HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VIREAD safely and effectively. See full prescribing information for VIREAD.

VIREAD® (tenofovir disoproxil fumarate) tablets

Initial U.S. Approval: 2001

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS

See full prescribing information for complete boxed warning.

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD. (5.1)**
- **Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely in these patients. If appropriate, resumption of anti-hepatitis B therapy may be warranted. (5.2)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	11/2008
Indications and Usage	
Chronic Hepatitis B (1.2)	10/2009
Warnings and Precautions	
New Onset or Worsening Renal Impairment (5.3)	10/2009
Decreases in Bone Mineral Density (5.6)	11/2008
Early Virologic Failure (5.9)	11/2008

----------INDICATIONS AND USAGE----------

VIREAD is a nucleotide analog HIV-1 reverse transcriptase and HBV polymerase inhibitor.

Viread is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. (1)

Viread is indicated for the treatment of chronic hepatitis B in adults. (1)

----------DOSAGE AND ADMINISTRATION----------

- Recommended dose for the treatment of HIV or chronic hepatitis B: 300 mg once daily taken orally without regard to food. (2.1)
- Dose recommended in renal impairment:
  Creatinine clearance 30-49 mL/min: 300 mg every 48 hours. (2.2)
  Creatinine clearance 10-29 mL/min: 300 mg every 72 to 96 hours. (2.2)
  Hemodialysis: 300 mg every 7 days or after approximately 12 hours of dialysis. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 300 mg. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess creatinine clearance (CrCl) before initiating treatment with VIREAD. Monitor CrCl and serum phosphorus in patients at risk. Avoid administering VIREAD with concurrent or recent use of nephrotoxic drugs. (5.3)
- Coadministration with Other Products: Do not use with other tenofovir-containing products (e.g., ATRIPLA and TRUVADA). Do not administer in combination with HEPSERA. (5.4)
- HIV testing: HIV antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD. VIREAD should only be used as part of an appropriate antiretroviral combination regimen in HIV-infected patients with or without HBV coinfection. (5.5)
- Decreases in bone mineral density (BMD): Observed in HIV-infected patients. Consider monitoring BMD in patients with a history of pathologic fracture or who are at risk for osteopenia. (5.6)
- Redistribution/accumulation of body fat: Observed in HIV-infected patients receiving antiretroviral combination therapy. (5.7)
- Immune reconstitution syndrome: Observed in HIV-infected patients. May necessitate further evaluation and treatment. (5.8)
- Triple nucleoside-only regimens: Early virologic failure has been reported in HIV-infected patients. Monitor carefully and consider treatment modification. (5.9)

----------ADVERSE REACTIONS----------

In HIV-infected patients: Most common adverse reactions (incidence ≥10%, Grades 2 - 4) are rash, diarrhea, headache, pain, depression, asthenia, and nausea. (6)

In HBV-infected patients: Most common adverse reaction (all grades) was nausea (9%). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Didanosine: Coadministration increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy). Consider dose reductions or discontinuations of didanosine if warranted. (7.1)
- Atazanavir: Coadministration decreases atazanavir concentrations and increases tenofovir concentrations. Use atazanavir with VIREAD only with additional ritonavir; monitor for evidence of tenofovir toxicity. (7.2)
- Lopinavir/ritonavir: Coadministration increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Pregnancy registry available. Enroll patients by calling 1-800-258-4263.
- Nursing mothers: Women infected with HIV should be instructed not to breast feed. (8.3)
- Safety and efficacy not established in patients less than 18 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals *[See Warnings and Precautions (5.1)]*.

Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted *[See Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 HIV-1 Infection

VIREAD® is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.

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

- VIREAD should not be used in combination with TRUVADA® or ATRIPLA® [*See Warnings and Precautions (5.4)*].

1.2 Chronic Hepatitis B

VIREAD is indicated for the treatment of chronic hepatitis B in adults.

The following points should be considered when initiating therapy with VIREAD for the treatment of HBV infection:

- This indication is based primarily on data from treatment of nucleoside-treatment-naïve subjects and a smaller number of subjects who had previously received lamivudine or adefovir. Subjects were adults with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease *[See Clinical Efficacy in Patients with Chronic Hepatitis B (14.2)]*.

