of tenofovir, the potential for CYP450 mediated interactions involving tenofovir with other medicinal products is low. (See Pharmacokinetics)

Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Co-administration of VIREAD with drugs that are eliminated by active tubular secretion may increase serum concentrations of either tenofovir or the co-administered drug, due to competition for this elimination pathway. Drugs that decrease renal function may also increase serum concentrations of tenofovir.

VIREAD has been evaluated in healthy volunteers in combination with didanosine, lamivudine, indinavir, efavirenz, and lopinavir/ritonavir. Tables 1 and 2 summarize pharmacokinetic effects of co-administered drug on tenofovir pharmacokinetics and effects of tenofovir on the pharmacokinetics of co-administered drug.

Table 1. Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[1] in the Presence of the Co-administered Drug

Co-administered Drug	Dose of Co-administered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters[2] (90% CI)		
			C_{max}	AUC	C_{min}
Lamivudine	150 twice daily x 7 days	15	⇔	⇔	⇔
Didanosine[3]	250 or 400 once daily x 7 days	14	⇔	⇔	⇔
Indinavir	800 three times daily x 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Lopinavir/ Ritonavir	400/100 twice daily x 14 days	21	↑ 31 (↑ 12 to ↑ 53)	↑ 34 (↑ 25 to ↑ 44)	↑ 29 (↑ 11 to ↑ 48)
Efavirenz	600 once daily x 14 days	29	⇔	⇔	⇔

1. Patients received VIREAD 300 mg once daily
2. Increase=↑ ; Decrease= ↓; No Effect= ⇔
3. Buffered formulation

Table 2. Drug Interactions: Changes in Pharmacokinetic Parameters for Co-administered Drug in the Presence of VIREAD 300 mg Once Daily

Co-administered Drug	Dose of Co-administered Drug (mg)	N	% Change of Co-administered Drug Pharmacokinetic Parameters[1] (90% CI)		
			C_{max}	AUC	C_{min}
Lamivudine	150 twice daily x 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Didanosine[2] (see PRECAUTIONS)	250 or 400 once daily x 7 days	14	↑ 28 (↑ 11 to ↑ 48)	↑ 44 (↑ 31 to ↑ 59)	-
Indinavir	800 three times daily x 7 days	12	↓ 11 (↓ 30 to ↑ 12	⇔	⇔
Lopinavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	21	↓ 15 (↓ 23 to ↓ 6)	↓ 15 (↓ 22 to ↓ 7)	⇔
Ritonavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	21	↓ 28 (↓ 43 to ↓ 9)	↓ 24 (↓ 33 to ↓ 13)	↑ 7 (↓ 22 to ↑ 37)
Efavirenz	600 once daily x 14 days	30	⇔	⇔	⇔

1. Increase=↑ ; Decrease= ↓; No Effect= ⇔
2. Buffered formulation

INDICATIONS AND USAGE

VIREAD is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in a controlled study of VIREAD of 24 weeks duration and in a controlled, dose ranging study of VIREAD of 48 weeks duration. Both studies were conducted in treatment experienced adults with evidence of HIV-1 viral replication despite ongoing antiretroviral therapy. Studies in antiretroviral naïve patients are ongoing; consequently, the risk-benefit ratio for this population has yet to be determined.

Additional important information regarding the use of VIREAD for the treatment of HIV infection:

- There are no study results demonstrating the effect of tenofovir on clinical progression of HIV.
- The use of VIREAD should be considered for treating adult patients with HIV strains that are expected to be susceptible to tenofovir as assessed by laboratory testing or treatment history. (See Description of Clinical Studies)

