f. 373 kcal, 8.2 g fat

g. Compared with didanosine (enteric-coated) 400 mg administered alone under fasting conditions.

h. Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are coadministered.

i. Aptivus Prescribing Information.

12.4 Microbiology

Mechanism of Action

Tenofovir DF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase and HBV 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 polymerases α, β, and mitochondrial DNA polymerase γ.

Activity against HIV

Antiviral Activity

The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} (50% effective concentration) values for tenofovir were in the range of 0.04 μM to 8.5 μM. In drug combination studies, tenofovir was not antagonistic with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir). Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5 μM to 2.2 μM) and strain-specific activity against HIV-2 (EC_{50} values ranged from 1.6 μM to 5.5 μM).

Resistance

HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in reverse transcriptase and showed a 2- to 4- fold reduction in susceptibility to tenofovir. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to tenofovir.

In Study 903 of treatment-naïve subjects (VIREAD + lamivudine + efavirenz versus stavudine + lamivudine + efavirenz) *[See Clinical Studies (14.1)]*, genotypic analyses of isolates from subjects with virologic failure through Week 144 showed development of efavirenz and lamivudine resistance-associated substitutions to occur most frequently and with no difference between the treatment arms. The K65R substitution occurred in 8/47 (17%) of analyzed patient isolates in the VIREAD arm and in 2/49 (4%) of analyzed patient isolates in the stavudine arm. Of the 8 subjects whose virus developed K65R in the VIREAD arm through 144 weeks, 7 occurred in the first 48 weeks of treatment and

one at Week 96. One patient in the VIREAD arm developed the K70E substitution in the virus. Other substitutions resulting in resistance to VIREAD were not identified in this trial.

In Study 934 of treatment-naïve subjects (VIREAD + EMTRIVA + efavirenz versus zidovudine (AZT)/lamivudine (3TC) + efavirenz) *[See Clinical Studies (14.1)]*, genotypic analysis performed on HIV-1 isolates from all confirmed virologic failure subjects with greater than 400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation showed development of efavirenz resistance-associated substitutions occurred most frequently and was similar between the two treatment arms. The M184V substitution, associated with resistance to EMTRIVA and lamivudine, was observed in 2/19 of analyzed subject isolates in the VIREAD + EMTRIVA group and in 10/29 of analyzed subject isolates in the zidovudine/lamivudine group. Through 144 weeks of Study 934, no subjects have developed a detectable K65R substitution in their HIV-1 as analyzed through standard genotypic analysis.

Cross Resistance

Cross resistance among certain reverse transcriptase inhibitors has been recognized. The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1 infected subjects treated with abacavir or didanosine. HIV-1 isolates with this substitution also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross resistance among these drugs may occur in patients whose virus harbors the K65R or K70E substitution. HIV-1 isolates from subjects (N=20) whose HIV-1 expressed a mean of three zidovudine-associated reverse transcriptase substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N), showed a 3.1-fold decrease in the susceptibility to tenofovir.

In Studies 902 and 907 conducted in treatment-experienced subjects (VIREAD + Standard Background Therapy (SBT) compared to placebo + SBT) *[See Clinical Studies (14.1)]*, 14/304 (5%) of the VIREAD-treated subjects with virologic failure through Week 96 had greater than 1.4-fold (median 2.7-fold) reduced susceptibility to tenofovir. Genotypic analysis of the baseline and failure isolates showed the development of the K65R substitution in the HIV-1 reverse transcriptase gene.

The virologic response to VIREAD therapy has been evaluated with respect to baseline viral genotype (N=222) in treatment-experienced subjects participating in Studies 902 and 907. In these clinical trials, 94% of the participants evaluated had baseline HIV-1 isolates expressing at least one NRTI substitution. Virologic responses for subjects in the genotype substudy were similar to the overall trial results.

Several exploratory analyses were conducted to evaluate the effect of specific substitutions and substitutional patterns on virologic outcome. Because of the large number of potential comparisons, statistical testing was not conducted. Varying degrees of cross resistance of VIREAD to pre-existing zidovudine resistance-associated substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) were observed and appeared to depend on the type and number of specific substitutions. VIREAD-treated subjects whose HIV-1 expressed 3 or more zidovudine resistance-associated substitutions that included either the M41L or L210W reverse transcriptase substitution 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 substitution did not appear to affect responses to VIREAD therapy. Subjects whose virus expressed an L74V substitution without zidovudine resistance associated substitutions (N=8) had reduced response to VIREAD. Limited data are available for subjects whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4), all of whom had a reduced response.

In the protocol defined analyses, virologic response to VIREAD was not reduced in subjects with HIV-1 that expressed the abacavir/emtricitabine/lamivudine resistance-associated M184V substitution. HIV-1 RNA responses among these subjects were durable through Week 48.

Studies 902 and 907 Phenotypic Analyses

Phenotypic analysis of baseline HIV-1 from treatment-experienced subjects (N=100) demonstrated a correlation between baseline susceptibility to VIREAD and response to VIREAD therapy. Table 15 summarizes the HIV-1 RNA response by baseline VIREAD susceptibility.