- The numbers of subjects in clinical trials who had lamivudine- or adefovir-associated substitutions at baseline were too small to reach conclusions of efficacy *[See Microbiology (12.4), Clinical Efficacy in Patients with Chronic Hepatitis B (14.2)]*.

- VIREAD has not been evaluated in patients with decompensated liver disease.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

For the treatment of HIV-1 or chronic hepatitis B: The dose of VIREAD is 300 mg once daily taken orally, without regard to food.

In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown.

2.2 Dose Adjustment for Renal Impairment

Significantly increased drug exposures occurred when VIREAD was administered to subjects with moderate to severe renal impairment *[See Clinical Pharmacology (12.3)]*. Therefore, the dosing interval of VIREAD should be adjusted in patients with baseline creatinine clearance <50 mL/min using the recommendations in Table 1. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate or severe renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients *[See Warnings and Precautions (5.3)]*.

No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment *[See Warnings and Precautions (5.3)]*.

Table 1 Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)[a]			
	≥50	30–49	10–29	Hemodialysis Patients
Recommended 300 mg Dosing Interval	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis[b]

a. Calculated using ideal (lean) body weight.

b. Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. VIREAD should be administered following completion of dialysis.

The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients.

3 DOSAGE FORMS AND STRENGTHS

VIREAD is available as tablets. Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil. The tablets are almond-

shaped, light blue, film-coated, and debossed with "GILEAD" and "4331" on one side and with "300" on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis/Severe Hepatomegaly with Steatosis

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

5.2 Exacerbation of Hepatitis after Discontinuation of Treatment

Discontinuation of anti-HBV therapy, including VIREAD, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue VIREAD should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

5.3 New Onset or Worsening Renal Impairment

Tenofovir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of VIREAD *[See Adverse Reactions (6.2)]*.

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with VIREAD. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment, including patients who have previously experienced renal events while receiving HEPSERA.

Dosing interval adjustment of VIREAD and close monitoring of renal function are recommended in all patients with creatinine clearance <50 mL/min *[See Dosage and Administration (2.2)]*. No safety or efficacy data are available in patients with renal impairment who received VIREAD using these dosing guidelines, so the potential benefit of VIREAD therapy should be assessed against the potential risk of renal toxicity.

VIREAD should be avoided with concurrent or recent use of a nephrotoxic agent.

5.4 Coadministration with Other Products

VIREAD should not be used in combination with the fixed-dose combination products TRUVADA or ATRIPLA since tenofovir disoproxil fumarate is a component of these products.

VIREAD should not be administered in combination with HEPSERA® (adefovir dipivoxil) *[See Drug Interactions (7.4)].*

5.5 Patients Coinfected with HIV-1 and HBV

Due to the risk of development of HIV-1 resistance, VIREAD should only be used in HIV-1 and HBV coinfected patients as part of an appropriate antiretroviral combination regimen.

HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD. It is also recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment with VIREAD.

5.6 Decreases in Bone Mineral Density

Bone mineral density (BMD) monitoring should be considered for patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

In HIV-infected subjects treated with VIREAD in Study 903 through 144 weeks, decreases from baseline in BMD were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving VIREAD + lamivudine + efavirenz (-2.2% ± 3.9) compared with subjects receiving stavudine + lamivudine + efavirenz (-1.0% ± 4.6). Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the VIREAD group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through Week 144. Twenty-eight percent of VIREAD-treated subjects vs. 21% of the stavudine-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the VIREAD group and 6 subjects in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) in the VIREAD group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in the VIREAD group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of VIREAD *[See Adverse Reactions (6.2)]*.

The bone effects of VIREAD have not been studied in patients with chronic HBV infection.

5.7 Fat Redistribution

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

5.8 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including VIREAD. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

5.9 Early Virologic Failure

Clinical studies in HIV-infected subjects have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTI) are generally less effective than triple drug regimens containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or a HIV-1 protease inhibitor. In particular, early virological failure and high rates of resistance substitutions have been reported. Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[See Boxed Warning, Warnings and Precautions (5.1)]*.
- Severe Acute Exacerbation of Hepatitis *[See Boxed Warning, Warnings and Precautions (5.2)]*.
- New Onset or Worsening Renal Impairment *[See Warnings and Precautions (5.3)]*.
- Decreases in Bone Mineral Density *[See Warnings and Precautions (5.6)]*.
- Immune Reconstitution Syndrome *[See Warnings and Precautions (5.8)]*.