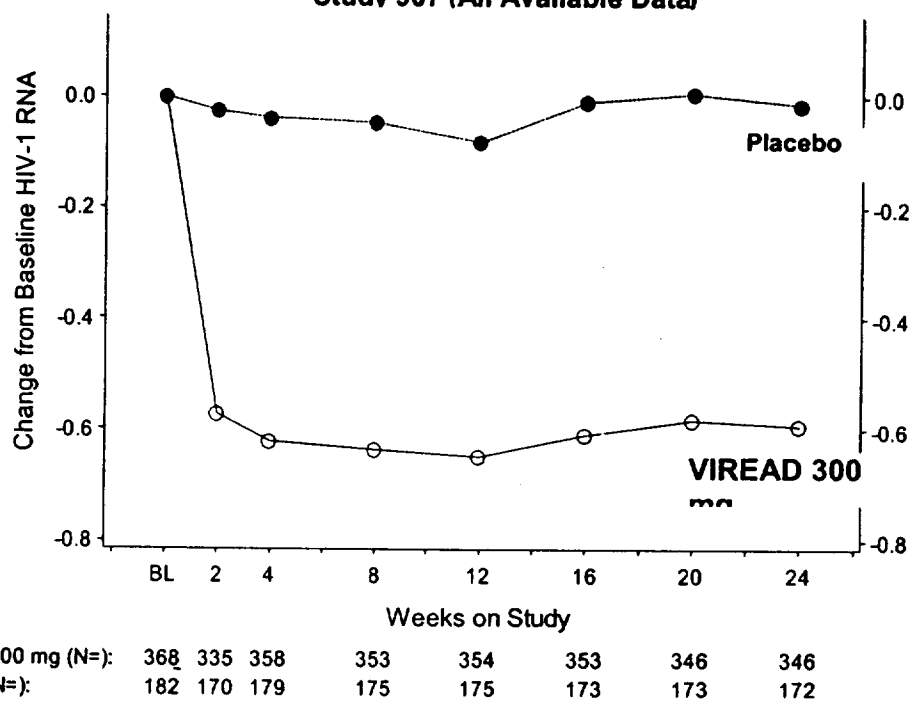
Description of Clinical Studies: Treatment Experienced Patients

Study 907: VIREAD + Standard Background Therapy (SBT) Compared to Placebo + SBT

Study 907 was a 24 week, double-blind placebo-controlled multicenter study of VIREAD added to a stable background regimen of antiretroviral agents in 550 treatment-experienced patients. Patients had a mean baseline CD4 cell count of 426 cells/mm^3(range 23-1385), median baseline plasma HIV RNA of 2340 (range 50-75,900) copies/mL, and mean duration of prior HIV treatment was 5.4 years. Mean age of the patients was 42 years, 85% were male and 69% were Caucasian, 17% African-American and 12% Hispanic.

Changes from baseline in $\log_0$ copies/mL plasma HIV RNA levels over time up to week 24 are presented below in Figure 1.

Figure 1
Mean Change from Baseline in Plasma HIV RNA ($\log_0$ copies/mL) Through Week 24: Study 907 (All Available Data)



The percent of patients with HIV RNA <400 copies/mL, < 50 copies/mL and outcomes of patients through 24 weeks are summarized in Table 3.

Table 3. Outcomes of Randomized Treatment at Week 24 (Study 907)

Outcomes	VIREAD 300 mg (N=368)	Placebo (N=182)
HIV RNA <400 copies/mL	149 (40%)	20 (11%)
HIV RNA >400 copies/mL	189 (51%)	146 (80%)
HIV RNA <50 copies/mL	71 (19%)	2 (1%)
HIV RNA >50 copies/mL	267 (73%)	164 (90%)

Discontinued due to adverse reactions	11 (3%)	5 (3%)
Discontinued due to virologic failure	0	1 (1%)
Discontinued due to other reasons[1]	12 (3%)	5 (3%)
Missing HIV RNA level	7 (2%)	5 (3%)

1. Includes discontinuations due to consent withdrawn, lost to follow up, non-compliance, protocol violations, pregnancy, and other reasons.

Mean change in absolute CD4 counts by week 24 was +11 cells/mm^3 for the VIREAD group and -5 cells/mm^3 for the placebo group.