Table 15 HIV-1 RNA Response at Week 24 by Baseline VIREAD Susceptibility (Intent-To-Treat)[a]

Baseline VIREAD Susceptibility[b]	Change in HIV-1 RNA[c] (N)
<1	−0.74 (35)
>1 and ≤3	−0.56 (49)
>3 and ≤4	−0.3 (7)
>4	−0.12 (9)

a. Tenofovir susceptibility was determined by recombinant phenotypic Antivirogram assay (Virco).

b. Fold change in susceptibility from wild-type.

c. Average HIV-1 RNA change from baseline through Week 24 ($DAVG_{24}$) in log_{10} copies/mL.

Activity against HBV

Antiviral Activity

The antiviral activity of tenofovir against HBV was assessed in the HepG2 2.2.15 cell line. The EC_{50} values for tenofovir ranged from 0.14 to 1.5 μM, with CC_{50} (50% cytotoxicity concentration) values greater than 100 μM. In cell culture combination antiviral activity studies of tenofovir with the nucleoside HBV reverse transcriptase inhibitors entecavir, lamivudine, and telbivudine, and with the nucleoside HIV-1 reverse transcriptase inhibitor emtricitabine, no antagonistic activity was observed.

Resistance

Cumulative VIREAD genotypic resistance has been evaluated annually for up to 384 weeks in Studies 0102, 0103, 0106, 0108, and 0121 with the paired HBV reverse transcriptase amino acid sequences of the pretreatment and on-treatment isolates from subjects who received at least 24 weeks of VIREAD monotherapy and remained viremic with HBV DNA greater than or equal to 400 copies/mL (69 IU/mL) at the end of each study year (or at discontinuation of VIREAD monotherapy) using an as-treated analysis. In the nucleotide-naïve population from Studies 0102 and 0103, HBeAg-positive subjects had a higher baseline viral load than HBeAg-negative subjects and a

significantly higher proportion of the subjects remained viremic at their last time point on VIREAD monotherapy (15% versus 5%, respectively).

HBV isolates from these subjects who remained viremic showed treatment-emergent substitutions (Table 16); however, no specific substitutions occurred at a sufficient frequency to be associated with resistance to VIREAD (genotypic and phenotypic analyses).

Table 16 Amino Acid Substitutions in Viremic Subjects across HBV Trials of VIREAD

	Compensated Liver Disease			
	Nucleotide-Naïve (N=417)[a]	**HEPSERA-Experienced (N=247)[b]**	**Lamivudine-Resistant (N=136)[c]**	**Decompensated Liver Disease (N=39)[d]**
Viremic at Last Time Point on VIREAD	38/417 (9%)	37/247 (15%)	9/136 (7%)	7/39 (18%)
Treatment-Emergent Amino Acid Substitutions[e]	18[f]/32 (56%)	11[g]/31 (35%)	6[h]/8 (75%)	3/5 (60%)

a. Nucleotide-naïve subjects from Studies 0102 (N=246) and 0103 (N=171) receiving up to 384 weeks of treatment with VIREAD.

b. HEPSERA-experienced subjects from Studies 0102/0103 (N=195) and 0106 (N=52) receiving up to 336 weeks of treatment with VIREAD after switching to VIREAD from HEPSERA. Study 0106, a randomized, double-blind, 168-week Phase 2 trial, has been completed.

c. Lamivudine-resistant subjects from Study 0121 (N=136) receiving up to 96 weeks of treatment with VIREAD after switching to VIREAD from lamivudine.

d. Subjects with decompensated liver disease from Study 0108 (N=39) receiving up to 48 weeks of treatment with VIREAD.

e. Denominator includes those subjects who were viremic at last time point on VIREAD monotherapy and had evaluable paired genotypic data.

f. Of the 18 subjects with treatment-emergent amino acid substitutions during Studies 0102 and 0103, 5 subjects had substitutions at conserved sites and 13 subjects had substitutions only at polymorphic sites, and 8 subjects had only transient substitutions that were not detected at the last time point on VIREAD.

g. Of the 11 HEPSERA-experienced subjects with treatment-emergent amino acid substitutions, 2 subjects had substitutions at conserved sites and 9 had substitutions only at polymorphic sites.

h. Of the 6 lamivudine-resistant subjects with treatment-emergent substitutions during Study 0121, 3 subjects had substitutions at conserved sites and 3 had substitutions only at polymorphic sites.

Cross Resistance

Cross resistance has been observed between HBV nucleoside/nucleotide analogue reverse transcriptase inhibitors.

In cell based assays, HBV strains expressing the rtV173L, rtL180M, and rtM204I/V substitutions associated with resistance to lamivudine and telbivudine showed a susceptibility to tenofovir ranging from 0.7- to 3.4-fold that of wild type virus. The rtL180M and rtM204I/V double substitutions conferred 3.4-fold reduced susceptibility to tenofovir.

HBV strains expressing the rtL180M, rtT184G, rtS202G/I, rtM204V, and rtM250V substitutions associated with resistance to entecavir showed a susceptibility to tenofovir ranging from 0.6- to 6.9-fold that of wild type virus.