6.1 Adverse Reactions from Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials in Patients with HIV Infection

More than 12,000 subjects have been treated with VIREAD alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in clinical trials and expanded access studies. A total of 1,544 subjects have received VIREAD 300 mg once daily in clinical trials; over 11,000 subjects have received VIREAD in expanded access studies.

The most common adverse reactions (incidence ≥10%, Grades 2–4) identified from any of the 3 large controlled clinical trials include rash, diarrhea, headache, pain, depression, asthenia, and nausea.

Treatment-Naïve Patients

Study 903 - Treatment-Emergent Adverse Reactions: The most common adverse reactions seen in a double-blind comparative controlled study in which 600 treatment-naïve subjects received VIREAD (N=299) or stavudine (N=301) in combination with lamivudine and efavirenz for 144 weeks (Study 903) were mild to moderate gastrointestinal events and dizziness.

Mild adverse reactions (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhea, and nausea. Selected treatment-emergent moderate to severe adverse reactions are summarized in Table 2.

Table 2 Selected Treatment-Emergent Adverse Reactions[a] (Grades 2–4) Reported in ≥5% in Any Treatment Group in Study 903 (0–144 Weeks)

	VIREAD + 3TC + EFV	d4T + 3TC + EFV
	N=299	N=301
Body as a Whole		
Headache	14%	17%
Pain	13%	12%
Fever	8%	7%
Abdominal pain	7%	12%
Back pain	9%	8%
Asthenia	6%	7%
Digestive System		
Diarrhea	11%	13%
Nausea	8%	9%
Dyspepsia	4%	5%
Vomiting	5%	9%
Metabolic Disorders		
Lipodystrophy[b]	1%	8%
Musculoskeletal		
Arthralgia	5%	7%
Myalgia	3%	5%
Nervous System		
Depression	11%	10%
Insomnia	5%	8%
Dizziness	3%	6%
Peripheral neuropathy[c]	1%	5%
Anxiety	6%	6%
Respiratory		
Pneumonia	5%	5%
Skin and Appendages		
Rash event[d]	18%	12%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

b. Lipodystrophy represents a variety of investigator-described adverse events not a protocol-defined syndrome.

c. Peripheral neuropathy includes peripheral neuritis and neuropathy.

d. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

Laboratory Abnormalities: With the exception of fasting cholesterol and fasting triglyceride elevations that were more common in the stavudine group (40% and 9%) compared with VIREAD (19% and 1%) respectively, laboratory abnormalities observed

in this study occurred with similar frequency in the VIREAD and stavudine treatment arms. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 3.

Table 3 Grade 3/4 Laboratory Abnormalities Reported in ≥1% of VIREAD-Treated Subjects in Study 903 (0–144 Weeks)

	VIREAD + 3TC + EFV	d4T + 3TC + EFV
	N=299	N=301
Any ≥ Grade 3 Laboratory Abnormality	36%	42%
Fasting Cholesterol (>240 mg/dL)	19%	40%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	12%	12%
Serum Amylase (>175 U/L)	9%	8%
AST (M: >180 U/L) (F: >170 U/L)	5%	7%
ALT (M: >215 U/L) (F: >170 U/L)	4%	5%
Hematuria (>100 RBC/HPF)	7%	7%
Neutrophils (<750/mm^3)	3%	1%
Fasting Triglycerides (>750 mg/dL)	1%	9%

Study 934 - Treatment Emergent Adverse Reactions: In Study 934, 511 antiretroviral-naïve subjects received either VIREAD + EMTRIVA® administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254). Adverse reactions observed in this study were generally consistent with those seen in previous studies in treatment-experienced or treatment-naïve subjects (Table 4).

Table 4 Selected Treatment-Emergent Adverse Reactions[a] (Grades 2–4) Reported in ≥5% in Any Treatment Group in Study 934 (0–144 Weeks)

	VIREAD[b] + FTC + EFV	AZT/3TC + EFV
	N=257	N=254
Gastrointestinal Disorder		
Diarrhea	9%	5%
Nausea	9%	7%
Vomiting	2%	5%
General Disorders and Administration Site Condition		
Fatigue	9%	8%
Infections and Infestations		
Sinusitis	8%	4%
Upper respiratory tract infections	8%	5%
Nasopharyngitis	5%	3%
Nervous System Disorders		
Headache	6%	5%
Dizziness	8%	7%
Psychiatric Disorders		
Depression	9%	7%
Insomnia	5%	7%
Skin and Subcutaneous Tissue Disorders		
Rash event[c]	7%	9%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

b. From Weeks 96 to 144 of the study, subjects received TRUVADA with efavirenz in place of VIREAD + EMTRIVA with efavirenz.

c. Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and rash vesicular.