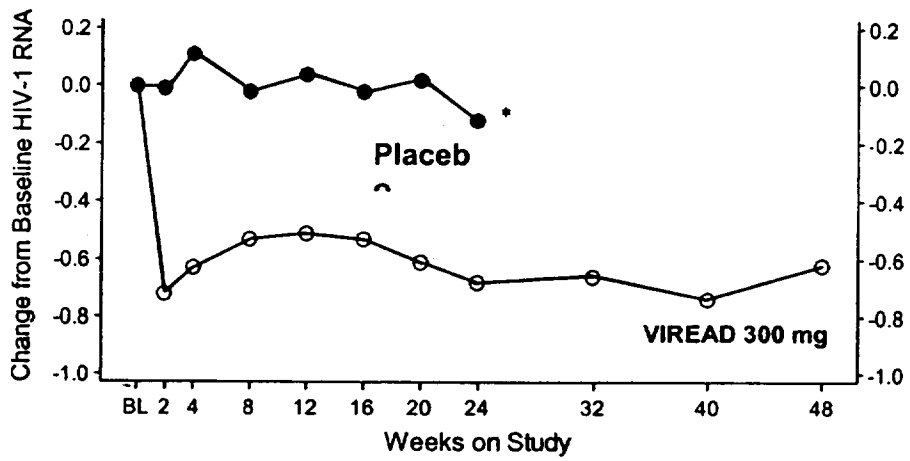
One patient in the VIREAD group and no patients in the placebo arm experienced a new CDC Class C event

Study 902: VIREAD + Standard Background Therapy (SBT) Compared to Placebo + SBT

Study 902 was a double-blind placebo-controlled multicenter study evaluating treatment with VIREAD at three dose levels (75 mg QD, 150 mg QD and 300 mg QD) when added to a stable background regimen of antiretroviral agents in 186 treatment-experienced patients. Placebo patients received VIREAD 300 mg QD at week 24. All patients received open label VIREAD 300 mg QD after week 48. Patients had a mean baseline CD4 cell count of 374 cells/mm^3 (range 9-1240), median baseline plasma HIV RNA of 5010 copies/mL (range 52-575,000), and mean duration of prior HIV treatment was 4.6 years. Mean age was 42 years, 92% were male and 74% were Caucasian, 13% African-American, and 11% Hispanic. At week 24, the rate of drug discontinuation was 11% for the VIREAD group versus 25% for the placebo group.

Changes from baseline in $\log_0$ copies/mL plasma HIV RNA levels over time up to week 48 are presented below in Figure 2.

Figure 2
Mean Change from Baseline in Plasma HIV RNA ($\log_{10}$ copies/mL) Through Week 48: Study 902 (All Available Data)



○ VIREAD 300 mg (N=):	54	52	51	52	52	50	49	48	49	43	43
● Placebo (N=):	28	28	27	27	26	26	22	23	0	0	0

*At week 24, 21 placebo patients crossed over to receive VIREAD 300mg once daily. At week 48 mean change from week 24 was -0.56 $\log_{10}$ copies/mL.

Through week 24 the proportion of patients achieving < 400 copies/mL was 19% VIREAD vs. 7% placebo and < 50 copies/mL was 11% VIREAD vs. 0% placebo. The differences for these secondary endpoints were not statistically significant.

Mean change in absolute CD4 counts by week 24 were -14 cells/mm^3 for the VIREAD group and +20 cells/mm^3 for the placebo group. This result was not statistically significant. Mean change in CD4 count at week 48 was +11 cells/mm^3 for the VIREAD group.

No patients experienced a new CDC Class C event through week 24.

Genotypic Analyses of VIREAD in Patients with Previous Antiretroviral Therapy (Studies 902 and 907):

The virologic response to VIREAD therapy has been evaluated with respect to baseline viral genotype (N=222) in treatment experienced patients participating in trials 902 and 907. In both of these studies, 94% of the participants evaluated had baseline HIV isolates expressing at least one NRTI mutation. These included resistance mutations associated with zidovudine (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N), the lamivudine/abacavir-associated mutation (M184V), and others. In addition the majority of participants evaluated had mutations associated with either PI or NNRTI use. Virologic responses for patients in the genotype substudy were similar to the overall results in studies 902 and 907.

The use of resistance testing and the clinical interpretation of genotypic mutations is a complex and evolving field. Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change pending additional data.

Several exploratory analyses were conducted to evaluate the effect of specific mutations and mutational patterns on virologic outcome. Descriptions of numerical differences in HIV RNA response are displayed in Table 4. Because of the large number of potential comparisons, statistical testing was not conducted.

