

1 **PROPOSED PACKAGE INSERT FOR VIREAD TABLETS – Version 13**

2
3 **VIREAD™**

4 (tenofovir disoproxil fumarate) Tablets

5]Only

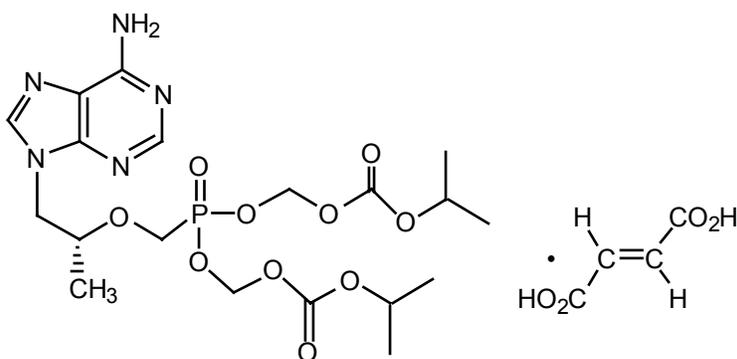
6 **WARNING**

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

11 **DESCRIPTION**

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

17 The chemical name of tenofovir disoproxil fumarate is 9-[(*R*)-2-[[bis[[isopropoxycarbonyl]
18 oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of
19 C₁₉H₃₀N₅O₁₀P • C₄H₄O₄ and a molecular weight of 635.52. It has the following structural
20 formula:



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

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

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

33

34 **CLINICAL PHARMACOLOGY**

35

36 **Microbiology**

37

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

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

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

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

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

69 **In Vivo Resistance:**

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

76 Phenotypic analyses of HIV isolates after 48 weeks (Study 902, n=30) or 24 weeks (Study
77 907, n=35) of VIREAD therapy showed no significant changes in VIREAD susceptibility unless
78 the K65R mutation had developed.

79

80 **Pharmacokinetics**

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

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

89 The pharmacokinetics of tenofovir are dose proportional over a VIREAD dose range of 75 to
90 600 mg and are not affected by repeated dosing.

91 **Effects of Food on Oral Absorption:** Administration of VIREAD following a high-fat meal
92 (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an
93 increase in tenofovir $AUC_{0-\infty}$ of approximately 40% and an increase in C_{max} of approximately
94 14%. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of
95 tenofovir are 326 ± 119 ng/mL and 3324 ± 1370 ng*h/mL following multiple doses of VIREAD
96 300 mg once daily in the fed state. VIREAD should be taken with a meal to enhance the
97 bioavailability of tenofovir.

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

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

104 Following IV administration of tenofovir, approximately 70-80% of the dose is recovered in the
105 urine as unchanged tenofovir within 72 hours of dosing. After multiple oral doses of VIREAD
106 300 mg once daily (under fed conditions), $32 \pm 10\%$ of the administered dose is recovered in
107 urine over 24 hours.

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

111 **Special Populations:**

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

114 Tenofovir pharmacokinetics are similar in male and female patients.

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

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

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

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

123 **Drug Interactions:**

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

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

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

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Table 1. Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir¹ 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	↔	↔	↔

- 143 1. Patients received VIREAD 300 mg once daily
 144 2. Increase=↑ ; Decrease= ↓; No Effect= ↔
 145 3. Buffered formulation
 146

147 **Table 2. Drug Interactions: Changes in Pharmacokinetic Parameters for Co-**
 148 **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)