Laboratory Abnormalities: Laboratory abnormalities observed in this study were generally consistent with those seen in previous studies (Table 5).

Table 5 Significant Laboratory Abnormalities Reported in ≥1% of Subjects in Any Treatment Group in Study 934 (0–144 Weeks)

	VIREAD[a] + FTC + EFV	AZT/3TC + EFV
	N=257	N=254
Any ≥ Grade 3 Laboratory Abnormality	30%	26%
Fasting Cholesterol (>240 mg/dL)	22%	24%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%
ALT (M: >215 U/L) (F: >170 U/L)	2%	3%
Hemoglobin (<8.0 mg/dL)	0%	4%
Hyperglycemia (>250 mg/dL)	2%	1%
Hematuria (>75 RBC/HPF)	3%	2%
Glycosuria (≥3+)	<1%	1%
Neutrophils (<750/mm^3)	3%	5%
Fasting Triglycerides (>750 mg/dL)	4%	2%

a. From Weeks 96 to 144 of the study, subjects received TRUVADA with efavirenz in place of VIREAD + EMTRIVA with efavirenz.

Treatment-Experienced Patients

Treatment-Emergent Adverse Reactions: The adverse reactions seen in treatment experienced subjects were generally consistent with those seen in treatment naïve subjects including mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting, and flatulence. Less than 1% of subjects discontinued participation in the clinical studies due to gastrointestinal adverse reactions (Study 907).

A summary of moderate to severe, treatment-emergent adverse reactions that occurred during the first 48 weeks of Study 907 is provided in Table 6.

Table 6 **Selected Treatment-Emergent Adverse Reactions[a] (Grades 2–4) Reported in ≥3% in Any Treatment Group in Study 907 (0–48 Weeks)**

	VIREAD (N=368) (Week 0–24)	Placebo (N=182) (Week 0–24)	VIREAD (N=368) (Week 0–48)	Placebo Crossover to VIREAD (N=170) (Week 24–48)
Body as a Whole				
Asthenia	7%	6%	11%	1%
Pain	7%	7%	12%	4%
Headache	5%	5%	8%	2%
Abdominal pain	4%	3%	7%	6%
Back pain	3%	3%	4%	2%
Chest pain	3%	1%	3%	2%
Fever	2%	2%	4%	2%
Digestive System				
Diarrhea	11%	10%	16%	11%
Nausea	8%	5%	11%	7%
Vomiting	4%	1%	7%	5%
Anorexia	3%	2%	4%	1%
Dyspepsia	3%	2%	4%	2%
Flatulence	3%	1%	4%	1%
Respiratory				
Pneumonia	2%	0%	3%	2%
Nervous System				
Depression	4%	3%	8%	4%
Insomnia	3%	2%	4%	4%
Peripheral neuropathy[b]	3%	3%	5%	2%
Dizziness	1%	3%	3%	1%
Skin and Appendage				
Rash event[c]	5%	4%	7%	1%
Sweating	3%	2%	3%	1%
Musculoskeletal				
Myalgia	3%	3%	4%	1%
Metabolic				
Weight loss	2%	1%	4%	2%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
b. Peripheral neuropathy includes peripheral neuritis and neuropathy.
c. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

Laboratory Abnormalities: Laboratory abnormalities observed in this study occurred with similar frequency in the VIREAD and placebo-treated groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 7.