Varying degrees of cross-resistance of VIREAD to pre-existing zidovudine-associated mutations were observed and appeared to depend on the number of specific mutations. VIREAD-treated patients whose HIV expressed 3 or more zidovudine-associated mutations that included either the M41L or L210W reverse transcriptase mutation showed reduced responses to VIREAD therapy; however, these responses were still improved compared with placebo. The presence of the D67N, K70R, T215Y/F or K219Q/E/N mutation did not appear to affect responses to VIREAD therapy. The HIV RNA responses by number and type of baseline zidovudine-associated mutations are shown in Table 4.

Table 4. HIV RNA Response at Week 24 by Number of Baseline Zidovudine-Associated Mutations in Studies 902 and 907 (Intent-To-Treat)[1]

Number of baseline zidovudine-associated mutations[2]	Change in HIV RNA[3] (N)	
	VIREAD 300 mg	Placebo
None	-0.80 (68)	-0.11 (29)
Any	-0.50 (154)	0 (81)
1 – 2	-0.66 (55)	-0.04 (33)
≥ 3 including M41L or L210W	-0.21 (57)	+0.01 (29)
≥ 3 without M41L or L210W	-0.67 (42)	+0.07 (19)

1. Genotypic testing performed by Virco Laboratories and Visible Genetics TruGene™ technology
2. M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N in RT
3. Average HIV RNA change from baseline through week 24 ($DAVG_{24}$) in log_{10} copies/mL

In the protocol defined analyses, virologic response to VIREAD was not reduced in patients with HIV that expressed the lamivudine/ abacavir-associated M184V mutation. In the absence of zidovudine-associated mutations, patients with the M184V mutation receiving

VIREAD showed a –0.84 $\log_{10}$ copies/mL decrease in their HIV RNA relative to placebo. In the presence of zidovudine-associated mutations, the M184V mutation did not affect the mean HIV RNA responses to VIREAD treatment. More data are needed to determine the impact of M184V alone (in the absence of all other NRTI mutations) on subsequent virologic response in patients receiving VIREAD.

There were limited data on patients expressing some primary nucleoside reverse transcriptase inhibitor mutations and multi-drug resistant mutations at baseline. However, patients expressing mutations at K65R (N=6), or L74V without zidovudine-associated mutations (N=6) appeared to have reduced virologic responses to VIREAD.

The presence of at least one HIV protease inhibitor or non nucleoside reverse transcriptase inhibitor mutation at baseline did not appear to affect the virologic response to VIREAD. Cross-resistance between VIREAD and HIV protease inhibitors is unlikely because of the different enzyme targets involved.

Phenotypic Analyses of VIREAD in Patients with Previous Antiretroviral Therapy (Studies 902 and 907)

The virologic response to VIREAD therapy has been evaluated with respect to baseline phenotype (N=100) in treatment experienced patients participating in trials 902 and 907. Phenotypic analysis of baseline HIV from patients in Studies 902 and 907 demonstrated a correlation between baseline susceptibility to VIREAD and response to VIREAD therapy. Table 5 summarizes the HIV RNA response by baseline VIREAD susceptibility.

Table 5. HIV RNA Response at Week 24 by Baseline VIREAD Susceptibility in Studies 902 and 907 (Intent-To-Treat)[1]

Baseline VIREAD Susceptibility [2]	Change in HIV RNA[3] (N)
≤ 1	-0.74 (35)
> 1 and ≤ 3	-0.56 (49)
> 3 and ≤ 4	-0.3 (7)
≤ 4	-0.61 (91)
> 4	-0.12 (9)

1. Tenofovir susceptibility was determined by recombinant phenotypic Antivirogram™ assay (Virco)
2. Fold change in susceptibility from wild-type
3. Average HIV RNA change from baseline through week 24 ($DAVG_{24}$) in $\log_{10}$ copies/mL

CONTRAINDICATIONS

VIREAD is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.

WARNINGS

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with VIREAD should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic

acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Renal Impairment

Tenofovir is principally eliminated by the kidney. VIREAD should not be administered to patients with renal insufficiency (creatinine clearance < 60 mL/min) until data become available describing the disposition of VIREAD in these patients.