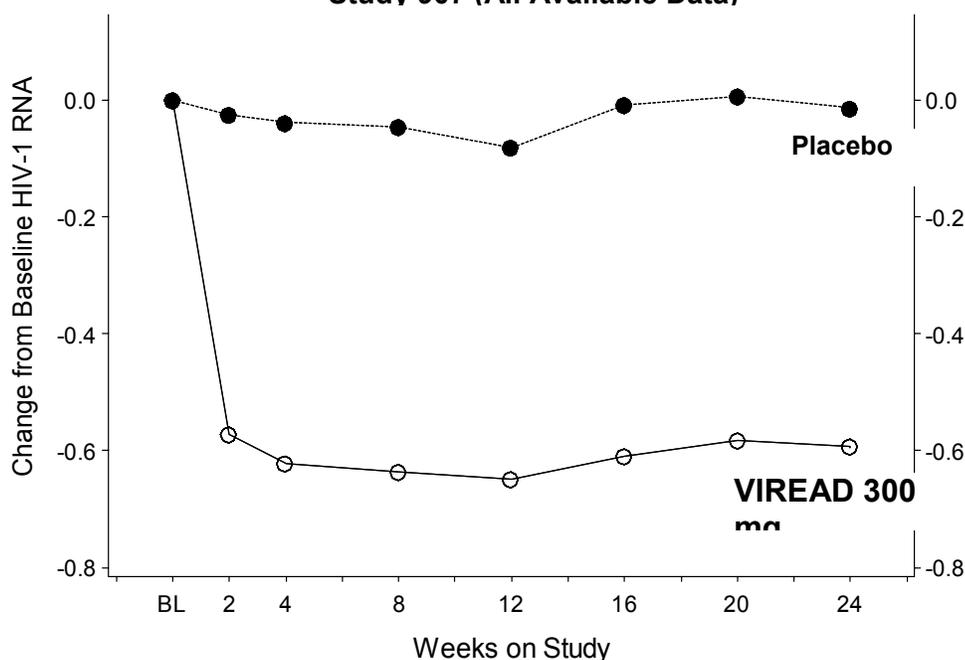
Description of Clinical Studies: Treatment Experienced Patients

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

169 Study 907 was a 24 week, double-blind placebo-controlled multicenter study of VIREAD
 170 added to a stable background regimen of antiretroviral agents in 550 treatment-experienced
 171 patients. Patients had a mean baseline CD4 cell count of 426 cells/mm³ (range 23-1385),
 172 median baseline plasma HIV RNA of 2340 (range 50-75,900) copies/mL, and mean duration
 173 of prior HIV treatment was 5.4 years. Mean age of the patients was 42 years, 85% were male
 174 and 69% were Caucasian, 17% African-American and 12% Hispanic.

175 Changes from baseline in log₁₀ copies/mL plasma HIV RNA levels over time up to week 24
 176 are presented below in Figure 1.

Figure 1
Mean Change from Baseline in Plasma HIV RNA (log₁₀ copies/mL) Through Week 24:
Study 907 (All Available Data)



○ VIREAD 300 mg (N=):	368	335	358	353	354	353	346	346
● Placebo (N=):	182	170	179	175	175	173	173	172

177

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

180

181 **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%)

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

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Mean change in absolute CD4 counts by week 24 was +11 cells/mm³ for the VIREAD group and -5 cells/mm³ for the placebo group.

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

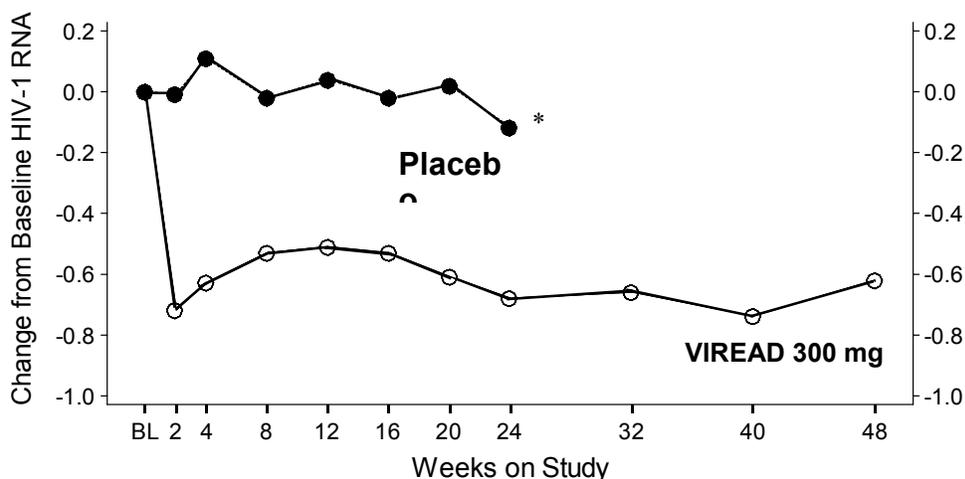
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Study 902: VIREAD + Standard Background Therapy (SBT) Compared to Placebo + SBT