HBV strains expressing the adefovir resistance-associated substitutions rtA181V and/or rtN236T showed reductions in susceptibility to tenofovir ranging from 2.9- to 10-fold that of wild type virus. Strains containing the rtA181T substitution showed changes in susceptibility to tenofovir ranging from 0.9- to 1.5-fold that of wild type virus.

One hundred fifty-two subjects initiating VIREAD therapy in Studies 0102, 0103, 0106, 0108, and 0121 harbored HBV with known resistance substitutions to HBV nucleos(t)ide analogue reverse transcriptase inhibitors: 14 with adefovir resistance-associated substitutions (rtA181S/T/V and/or rtN236T), 135 with lamivudine resistance-associated substitutions (rtM204I/V), and 3 with both adefovir and lamivudine resistance-associated substitutions. Following up to 384 weeks of VIREAD treatment, 10 of the 14 subjects with adefovir-resistant HBV, 124 of the 135 subjects with lamivudine-resistant HBV, and 2 of the 3 subjects with both adefovir- and lamivudine-resistant HBV achieved and maintained virologic suppression (HBV DNA less than 400 copies/mL [69 IU/mL]). Three of the 5 subjects whose virus harbored both the rtA181T/V and rtN236T substitutions remained viremic.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term oral carcinogenicity studies of tenofovir DF in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

Mutagenesis

Tenofovir DF 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 DF was negative when administered to male mice.

Impairment of Fertility

There were no effects on fertility, mating performance or early embryonic development when tenofovir DF was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons 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.

13.2 Animal Toxicology and/or Pharmacology

Tenofovir and tenofovir DF administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6 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.

14 CLINICAL STUDIES

14.1 Clinical Efficacy in Adults with HIV-1 Infection

Treatment-Naïve Adult Patients

Study 903

Data through 144 weeks are reported for Study 903, a double-blind, active-controlled multicenter trial comparing VIREAD (300 mg once daily) administered in combination with lamivudine and efavirenz versus stavudine (d4T), lamivudine, and efavirenz in 600 antiretroviral-naïve subjects. Subjects had a mean age of 36 years (range 18−64); 74% were male, 64% were Caucasian, and 20% were Black. The mean baseline CD4+ cell count was 279 cells/mm^3 (range 3−956) and median baseline plasma HIV-1 RNA was 77,600 copies/mL (range 417−5,130,000). Subjects were stratified by baseline HIV-1 RNA and CD4+ cell count. Forty-three percent of subjects had baseline viral loads >100,000 copies/mL and 39% had CD4+ cell counts <200 cells/mm^3. Treatment outcomes through 48 and 144 weeks are presented in Table 17.

Table 17 Outcomes of Randomized Treatment at Week 48 and 144 (Study 903)

Outcomes	At Week 48		At Week 144	
	VIREAD+3TC +EFV (N=299)	d4T+3TC +EFV (N=301)	VIREAD+3TC +EFV (N=299)	d4T+3TC +EFV (N=301)
Responder[a]	79%	82%	68%	62%
Virologic failure[b]	6%	4%	10%	8%
Rebound	5%	3%	8%	7%
Never suppressed	0%	1%	0%	0%
Added an antiretroviral agent	1%	1%	2%	1%
Death	<1%	1%	<1%	2%
Discontinued due to adverse event	6%	6%	8%	13%
Discontinued for other reasons[c]	8%	7%	14%	15%

a. Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48 and 144.
b. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48 and 144.
c. Includes lost to follow-up, subject's withdrawal, noncompliance, protocol violation and other reasons.

Achievement of plasma HIV-1 RNA concentrations of less than 400 copies/mL at Week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (> or ≤100,000 copies/mL) and CD4+ cell count (< or ≥200 cells/mm^3). Through 144 weeks of therapy, 62% and 58% of subjects in the VIREAD and stavudine arms, respectively, achieved and maintained confirmed HIV-1 RNA <50 copies/mL. The mean increase from baseline in CD4+ cell count was 263 cells/mm^3 for the VIREAD arm and 283 cells/mm^3 for the stavudine arm.

Through 144 weeks, 11 subjects in the VIREAD group and 9 subjects in the stavudine group experienced a new CDC Class C event.

Study 934

Data through 144 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter trial comparing emtricitabine + VIREAD administered in combination with efavirenz versus zidovudine/lamivudine fixed-dose combination administered in combination with efavirenz in 511 antiretroviral-naïve subjects. From Weeks 96 to 144 of the trial, subjects received a fixed-dose combination of emtricitabine and tenofovir DF with efavirenz in place of emtricitabine + VIREAD with efavirenz. Subjects 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). Subjects were stratified by baseline CD4+ cell count (< or ≥200 cells/mm^3); 41% had CD4+ cell counts <200 cells/mm^3 and 51% of subjects had baseline viral loads >100,000 copies/mL. Treatment outcomes through 48 and 144 weeks for those subjects who did not have efavirenz resistance at baseline are presented in Table 18.

Table 18 Outcomes of Randomized Treatment at Week 48 and 144 (Study 934)

Outcomes	At Week 48		At Week 144	
	FTC +VIREAD +EFV (N=244)	AZT/3TC +EFV (N=243)	FTC +VIREAD +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. Subjects who were responders at Week 48 or Week 96 (HIV-1 RNA <400 copies/mL) but did not consent to continue the trial after Week 48 or Week 96 were excluded from analysis.

b. Subjects 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, subject withdrawal, noncompliance, protocol violation and other reasons.