PRECAUTIONS

Drug Interactions

When administered with VIREAD, C_{max} and AUC of didanosine (administered as the buffered formulation) increased by 28% and 44%, respectively. The mechanism for this interaction is unknown. Although an increased rate of didanosine-associated adverse events has not been observed in pooled clinical studies at this time, long term effects are unknown. Patients taking VIREAD and didanosine concomitantly should be monitored for long term didanosine-associated adverse events. (See CLINICAL PHARMACOLOGY, Drug Interactions and DOSAGE AND ADMINISTRATION)

Since tenofovir is primarily eliminated by the kidneys, co-administration of VIREAD with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to, cidofovir, acyclovir, valacyclovir, ganciclovir and valganciclovir.

Hepatic Impairment

The pharmacokinetics of tenofovir have not been studied in patients with hepatic impairment. As tenofovir and tenofovir disoproxil are not metabolized by liver enzymes, the impact of liver impairment should be limited. However, because tenofovir is not entirely renally excreted (70-80%), tenofovir pharmacokinetics may be altered in patients with hepatic insufficiency.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Animal Toxicology

Tenofovir and tenofovir disoproxil fumarate administered in toxicology studies to rats, dogs and monkeys at exposures (based on AUCs) between 6 and 12 fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2-20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

Clinical Monitoring for Bone and Renal Toxicity

It is not known if long term administration of VIREAD (> 1 year) will cause bone abnormalities. Therefore if bone abnormalities are suspected then appropriate consultation should be obtained.

Although tenofovir-associated renal toxicity has not been observed in pooled clinical studies for up to one year, long term renal effects are unknown. Consideration should be given to monitoring for changes in serum creatinine and serum phosphorus in patients at risk or with a history of renal dysfunction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies of tenofovir disoproxil fumarate in rats and mice are in progress.

Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, tenofovir disoproxil fumarate was negative at doses up to 2000 mg/kg when administered to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered at 600 mg/kg/day to male rats for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats. A dose of 600 mg/kg/day is equivalent to 10 times the human dose based on body surface area comparisons.

Pregnancy

Pregnancy category B: Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VIREAD should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to VIREAD, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants**mothers should be instructed not to breast-feed if they are receiving VIREAD.**

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of VIREAD did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

More than 1000 patients have been treated with VIREAD alone or in combination with other antiretroviral medicinal products for periods of 28 days to 143 weeks in Phase I-III clinical trials and a compassionate access study.

Assessment of adverse reactions is based on two studies (902 and 907) in which 653 treatment experienced patients received double-blind treatment with VIREAD 300 mg (n=443) or placebo (n=210) for 24 weeks followed by extended treatment with VIREAD.

Treatment-Related Adverse Events: The most common adverse events that occurred in patients receiving VIREAD with other antiretroviral agents in clinical trials were mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting and flatulence. Less than 1% of patients discontinued participation in the clinical studies due to gastrointestinal adverse events.

A summary of treatment related adverse events is provided in Table 6 below.

Table 6. Treatment-Related Adverse Events (Grades 1-4) Reported in ≥3% of VIREAD-Treated Patients in the Pooled 902 - 907 Studies (0-24 weeks)

	VIREAD 300 mg	Placebo
Number of Patients Treated	443	210
Nausea	11%	10%
Diarrhea	9%	8%
Asthenia	8%	8%
Headache	6%	7%
Vomiting	5%	2%
Flatulence	4%	0%
Abdominal Pain	3%	3%
Anorexia	3%	1%

392 ***Laboratory Abnormalities:*** Laboratory abnormalities observed in these studies occurred
393 with similar frequency in the VIREAD and placebo treated groups. A summary of Grade 3
394 and 4 laboratory abnormalities is provided in Table 7 below.