190 Study 902 was a double-blind placebo-controlled multicenter study evaluating treatment with
 191 VIREAD at three dose levels (75 mg QD, 150 mg QD and 300 mg QD) when added to a
 192 stable background regimen of antiretroviral agents in 186 treatment-experienced patients.
 193 Placebo patients received VIREAD 300 mg QD at week 24. All patients received open label
 194 VIREAD 300 mg QD after week 48. Patients had a mean baseline CD4 cell count of 374
 195 cells/mm³ (range 9-1240), median baseline plasma HIV RNA of 5010 copies/mL (range 52-
 196 575,000), and mean duration of prior HIV treatment was 4.6 years. Mean age was 42 years,
 197 92% were male and 74% were Caucasian, 13% African-American, and 11% Hispanic. At
 198 week 24, the rate of drug discontinuation was 11% for the VIREAD group versus 25% for the
 199 placebo group.

200 Changes from baseline in log₁₀ copies/mL plasma HIV RNA levels over time up to week 48
 201 are presented below in Figure 2.

Figure 2
Mean Change from Baseline in Plasma HIV RNA (log₁₀ 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

202 *At week 24, 21 placebo patients crossed over to receive VIREAD 300mg once daily. At week 48 mean change
 203 from week 24 was -0.56 log₁₀ copies/mL.

204 Through week 24 the proportion of patients achieving < 400 copies/mL was 19% VIREAD vs.
 205 7% placebo and < 50 copies/mL was 11% VIREAD vs. 0% placebo. The differences for these
 206 secondary endpoints were not statistically significant.

207 Mean change in absolute CD4 counts by week 24 were -14 cells/mm³ for the VIREAD group
 208 and +20 cells/mm³ for the placebo group. This result was not statistically significant. Mean
 209 change in CD4 count at week 48 was +11 cells/mm³ for the VIREAD group.

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

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

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

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

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

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

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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)

239 1. Genotypic testing performed by Virco Laboratories and Visible Genetics TruGene™ technology
 240 2. M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N in RT
 241 3. Average HIV RNA change from baseline through week 24 (DAVG₂₄) in log₁₀ copies/mL
 242

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

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

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

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

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

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

266
 267 Table 5. HIV RNA Response at Week 24 by Baseline VIREAD
 268 Susceptibility in Studies 902 and 907 (Intent-To-Treat)¹

Baseline VIREAD Susceptibility ²	Change in HIV RNA ³ (N)
≤ 1	-0.74 (35)
$> 1 \text{ and } \leq 3$	-0.56 (49)
$> 3 \text{ and } \leq 4$	-0.3 (7)
≤ 4	-0.61 (91)
> 4	-0.12 (9)

269 1. Tenofovir susceptibility was determined by recombinant phenotypic Antivirogram™ assay (Virco)
 270 2. Fold change in susceptibility from wild-type
 271 3. Average HIV RNA change from baseline through week 24 (DAVG₂₄) in \log_{10} copies/mL

272

273 **CONTRAINDICATIONS**

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

276

277 **WARNINGS**

278 **Lactic Acidosis/Severe Hepatomegaly with Steatosis**

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

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

288 **Renal Impairment**

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

292

293 **PRECAUTIONS**

294 **Drug Interactions**

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

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

307 **Hepatic Impairment**

308 The pharmacokinetics of tenofovir have not been studied in patients with hepatic impairment.
309 As tenofovir and tenofovir disoproxil are not metabolized by liver enzymes, the impact of liver
310 impairment should be limited. However, because tenofovir is not entirely renally excreted (70-
311 80%), tenofovir pharmacokinetics may be altered in patients with hepatic insufficiency.

312 **Fat Redistribution**

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

318 **Animal Toxicology**

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

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

330 **Clinical Monitoring for Bone and Renal Toxicity**

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

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

338 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

351 **Pregnancy**

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

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

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

367 **Pediatric Use**

368 Safety and effectiveness in pediatric patients have not been established.

369 **Geriatric Use**

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

374

375 **ADVERSE REACTIONS**

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

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

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

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

388

389 **Table 6. Treatment-Related Adverse Events (Grades 1-4) Reported in ≥3% of**
 390 **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%

391

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 \geq 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).