Through Week 48, 84% and 73% of subjects in the emtricitabine + VIREAD 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 subjects 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 trial. In addition, 80% and 70% of subjects in the emtricitabine + VIREAD 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/mm^3 in the EMTRIVA + VIREAD group and 158 cells/mm^3 in the zidovudine/lamivudine group at Week 48 (312 and 271 cells/mm^3 at Week 144).

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

Treatment-Experienced Adult Patients

Study 907

Study 907 was a 24-week, double-blind, placebo-controlled multicenter trial of VIREAD added to a stable background regimen of antiretroviral agents in 550 treatment-experienced subjects. After 24 weeks of blinded trial treatment, all subjects continuing on trial were offered open-label VIREAD for an additional 24 weeks. Subjects had a mean baseline CD4+ cell count of 427 cells/mm^3 (range 23−1385), median baseline

plasma HIV-1 RNA of 2340 (range 50−75,000) copies/mL, and mean duration of prior HIV-1 treatment was 5.4 years. Mean age of the subjects was 42 years; 85% were male, 69% Caucasian, 17% Black, and 12% Hispanic.

The percent of subjects with HIV-1 RNA <400 copies/mL and outcomes of subjects through 48 weeks are summarized in Table 19.

Table 19 Outcomes of Randomized Treatment (Study 907)

Outcomes	0-24 weeks		0-48 weeks	24-48 weeks
	VIREAD (N=368)	Placebo (N=182)	VIREAD (N=368)	Placebo Crossover to VIREAD (N=170)
HIV-1 RNA <400 copies/mL [a]	40%	11%	28%	30%
Virologic failure[b]	53%	84%	61%	64%
Discontinued due to adverse event	3%	3%	5%	5%
Discontinued for other reasons[c]	3%	3%	5%	1%

a. Subjects with HIV-1 RNA <400 copies/mL and no prior study drug discontinuation at Week 24 and 48, respectively.

b. Subjects with HIV-1 RNA ≥400 copies/mL efficacy failure or missing HIV-1 RNA at Week 24 and 48, respectively.

c. Includes lost to follow-up, subject withdrawal, noncompliance, protocol violation, and other reasons.

At 24 weeks of therapy, there was a higher proportion of subjects in the VIREAD arm compared to the placebo arm with HIV-1 RNA <50 copies/mL (19% and 1%, respectively). Mean change in absolute CD4+ cell counts by Week 24 was +11 cells/mm^3 for the VIREAD group and −5 cells/mm^3 for the placebo group. Mean change in absolute CD4+ cell counts by Week 48 was +4 cells/mm^3 for the VIREAD group.

Through Week 24, one subject in the VIREAD group and no subjects in the placebo arm experienced a new CDC Class C event.

14.2 Clinical Efficacy in Adults with Chronic Hepatitis B

HBeAg-Negative Chronic Hepatitis B

Study 0102 was a Phase 3, randomized, double-blind, active-controlled trial of VIREAD 300 mg compared to HEPSERA 10 mg in 375 HBeAg- (anti-HBe+) subjects with compensated liver function, the majority of whom were nucleoside-naïve. The mean age of subjects was 44 years; 77% were male, 25% were Asian, 65% were Caucasian, 17% had previously received alpha-interferon therapy, and 18% were nucleoside-experienced (16% had prior lamivudine experience). At baseline, subjects had a mean Knodell necroinflammatory score of 7.8; mean plasma HBV DNA was 6.9 $\log_{10}$ copies/mL; and mean serum ALT was 140 U/L.

HBeAg-Positive Chronic Hepatitis B

Study 0103 was a Phase 3, randomized, double-blind, active-controlled trial of VIREAD 300 mg compared to HEPSERA 10 mg in 266 HBeAg+ nucleoside-naïve subjects with compensated liver function. The mean age of subjects was 34 years; 69% were male, 36% were Asian, 52% were Caucasian, 16% had previously received alpha-interferon therapy, and <5% were nucleoside experienced. At baseline, subjects had a mean Knodell necroinflammatory score of 8.4; mean plasma HBV DNA was 8.7 $\log_{10}$ copies /mL; and mean serum ALT was 147 U/L.

The primary data analysis was conducted after all subjects reached 48 weeks of treatment and results are summarized below.

The primary efficacy endpoint in both trials was complete response to treatment defined as HBV DNA <400 copies/mL (69 IU/mL) and Knodell necroinflammatory score improvement of at least 2 points, without worsening in Knodell fibrosis at Week 48 (Table 20).