395

396 **Table 7: Grade 3/4 Laboratory Abnormalities Reported in ≥ 1% of VIREAD-Treated**
397 **Patients in the Pooled 902 - 907 Studies (0-24 weeks)**

	VIREAD 300 mg	Placebo
Number of Patients Treated	443	210
Number of Patients with Grade 3 or 4 Laboratory Abnormalities	117 (26%)	78 (37%)
Laboratory abnormalities		
Triglyceride (>750 mg/dL)	37 (8%)	28 (13%)
Creatine kinase (>782 U/L)	53 (12%)	38 (18%)
Serum amylase (>175 U/L)	21 (5%)	14 (7%)
AST (M; >180 U/L) (F: >170 U/L)	16 (4%)	6 (3%)
Urine glucose (3+ or 4+)	12 (3%)	6 (3%)
ALT elevation (M: >215 U/L) (F: >170 U/L)	10 (2%)	4 (2%)
Serum glucose (>250 mg/dL)	8 (2%)	8 (4%)
Neutrophil (<650/mm^3)	6 (1%)	3 (1%)

398

399 **OVERDOSAGE**

400 Limited clinical experience at doses higher than the therapeutic dose of VIREAD 300 mg is
401 available. In Study 901 tenofovir disoproxil fumarate 600 mg was administered to 8 patients
402 orally for 28 days. No severe adverse reactions were reported. The effects of higher doses
403 are not known.

404 If overdose occurs the patient must be monitored for evidence of toxicity, and standard
405 supportive treatment applied as necessary.

406 It is not known whether peritoneal dialysis or hemodialysis increases the rate of elimination of
407 tenofovir.

408

409 **DOSAGE AND ADMINISTRATION**

410 The dose of VIREAD (tenofovir disoproxil fumarate) is 300 mg once daily taken orally with a
411 meal.

412 Concomitant administration: Didanosine. When administered with didanosine VIREAD should
413 be administered 2 hours before or one hour after administration of didanosine (See
414 PRECAUTIONS, Drug Interactions).

HOW SUPPLIED

VIREAD is available as tablets. Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil. The tablets are almond-shaped, light blue film-coated, and debossed with "GILEAD" and "4331" on one side and with "300" on the other side. They are packaged as follows: Bottles of 30 tablets (NDC 61958-0401-1) containing a desiccant (silica gel canister or sachet) and closed with child-resistant closure.

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) (see USP Controlled Room Temperature).

GILEAD
SCIENCES

Gilead Sciences, Inc.
Foster City, CA 94404

26 October 2001

VIREAD(TM) is a trademark of Gilead Sciences, Inc

© 2001, Gilead sciences, Inc.

VIREAD™

(tenofovir disoproxil fumarate) Tablets

Patient Information

VIREAD (VEER ee ad)

Generic Name: tenofovir disoproxil fumarate (te NOE' fo veer dye soe PROX il FYOU-mar-ate)

Read this leaflet carefully before you start taking VIREAD. Also, read it each time you get your VIREAD prescription refilled, in case something has changed. This information does not take the place of talking with your doctor when you start this medicine and at check ups. You should stay under a doctor's care when taking VIREAD. Do not change or stop your medicine without first talking with your doctor. Talk to your doctor if you have any questions about VIREAD.

What is VIREAD and how does it work?

VIREAD is a type of medicine called an HIV (human immunodeficiency virus) nucleotide analog reverse transcriptase inhibitor (NRTI). VIREAD is always used in combination with other anti-HIV medicines to treat people with HIV infection. VIREAD is for adults age 18 and older.

HIV infection destroys CD4 (T) cells, which are important to the immune system. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops.

VIREAD helps to block HIV reverse transcriptase, a chemical in your body (enzyme) that is needed for HIV to multiply. VIREAD lowers the amount of HIV in the blood (called viral load) and may help to increase the number of T cells (called CD4 cells). Lowering the amount of HIV in the blood lowers the chance of death or infections that happen when your immune system is weak (opportunistic infections).

Does VIREAD cure HIV or AIDS? VIREAD does not cure HIV infection or AIDS. The long-term effects of VIREAD™ are not known at this time. People taking VIREAD may still get opportunistic infections or other conditions that happen with HIV infection. Opportunistic infections are infections that develop because the immune system is weak. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infections.

Does VIREAD reduce the risk of passing HIV to others? VIREAD does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles.

Who should not take VIREAD?