415

416 **HOW SUPPLIED**

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

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

424



425

426

427 Gilead Sciences, Inc.

428 Foster City, CA 94404

429

430 26 October 2001

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

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433 **VIREAD™**

434 (tenofovir disoproxil fumarate) Tablets

435

436 **Patient Information**

437 **VIREAD (VEER ee ad)**

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

440

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

447

448 **What is VIREAD and how does it work?**

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

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

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

461

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

468

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

472

473 **Who should not take VIREAD?**

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

475

476 Do not take VIREAD if

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

479

480 **What should I tell my doctor before taking VIREAD?**

481 *Tell your doctor*

- 482 • *If you are pregnant or planning to become pregnant:* The effects of VIREAD on pregnant
483 women or their unborn babies are not known.

- 484 • *If you are breast-feeding:* Do not breast-feed if you are taking VIREAD. Do not breast-
485 feed if you have HIV. If you are a woman who has or will have a baby, talk with your
486 doctor about the best way to feed your baby. If your baby does not already have HIV,
487 there is a chance that the baby can get HIV through breast-feeding.

- 488 • **Tell your doctor about all your medical conditions**, especially liver and kidney
489 problems.

- 490 • **Tell your doctor about all the medicines you take**, including prescription and non-
491 prescription medicines and dietary supplements. VIREAD may increase the amount of
492 Videx (didanosine) in your blood. You may need to be followed more carefully if you are
493 taking these two drugs together.

494

495 It is a good idea to keep a complete list of all the medicines that you take. Make a new list
496 when medicines are added or stopped. Give copies of this list to all of your healthcare
497 providers **every** time you visit your doctor or fill a prescription.
498

499 **How should I take VIREAD?**

- 500 • Stay under a doctor's care when taking VIREAD. Do not change your treatment or stop
501 treatment without first talking with your doctor.

- 502 • Take VIREAD every day exactly as your doctor prescribed it. Follow the directions from
503 your doctor, exactly as written on the label. Set up a dosing schedule and follow it
504 carefully.

- 505 • The usual dose of VIREAD is 1 tablet once a day, in combination with other anti-HIV
506 medicines.

- 507 • Take VIREAD with a meal. The amount of VIREAD in your blood increases with food.
508 Taking it with food helps it work better.

- 509 • If you are also taking didanosine you should take VIREAD two hours before or one hour
510 after didanosine.

511 • When your VIREAD supply starts to run low, get more from your doctor or pharmacy. This
512 is very important because the amount of virus in your blood may increase if the medicine
513 is stopped for even a short time. The virus may develop resistance to VIREAD and
514 become harder to treat.

515 • Only take medicine that has been prescribed specifically for you. Do not give VIREAD to
516 others or take medicine prescribed for someone else.

517

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

522

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

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

527

528 **What should I avoid while taking VIREAD?**

529

530 • Do not breast feed. See “What should I tell my doctor before taking VIREAD?”

531

532 **What are the possible side effects of VIREAD?**

533 • The most common side effects of VIREAD are: diarrhea, nausea, vomiting, and flatulence
534 (intestinal gas).

535 • VIREAD caused harm to the bones of animals. These effects have not been seen in
536 persons taking VIREAD for up to one year. It is not known if the effects will be seen in
537 persons taking VIREAD for longer periods of time.

538 • Changes in body fat have been seen in some patients taking anti-HIV medicine. These
539 changes may include increased amount of fat in the upper back and neck (“buffalo
540 hump”), breast, and around the main part of your body (trunk). Loss of fat from the legs,
541 arms and face may also happen. The cause and long term health effects of these
542 conditions are not known at this time.

543 • There have been other side effects in patients taking VIREAD. However, these side
544 effects may have been due to other medicines that patients were taking or to the illness
545 itself. Some of these side effects can be serious.

546 • This list of side effects is **not** complete. If you have questions about side effects, ask your
547 doctor, nurse, or pharmacist. You should report any new or continuing symptoms to your
548 doctor right away. Your doctor may be able to help you manage these side effects.

549

550 **How do I store VIREAD?**

551 • Keep VIREAD and all other medications out of reach of children.

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

557

558 **General advice about prescription medicines:**

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

566 Revised: October 2001

567

568



569

570

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this page is the manifestation of the electronic signature.**

/s/

Mark Goldberger
10/26/01 05:00:20 PM