Table 20 Histological, Virological, Biochemical, and Serological Response at Week 48

	0102 (HBeAg-)		0103 (HBeAg+)	
	VIREAD (N=250)	**HEPSERA (N=125)**	**VIREAD (N=176)**	**HEPSERA (N=90)**
Complete Response	71%	49%	67%	12%
Histology Histological Response[a]	72%	69%	74%	68%
HBV DNA <400 copies/mL (<69 IU/mL)	93%	63%	76%	13%
ALT Normalized ALT[b]	76%	77%	68%	54%
Serology HBeAg Loss/ Seroconversion	NA[c]	NA[c]	20%/19%	16%/16%
HBsAg Loss/ Seroconversion	0/0	0/0	3%/1%	0/0

a. Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis.

b. The population used for analysis of ALT normalization included only subjects with ALT above ULN at baseline.

c. NA = Not Applicable

Treatment Beyond 48 Weeks

In Studies 0102 (HBeAg-negative) and 0103 (HBeAg-positive), subjects who completed double-blind treatment (389 and 196 subjects who were originally randomized to VIREAD and HEPSERA, respectively) were eligible to roll over to open-label VIREAD with no interruption in treatment.

In Study 0102, 266 of 347 subjects who entered the open-label period (77%) continued in the study through Week 384. Among subjects randomized to VIREAD followed by open-label treatment with VIREAD, 73% had HBV DNA <400 copies/ml (69 IU/ml), and 63% had ALT normalization at Week 384. Among subjects randomized to HEPSERA followed by open-label treatment with VIREAD, 80% had HBV DNA <400 copies/mL (69 IU/mL) and 70% had ALT normalization through Week 384. At Week 384, both HBsAg loss and seroconversion were approximately 1% in both treatment groups.

In Study 0103, 146 of 238 subjects who entered the open-label period (61%) continued in the study through Week 384. Among subjects randomized to VIREAD, 49% had HBV DNA <400 copies/mL (69 IU/mL), 42% had ALT normalization, and 20% had HBeAg loss (13% seroconversion to anti-HBe antibody) through Week 384. Among subjects randomized to HEPSERA followed by open-label treatment with VIREAD, 56% had HBV DNA <400 copies/mL (69 IU/mL), 50% had ALT normalization, and 28% had HBeAg loss (19% seroconversion to anti-HBe antibody) through Week 384. At Week 384, HBsAg loss and seroconversion were 11% and 8%, respectively, in subjects initially randomized to VIREAD and 12% and 10%, respectively, in subjects initially randomized to HEPSERA.

Of the originally randomized and treated 641 subjects in the two studies, liver biopsy data from 328 subjects who received continuing open-label treatment with VIREAD monotherapy were available for analysis at baseline, Week 48, and Week 240. There were no apparent differences between the subset of subjects who had liver biopsy data at Week 240 and those subjects remaining on open-label VIREAD without biopsy data that would be expected to affect histological outcomes at Week 240. Among the 328 subjects evaluated, the observed histological response rates were 80% and 88% at Week 48 and Week 240, respectively. In the subjects without cirrhosis at baseline (Ishak fibrosis score 0−4), 92% (216/235) and 95% (223/235) had either improvement or no change in Ishak fibrosis score at Week 48 and Week 240, respectively. In subjects with cirrhosis at baseline (Ishak fibrosis score 5−6), 97% (90/93) and 99% (92/93) had either improvement or no change in Ishak fibrosis score at Week 48 and Week 240, respectively. Twenty-nine percent (27/93) and 72% (67/93) of subjects with cirrhosis at baseline experienced regression of cirrhosis by Week 48 and Week 240, respectively, with a reduction in Ishak fibrosis score of at least 2 points. No definitive conclusions can be established about the remaining study population who were not part of this subset analysis.

Patients with Lamivudine-Resistant Chronic Hepatitis B

Study 121 was a randomized, double-blind, active-controlled trial evaluating the safety and efficacy of VIREAD compared to an unapproved antiviral regimen in subjects with chronic hepatitis B, persistent viremia (HBV DNA ≥1,000 IU/mL), and genotypic evidence of lamivudine resistance (rtM204I/V +/- rtL180M). One hundred forty-one adult subjects were randomized to the VIREAD treatment arm. The mean age of subjects randomized to VIREAD was 47 years (range 18−73); 74% were male, 59% were Caucasian, and 37% were Asian. At baseline, 54% of subjects were HBeAg-negative, 46% were HBeAg-positive, and 56% had abnormal ALT. Subjects had a mean HBV DNA of 6.4 $\log_{10}$ copies/mL and mean serum ALT of 71 U/L at baseline.

After 96 weeks of treatment, 126 of 141 subjects (89%) randomized to VIREAD had HBV DNA <400 copies/mL (69 IU/mL), and 49 of 79 subjects (62%) with abnormal ALT at baseline had ALT normalization. Among the HBeAg-positive subjects randomized to VIREAD, 10 of 65 subjects (15%) experienced HBeAg loss and 7 of 65 subjects (11%) experienced anti-HBe seroconversion through Week 96. The proportion of subjects with HBV DNA concentrations below 400 copies/mL (69 IU/mL) at Week 96 was similar between the VIREAD monotherapy and the comparator arms.

Across the combined chronic hepatitis B treatment trials, the number of subjects with adefovir-resistance associated substitutions at baseline was too small to establish efficacy in this subgroup.

Patients with Chronic Hepatitis B and Decompensated Liver Disease

VIREAD was studied in a small randomized, double-blind, active-controlled trial evaluating the safety of VIREAD compared to other antiviral drugs in subjects with chronic hepatitis B and decompensated liver disease through 48 weeks (Study 0108).