Together with your doctor, you need to decide whether VIREAD is right for you.

Do not take VIREAD if

- you have kidney problems. VIREAD has not been studied in people with kidney problems
- you are allergic to VIREAD or any of its ingredients

What should I tell my doctor before taking VIREAD?

Tell your doctor

- *If you are pregnant or planning to become pregnant* The effects of VIREAD on pregnant women or their unborn babies are not known.
- *If you are breast-feeding:* Do not breast-feed if you are taking VIREAD. Do not breast-feed if you have HIV. If you are a woman who has or will have a baby, talk with your doctor about the best way to feed your baby. If your baby does not already have HIV, there is a chance that the baby can get HIV through breast-feeding.
- **Tell your doctor about all your medical conditions,** especially liver and kidney problems.
- **Tell your doctor about all the medicines you take**, including prescription and non-prescription medicines and dietary supplements. VIREAD may increase the amount of Videx (didanosine) in your blood. You may need to be followed more carefully if you are taking these two drugs together.

  It is a good idea to keep a complete list of all the medicines that you take. Make a new list when medicines are added or stopped. Give copies of this list to all of your healthcare providers **every** time you visit your doctor or fill a prescription.

How should I take VIREAD?

- Stay under a doctor's care when taking VIREAD. Do not change your treatment or stop treatment without first talking with your doctor.
- Take VIREAD every day exactly as your doctor prescribed it. Follow the directions from your doctor, exactly as written on the label. Set up a dosing schedule and follow it carefully.
- The usual dose of VIREAD is 1 tablet once a day, in combination with other anti-HIV medicines.
- Take VIREAD with a meal. The amount of VIREAD in your blood increases with food. Taking it with food helps it work better.
- If you are also taking didanosine you should take VIREAD two hours before or one hour after didanosine.

- When your VIREAD supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to VIREAD and become harder to treat.
- Only take medicine that has been prescribed specifically for you. Do not give VIREAD to others or take medicine prescribed for someone else.

What should I do if I miss a dose of VIREAD? It is important that you do not miss any doses. If you miss a dose of VIREAD, take it as soon as possible and then take your next scheduled dose at its regular time. If it is almost time for your next dose, do not take the missed dose. Wait and take the next dose at the regular time. Do not double the next dose.

What happens if I take too much VIREAD? If you suspect that you took more than the prescribed dose of VIREAD, contact your local poison control center or emergency room right away.

As with all medicines, VIREAD should be kept out of reach of children.

What should I avoid while taking VIREAD?

- Do not breast feed. See "What should I tell my doctor before taking VIREAD?"

What are the possible side effects of VIREAD?

- The most common side effects of VIREAD are: diarrhea, nausea, vomiting, and flatulence (intestinal gas).
- VIREAD caused harm to the bones of animals. These effects have not been seen in persons taking VIREAD for up to one year. It is not known if the effects will be seen in persons taking VIREAD for longer periods of time.
- Changes in body fat have been seen in some patients taking anti-HIV medicine. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms and face may also happen. The cause and long term health effects of these conditions are not known at this time.
- There have been other side effects in patients taking VIREAD. However, these side effects may have been due to other medicines that patients were taking or to the illness itself. Some of these side effects can be serious.
- This list of side effects is **not** complete. If you have questions about side effects, ask your doctor, nurse, or pharmacist. You should report any new or continuing symptoms to your doctor right away. Your doctor may be able to help you manage these side effects.

How do I store VIREAD?

- Keep VIREAD and all other medications out of reach of children.

- Store VIREAD at room temperature 77° F (25°C). It should remain stable until the expiration date printed on the label.
- Do not keep your medicine in places that are too hot or cold.
- Do not keep medicine that is out of date or that you no longer need. If you throw any medicines away make sure that children will not find them.

General advice about prescription medicines:

Talk to your doctor or other health care provider if you have any questions about this medicine or your condition. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you have any concerns about this medicine, ask your doctor. Your doctor or pharmacist can give you information about this medicine that was written for health care professionals. Do not use this medicine for a condition for which it was not prescribed. Do not share this medicine with other people.

Revised: October 2001

GILEAD
SCIENCES