Table 7 Grade 3/4 Laboratory Abnormalities Reported in ≥1% of VIREAD-Treated Subjects in Study 907 (0–48 Weeks)

	VIREAD (N=368) (Week 0–24)	Placebo (N=182) (Week 0–24)	VIREAD (N=368) (Week 0–48)	Placebo Crossover to VIREAD (N=170) (Week 24–48)
Any ≥ Grade 3 Laboratory Abnormality	25%	38%	35%	34%
Triglycerides (>750 mg/dL)	8%	13%	11%	9%
Creatine Kinase (M: >990U/L) (F: >845 U/L)	7%	14%	12%	12%
Serum Amylase (>175 U/L)	6%	7%	7%	6%
Glycosuria (≥3+)	3%	3%	3%	2%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%	4%	5%
ALT (M: >215 U/L) (F: >170 U/L)	2%	2%	4%	5%
Serum Glucose (>250 U/L)	2%	4%	3%	3%
Neutrophils (<750/mm^3)	1%	1%	2%	1%

Clinical Trials in Patients with Chronic Hepatitis B

Treatment-Emergent Adverse Reactions: In controlled clinical trials in subjects with chronic hepatitis B (0102 and 0103), more subjects treated with VIREAD during the 48-week double-blind period experienced nausea: 9% with VIREAD versus 2% with HEPSERA. Other treatment-emergent adverse reactions reported in >5% of subjects treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain and skin rash.

No significant change in the tolerability profile (frequency, nature, or severity of adverse reactions) was observed in subjects continuing treatment with VIREAD for up to 96 weeks in these studies.

Laboratory Abnormalities: A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 8.

Table 8. Grade 3/4 Laboratory Abnormalities Reported in ≥1% of VIREAD-Treated Subjects in Studies 0102 and 0103 (0-48 Weeks)

	VIREAD (N=426)	HEPSERA (N=215)
Any ≥ Grade 3 Laboratory Abnormality	19%	13%
Creatine Kinase (M: >990U/L) (F: >845 U/L)	2%	3%
Serum Amylase (>175 U/L)	4%	1%
Glycosuria (≥3+)	3%	<1%
AST (M: >180 U/L) (F: >170 U/L)	4%	4%
ALT (M: >215 U/L) (F: >170 U/L)	10%	6%

The overall incidence of on-treatment ALT elevations (defined as serum ALT >2 × baseline and >10 × ULN, with or without associated symptoms) was similar between VIREAD (2.6%) and HEPSERA (2%). ALT elevations generally occurred within the first 4–8 weeks of treatment and were accompanied by decreases in HBV DNA levels. No subject had evidence of decompensation. ALT flares typically resolved within 4 to 8 weeks without changes in study medication.

Grade 3/4 laboratory abnormalities were similar in nature and frequency in subjects continuing treatment for up to 96 weeks in these studies.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of VIREAD. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders
allergic reaction, including angioedema

Metabolism and Nutrition Disorders
lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, and Mediastinal Disorders
dyspnea

Gastrointestinal Disorders
pancreatitis, increased amylase, abdominal pain

Hepatobiliary Disorders
hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)

Skin and Subcutaneous Tissue Disorders
rash

Musculoskeletal and Connective Tissue Disorders
rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and Urinary Disorders
acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria

General Disorders and Administration Site Conditions
asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

7 DRUG INTERACTIONS

This section describes clinically relevant drug interactions with VIREAD. Drug interactions studies are described elsewhere in the labeling *[See Clinical Pharmacology (12.3)]*.

7.1 Didanosine

Coadministration of VIREAD and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions.

When administered with VIREAD, C_{max} and AUC of didanosine (administered as either the buffered or enteric-coated formulation) increased significantly *[See Clinical Pharmacology (12.3)]*. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. Suppression of $CD4^+$ cell counts has been observed in patients receiving tenofovir disoproxil fumarate (tenofovir DF) with didanosine 400 mg daily.

In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with VIREAD. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg. When coadministered, VIREAD and didanosine EC may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with VIREAD should be under fasted conditions.

7.2 Atazanavir

Atazanavir has been shown to increase tenofovir concentrations *[See Clinical Pharmacology (12.3)]*. The mechanism of this interaction is unknown. Patients receiving atazanavir and VIREAD should be monitored for VIREAD-associated adverse

reactions. VIREAD should be discontinued in patients who develop VIREAD-associated adverse reactions.

VIREAD decreases the AUC and C_{min} of atazanavir *[See Clinical Pharmacology (12.3)]*. When coadministered with VIREAD, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be coadministered with VIREAD.

7.3 Lopinavir/Ritonavir

Lopinavir/ritonavir has been shown to increase tenofovir concentrations *[See Clinical Pharmacology (12.3)]*. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir and VIREAD should be monitored for VIREAD-associated adverse reactions. VIREAD should be discontinued in patients who develop VIREAD-associated adverse reactions.