Forty-five adult subjects (37 males and 8 females) were randomized to the VIREAD treatment arm. At baseline, 69% subjects were HBeAg-negative and 31% were HBeAg-positive. Subjects had a mean Child-Pugh score of 7, a mean MELD score of 12, mean HBV DNA of 5.8 $\log_{10}$ copies/mL, and mean serum ALT of 61 U/L at baseline. Trial endpoints were discontinuation due to an adverse event and confirmed increase in serum creatinine ≥0.5 mg/dL or confirmed serum phosphorus of <2 mg/dL *[See Adverse Reactions (6.1)]*.

At 48 weeks, 31/44 (70%) and 12/26 (46%) VIREAD-treated subjects achieved an HBV DNA <400 copies/mL (69 IU/mL), and normalized ALT, respectively. The trial was not designed to evaluate treatment impact on clinical endpoints such as progression of liver disease, need for liver transplantation, or death.

16 HOW SUPPLIED/STORAGE AND HANDLING

Tablets

VIREAD tablets, 150 mg, are triangle-shaped, white, film-coated tablets containing 150 mg of tenofovir DF, which is equivalent to 123 mg of tenofovir disoproxil, and are debossed with “GSI” on one side and with “150” on the other side. Each bottle contains 30 tablets and a desiccant (silica gel canister or sachet), and is closed with a child-resistant closure. (NDC 61958-0404-1)

VIREAD tablets, 200 mg, are round-shaped, white, film-coated tablets containing 200 mg of tenofovir DF, which is equivalent to 163 mg of tenofovir disoproxil, and are debossed with “GSI” on one side and with “200” on the other side. Each bottle contains 30 tablets and a desiccant (silica gel canister or sachet), and is closed with a child-resistant closure. (NDC 61958-0405-1)

VIREAD tablets, 250 mg, are capsule-shaped, white, film-coated tablets containing 250 mg of tenofovir DF, which is equivalent to 204 mg of tenofovir disoproxil, and are debossed with “GSI” on one side and with “250” on the other side. Each bottle contains 30 tablets and a desiccant (silica gel canister or sachet), and is closed with a child-resistant closure. (NDC 61958-0406-1)

VIREAD tablets, 300 mg, are almond-shaped, light-blue, film-coated tablets containing 300 mg of tenofovir DF, which is equivalent to 245 mg of tenofovir disoproxil, and are debossed with “GILEAD” and “4331” on one side and with “300” on the other side. Each bottle contains 30 tablets and a desiccant (silica gel canister or sachet), and is closed with a child-resistant closure. (NDC 61958-0401-1)

Oral Powder

VIREAD oral powder consists of white, coated granules containing 40 mg of tenofovir DF, which is equivalent to 33 mg of tenofovir disoproxil, per gram of powder and is available in multi-use bottles containing 60 grams of oral powder, closed with a child-resistant closure, and co-packaged with a dosing scoop. (NDC 61958-0403-1)

Store VIREAD tablets and oral powder at 25 °C (77 °F), excursions permitted to 15-30 °C (59-86 °F) *(See USP Controlled Room Temperature).*
Keep the bottle tightly closed. Dispense only in original container. Do not use if seal over bottle opening is broken or missing.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Inform patients that VIREAD is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using VIREAD.

Advise patients to avoid doing things that can spread HIV or HBV to others.

- **Do not** share **needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** Tenofovir is excreted in breast milk and it is not known whether it can harm the baby. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Inform patients that:

- The long-term effects of VIREAD are unknown.
- VIREAD tablets and oral powder are for oral ingestion only.
- VIREAD should not be discontinued without first informing their physician.
- If you have HIV-1 infection, with or without HBV coinfection, it is important to take VIREAD with combination therapy.
- It is important to take VIREAD on a regular dosing schedule and to avoid missing doses.

- Severe acute exacerbations of hepatitis have been reported in patients who are infected with HBV or coinfected with HBV and HIV-1 and have discontinued VIREAD *[See Warnings and Precautions (5.1)]*.
- Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported. VIREAD should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) *[See Warnings and Precautions (5.2)]*.
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with VIREAD should be suspended in any patient who develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[See Warnings and Precautions (5.3)]*.
- VIREAD should not be coadministered with ATRIPLA, COMPLERA, DESCOVY, GENVOYA, ODEFSEY, STRIBILD, TRUVADA, or VEMLIDY *[See Warnings and Precautions (5.4)]*.
- VIREAD should not be administered in combination with HEPSERA *[See Warnings and Precautions (5.4)]*.
- Decreases in bone mineral density have been observed with the use of VIREAD. Bone mineral density monitoring should be considered in patients who have a history of pathologic bone fracture or at risk for osteopenia *[See Warnings and Precautions (5.6)]*.
- In some patients treated with combination antiretroviral therapy, including VIREAD, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Advise patients to inform their healthcare provider immediately of any symptoms of infection *[See Warnings and Precautions (5.7)].*
- In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown. The relationship between response and long-term prevention of outcomes such as hepatocellular carcinoma is not known.

Gilead Sciences, Inc.

Foster City, CA 94404

21356-GS-038

PATIENT INFORMATION

VIREAD® (VEER-ee-ad)

(tenofovir disoproxil fumarate)

tablets and oral powder

Read this Patient Information before you start taking VIREAD and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about VIREAD?

VIREAD can cause serious side effects, including:

Worsening of your Hepatitis B infection. Your hepatitis B Virus (HBV) infection may become worse (flare-up) if you take VIREAD and then stop it. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.

- Do not let your VIREAD run out. Refill your prescription or talk to your healthcare provider before your VIREAD is all gone.
- Do not stop taking VIREAD without first talking to your healthcare provider.
- If you stop taking VIREAD, your healthcare provider will need to check your health often and do blood tests regularly to check your HBV infection. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking VIREAD.

Talk to your doctor about taking an HIV test before starting treatment with VIREAD for chronic hepatitis B. You should also get a test for HBV if you are taking VIREAD for treatment of HIV.

What is VIREAD?

VIREAD is a prescription medicine used:

1. with other antiviral medicines to treat Human Immunodeficiency Virus-1 (HIV-1) in people 2 years of age and older. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).
    - When used with other HIV medicines, VIREAD may reduce the amount of HIV in your blood (called "viral load"). VIREAD may also help to increase the number of CD4 (T) cells in your blood which help fight off other infections. Reducing the amount of HIV and increasing the CD4 (T) cell count may improve your immune system. This may reduce your risk of death or infections that can happen when your immune system is weak (opportunistic infections).
    - **VIREAD does not cure HIV infection or AIDS.** People taking VIREAD may still develop infections or other conditions associated with HIV infection.
    - You must stay on continuous HIV therapy to control infection and decrease HIV-related illnesses.

- It is very important that you stay under the care of your healthcare provider.
- It is not known if VIREAD is safe and effective for the treatment of HIV-1 infection in children under the age of 2 years.

2. to treat chronic (long-lasting) hepatitis B virus (HBV) in people 12 years of age and older.

- VIREAD will not cure HBV.
- VIREAD may lower the amount of HBV in your body.
- VIREAD may improve the condition of your liver.
- The long-term effects of taking VIREAD for treatment of chronic hepatitis B infection are not known.
- It is not known if VIREAD is safe and effective for treatment of chronic hepatitis B in children under the age of 12 years.

What should I tell my healthcare provider before taking VIREAD?

Before you take VIREAD, tell your healthcare provider if you:

- have liver problems, including hepatitis B (HBV) infection.
- have kidney problems.
- have bone problems.
- have any other medical conditions, including HIV infection.
- are pregnant or plan to become pregnant. It is not known if VIREAD will harm your unborn baby.

  Pregnancy Registry. There is a pregnancy registry for women who take antiviral medicines during pregnancy. Its purpose is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. **Do not breastfeed if you are taking VIREAD.** Tenofovir passes into your breast milk. You should not breastfeed because of the risk of passing HIV to your baby. Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.

VIREAD may affect the way other medicines work, and other medicines may affect how VIREAD works.

Do not take VIREAD if you also take:

- other medicines that contain tenofovir (ATRIPLA®, COMPLERA®, DESCOVY®, GENVOYA®, ODEFSEY®, STRIBILD®, TRUVADA®, VEMLIDY®)
- adefovir (HEPSERA®)

Especially tell your healthcare provider if you take the following medications.

- didanosine (Videx, Videx EC)
- atazanavir (Reyataz)
- darunavir (Prezista)
- lopinavir with ritonavir (Kaletra)
- ledipasvir with sofosbuvir (HARVONI®)
- sofosbuvir with velpatasvir (EPCLUSA®)

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take VIREAD?

- See "What is the most important information I should know about VIREAD?"
- Take VIREAD exactly as your healthcare provider tells you to take it.
- Take VIREAD at the same time every day.
- For adults and children 12 years of age and older, the usual dose of VIREAD is one 300 mg tablet each day.
- If you are an adult with kidney problems, your healthcare provider may tell you to take VIREAD less often.
- Adults and children 12 years of age and older who are unable to swallow VIREAD tablets whole may take 7½ scoops of VIREAD oral powder.
- For children 2 to 12 years of age, your healthcare provider will prescribe the right dose of VIREAD oral powder or tablets based on your child's body weight.
- Tell your healthcare provider if your child has problems with swallowing tablets.
- See the "Instructions for Use" section at the end of this Patient Information leaflet for information about the right way to measure and take VIREAD oral powder.
- Take VIREAD tablets by mouth, with or without food.
- Do not miss a dose of VIREAD. If you miss a dose of VIREAD, take the missed dose as soon as you remember. If it is almost time for your next dose of VIREAD, do not take the missed dose. Take the next dose of VIREAD at your regular time.
- If you take too much VIREAD, call your local poison control center or go right away to the nearest hospital emergency room.

What are the possible side effects of VIREAD?

VIREAD may cause serious side effects, including:

- **See "What is the most important information I should know about VIREAD?"**
- **New or worse kidney problems, including kidney failure,** can happen in some people who take VIREAD. Your healthcare provider should do blood tests to check your kidneys before you start treatment with VIREAD. If you have had

kidney problems in the past or need to take another medicine that can cause kidney problems, your healthcare provider may need to do blood tests to check your kidneys during your treatment with VIREAD.