7.4 Drugs Affecting Renal Function

Since tenofovir is primarily eliminated by the kidneys *[See Clinical Pharmacology (12.3)]*, coadministration of VIREAD with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir. Drugs that decrease renal function may also increase serum concentrations of tenofovir.

In the treatment of chronic hepatitis B, VIREAD should not be administered in combination with HEPSERA (adefovir dipivoxil).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

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

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

8.3 Nursing Mothers

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1. Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in

nursing infants, **mothers should be instructed not to breast-feed if they are receiving VIREAD.**

8.4 Pediatric Use

Safety and effectiveness in patients less than 18 years of age have not been established.

8.5 Geriatric Use

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

8.6 Patients with Impaired Renal Function

It is recommended that the dosing interval for VIREAD be modified in patients with creatinine clearance <50 mL/min or in patients with ESRD who require dialysis *[See Dosage and Administration (2.2), Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

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

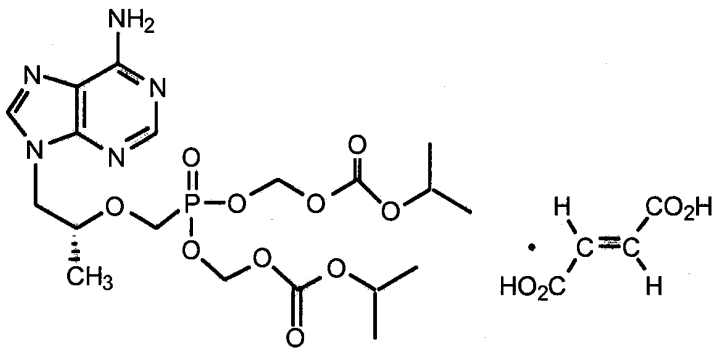
If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of VIREAD, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

11 DESCRIPTION

VIREAD is the brand name for tenofovir disoproxil fumarate (a prodrug of tenofovir) which is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. In vivo tenofovir disoproxil fumarate is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir exhibits activity against HIV-1 reverse transcriptase.

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



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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tenofovir disoproxil fumarate is an antiviral drug *[See Clinical Pharmacology (12.4)]*.

12.3 Pharmacokinetics

The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption

VIREAD is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from VIREAD in fasted subjects is approximately 25%. Following oral administration of a single dose of VIREAD 300 mg to HIV-1 infected subjects in the fasted state, maximum serum concentrations (C_{max}) are achieved in 1.0 ± 0.4 hrs. C_{max} and AUC values are 0.30 ± 0.09 µg/mL and 2.29 ± 0.69 µg·hr/mL, respectively.

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

Distribution

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

Metabolism and Elimination

In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP enzymes.

Following IV administration of tenofovir, approximately 70–80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of VIREAD, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of VIREAD 300 mg once daily (under fed conditions), 32 ± 10% of the administered dose is recovered in urine over 24 hours.

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

Effects of Food on Oral Absorption

Administration of VIREAD following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40% and an increase in C_{max} of approximately 14%. However, administration of VIREAD with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the drug. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 0.33 ± 0.12 μg/mL and 3.32 ± 1.37 μg·hr/mL following multiple doses of VIREAD 300 mg once daily in the fed state, when meal content was not controlled.

Special Populations

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

Gender: Tenofovir pharmacokinetics are similar in male and female subjects.

Pediatric and Geriatric Patients: Pharmacokinetic studies have not been performed in children (<18 years) or in the elderly (>65 years).

Patients with Impaired Renal Function: The pharmacokinetics of tenofovir are altered in subjects with renal impairment *[See Warnings and Precautions (5.3)]*. In subjects with creatinine clearance <50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, and $AUC_{0-\infty}$ of tenofovir were increased (Table 9). It is recommended that the dosing interval for VIREAD be modified in patients with creatinine clearance <50 mL/min or in patients with ESRD who require dialysis *[See Dosage and Administration (2.2)]*.

Table 9 Pharmacokinetic Parameters (Mean ± SD) of Tenofovir[a] in Subjects with Varying Degrees of Renal Function

Baseline Creatinine Clearance (mL/min)	>80 (N=3)	50–80 (N=10)	30–49 (N=8)	12–29 (N=11)
C_{max} (μg/mL)	0.34 ± 0.03	0.33 ± 0.06	0.37 ± 0.16	0.60 ± 0.19
$AUC_{0-\infty}$ (μg·hr/mL)	2.18 ± 0.26	3.06 ± 0.93	6.01 ± 2.50	15.98 ± 7.22
CL/F (mL/min)	1043.7 ± 115.4	807.7 ± 279.2	444.4 ± 209.8	177.0 ± 97.1
CL_{renal} (mL/min)	243.5 ± 33.3	168.6 ± 27.5	100.6 ± 27.5	43.0 ± 31.2

a. 300 mg, single dose of VIREAD

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of VIREAD, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

Patients with Hepatic Impairment: The pharmacokinetics of tenofovir following a 300 mg single dose of VIREAD have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects. No change in VIREAD dosing is required in patients with hepatic impairment.

Assessment of Drug Interactions

At concentrations substantially higher (~300-fold) than those observed in vivo, tenofovir did not inhibit in vitro drug metabolism mediated by any of the following human CYP isoforms: CYP3A4, CYP2D6, CYP2C9, or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on the results of in vitro experiments and the known elimination pathway of tenofovir, the potential for CYP mediated interactions involving tenofovir with other medicinal products is low *[See Clinical Pharmacology (12.3)]*.

VIREAD has been evaluated in healthy volunteers in combination with abacavir, atazanavir, didanosine, efavirenz, emtricitabine, entecavir, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin, saquinavir/ritonavir, and tacrolimus. Tables 10 and 11 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of VIREAD on the pharmacokinetics of coadministered drug.

Table 10 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[a] in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters[b] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	⇔	⇔	NC
Atazanavir[c]	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine (enteric-coated)	400 once	25	⇔	⇔	⇔
Didanosine (buffered)	250 or 400 once daily × 7 days	14	⇔	⇔	⇔
Efavirenz	600 once daily × 14 days	29	⇔	⇔	⇔
Emtricitabine	200 once daily × 7 days	17	⇔	⇔	⇔
Entecavir	1 mg once daily x 10 days	28	⇔	⇔	⇔
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Lamivudine	150 twice daily × 7 days	15	⇔	⇔	⇔
Lopinavir/ Ritonavir	400/100 twice daily × 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Nelfinavir	1250 twice daily × 14 days	29	⇔	⇔	⇔
Saquinavir/ Ritonavir	1000/100 twice daily × 14 days	35	⇔	⇔	↑ 23 (↑ 16 to ↑ 30)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↑ 13 (↑ 1 to ↑ 27)	⇔	⇔

a. Subjects received VIREAD 300 mg once daily.

b. Increase = ↑; Decrease = ↓; No Effect = ⇔; NC = Not Calculated

c. Reyataz Prescribing Information

Following multiple dosing to HIV- and HBV-negative subjects receiving either chronic methadone maintenance therapy or oral contraceptives, or single doses of ribavirin, steady state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating lack of clinically significant drug interactions between these agents and VIREAD.

Table 11 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of VIREAD

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[a] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	⇔	NA
Atazanavir[b]	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir[b]	Atazanavir/ Ritonavir 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25[c] (↓ 42 to ↓ 3)	↓ 23[c] (↓ 46 to ↑ 10)
Efavirenz	600 once daily × 14 days	30	⇔	⇔	⇔
Emtricitabine	200 once daily × 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Entecavir	1 mg once daily x 10 days	28	⇔	↑ 13 (↑ 11 to ↑ 15)	⇔
Indinavir	800 three times daily × 7 days	12	↓ 11 (↓ 30 to ↑ 12)	⇔	⇔
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Lopinavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	⇔	⇔	⇔
Ritonavir			⇔	⇔	⇔
Methadone[d]	40–110 once daily × 14 days[e]	13	⇔	⇔	⇔
Nelfinavir	1250 twice daily × 14 days	29	⇔	⇔	⇔
M8 metabolite			⇔	⇔	⇔
Oral Contraceptives[f]	Ethinyl Estradiol/ Norgestimate (Ortho-Tricyclen) once daily × 7 days	20	⇔	⇔	⇔
Ribavirin	600 once	22	⇔	⇔	NA
Saquinavir	Saquinavir/Ritonavir 1000/100 twice daily × 14 days	32	↑ 22 (↑ 6 to ↑ 41)	↑ 29[g] (↑ 12 to ↑ 48)	↑ 47[g] (↑ 23 to ↑ 76)
Ritonavir			⇔	⇔	↑ 23 (↑ 3 to ↑ 46)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	⇔	⇔	⇔

a. Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable

b. Reyataz Prescribing Information

c. In HIV-infected subjects, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.

d. R-(active), S- and total methadone exposures were equivalent when dosed alone or with VIREAD.

e. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.

f. Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with VIREAD.

g. 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.