- **Too much lactic acid in your blood (lactic acidosis).** Too much lactic acid is a serious but rare medical emergency that can lead to death. Tell your healthcare provider right away if you get these symptoms: weakness or being more tired than usual, unusual muscle pain, being short of breath or fast breathing, stomach pain with nausea and vomiting, cold or blue hands and feet, feel dizzy or lightheaded, or a fast or abnormal heartbeat.
- **Severe liver problems.** In rare cases, severe liver problems can happen that can lead to death. Tell your healthcare provider right away if you get these symptoms: skin or the white part of your eyes turns yellow, dark "tea-colored" urine, light-colored stools, loss of appetite for several days or longer, nausea, or stomach-area pain.
- **Bone problems** can happen in some people who take VIREAD. Bone problems include bone pain, softening or thinning (which may lead to fractures). Your healthcare provider may need to do additional tests to check your bones.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider if you start having new symptoms after starting your HIV medicine.

The most common side effects in all people who take VIREAD are:

- nausea
- rash
- diarrhea
- headache
- pain
- depression
- weakness

In some people with advanced HBV-infection, other common side effects may include:

- sleeping problems
- itching
- vomiting
- dizziness
- fever

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of VIREAD. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VIREAD?

- Store VIREAD tablets or oral powder at room temperature between 68 °F to 77 °F (20 °C to 25 °C).
- Keep VIREAD in the original container.
- Do not use VIREAD if the seal over the bottle opening is broken or missing.
- Keep the bottle tightly closed.

Keep VIREAD and all medicines out of the reach of children.

General information about VIREAD:

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use VIREAD for a condition for which it was not prescribed. Do not give VIREAD to other people, even if they have the same condition you have. It may harm them.

Avoid doing things that can spread HIV-1 or HBV infection to others.

Do not share or re-use needles or other injection equipment.

Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.

Do not have any kind of sex without protection. Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

A vaccine is available to protect people at risk for becoming infected with HBV. You can ask your healthcare provider for information about this vaccine.

This leaflet summarizes the most important information about VIREAD. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about VIREAD that is written for health professionals.

For more information, go to www.viread.com or call Gilead Sciences, Inc. at 1-800-GILEAD-5 (1-800-445-3235).

What are the ingredients in VIREAD?

Active Ingredient: tenofovir disoproxil fumarate

Inactive Ingredients:

VIREAD tablets: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch.

VIREAD Oral Powder: mannitol, hydroxypropyl cellulose, ethylcellulose, and silicon dioxide.

Tablet Coating:

VIREAD tablets 300 mg: Opadry II Y-30-10671-A, which contains FD&C blue #2 aluminum lake, hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin.

VIREAD tablets 150, 200 and 250 mg: Opadry II 32K-18425, which contains hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin.

Instructions for Use of VIREAD oral powder

Read the Instructions for Use below before you give VIREAD oral powder. Be sure you can understand and follow them. If you have any questions, ask your healthcare provider or pharmacist.

Important information

- VIREAD oral powder comes in a box that has a bottle of VIREAD and a dosing scoop (see Figure A).

Figure A

- **Only use the dosing scoop to measure VIREAD oral powder.**
- **Only mix VIREAD oral powder with soft foods** that can be swallowed without chewing. Examples of soft foods you can use are: applesauce, baby food, or yogurt.
- **Do not mix VIREAD oral powder with liquid**. The powder may float to the top even after stirring.
- **Give the entire dose right away after mixing** to avoid a bad taste.

How do I prepare and give VIREAD oral powder?

1. Wash and dry your hands.
2. Measure ¼ to ½ cup of soft food into a cup or bowl.
3. To open a new bottle of powder, press down on the bottle lid and turn to remove (see picture on the top of the bottle cap). Peel off the foil.
4. Measure the number of scoops prescribed by your healthcare provider.
    - For each full scoop prescribed:
        - Fill the dosing scoop to the top.
        - Use the flat edge of clean knife to make the powder even with the top of the scoop (see Figure B).

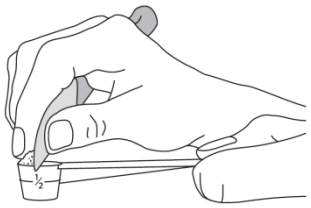

Figure B

    - For ½ scoop:

- Fill the dosing scoop up to the "½ line" on the side (see Figure C).

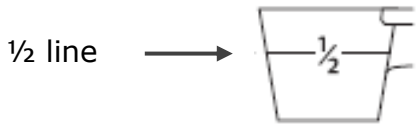

Figure C

5. Sprinkle the VIREAD oral powder on the soft food. Stir with a spoon until well mixed. **Give the entire dose right away after mixing** to avoid a bad taste.
6. Close the bottle of VIREAD tightly.
7. Wash and dry the dosing scoop. Do not store the dosing scoop in the bottle.

See the section "How should I store VIREAD?" for information about how to store VIREAD oral powder.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured for and distributed by:

Gilead Sciences, Inc.

Foster City, CA 94404

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