Table 12 summarizes the drug interaction between VIREAD and didanosine. Coadministration of VIREAD and didanosine should be undertaken with caution *[See Drug Interactions (7.1)]*. When administered with multiple doses of VIREAD, the C_{max} and AUC of didanosine 400 mg increased significantly. The mechanism of this interaction is unknown. When didanosine 250 mg enteric-coated capsules were administered with VIREAD, systemic exposures to didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.

Table 12 Drug Interactions: Pharmacokinetic Parameters for Didanosine in the Presence of VIREAD

Didanosine Dose (mg)/ Method of Administration	VIREAD Method of Administration[a]	N	% Difference (90% CI) vs. Didanosine 400 mg Alone, Fasted[b]	
			C_{max}	AUC
Buffered tablets				
400 once daily[c] × 7 days	Fasted 1 hour after didanosine	14	↑ 28 (↑ 11 to ↑ 48)	↑ 44 (↑ 31 to ↑ 59)
Enteric coated capsules				
400 once, fasted	With food, 2 hours after didanosine	26	↑ 48 (↑ 25 to ↑ 76)	↑ 48 (↑ 31 to ↑ 67)
400 once, with food	Simultaneously with didanosine	26	↑ 64 (↑ 41 to ↑ 89)	↑ 60 (↑ 44 to ↑ 79)
250 once, fasted	With food, 2 hours after didanosine	28	↓ 10 (↓ 22 to ↑ 3)	⇔
250 once, fasted	Simultaneously with didanosine	28	⇔	↑ 14 (0 to ↑ 31)
250 once, with food	Simultaneously with didanosine	28	↓ 29 (↓ 39 to ↓ 18)	↓ 11 (↓ 23 to ↑ 2)

a. Administration with food was with a light meal (~373 kcal, 20% fat).

b. Increase = ↑; Decrease = ↓; No Effect = ⇔

c. Includes 4 subjects weighing <60 kg receiving ddI 250 mg.

12.4 Microbiology

Mechanism of Action

Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator. Tenofovir

diphosphate inhibits the activity of HIV-1 reverse transcriptase and HBV polymerase 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 of tenofovir 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), additive to synergistic effects were observed. 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 2–4 fold reduction in 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%) analyzed patient isolates on the VIREAD arm and in 2/49 (4%) analyzed patient isolates on the stavudine arm. Of the 8 subjects whose virus developed K65R in the VIREAD arm through 144 weeks, 7 of these occurred in the first 48 weeks of treatment and one at Week 96. Other substitutions resulting in resistance to VIREAD were not identified in this study.

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 >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 analyzed subject isolates in the VIREAD + EMTRIVA group and in 10/29 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 substitution selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir, didanosine, or zalcitabine. HIV-1 isolates with this mutation also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors the K65R substitution. HIV-1 isolates from subjects (N=20) whose HIV-1 expressed a mean of 3 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 >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 studies, 94% of the participants evaluated had baseline HIV-1 isolates expressing at least one NRTI mutation. These included resistance substitutions associated with zidovudine (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N), the abacavir/emtricitabine/lamivudine resistance-associated substitution (M184V), and others. In addition the majority of participants evaluated had substitutions associated with either PI or NNRTI use. Virologic responses for subjects in the genotype substudy were similar to the overall study 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 were observed and appeared to depend on the 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

The virologic response to VIREAD therapy has been evaluated with respect to baseline phenotype (N=100) in treatment-experienced subjects participating in two controlled trials. Phenotypic analysis of baseline HIV-1 from subjects in these studies demonstrated a correlation between baseline susceptibility to VIREAD and response to VIREAD therapy. Table 13 summarizes the HIV-1 RNA response by baseline VIREAD susceptibility.

Table 13 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 >100 μM. In cell culture combination antiviral activity studies of tenofovir with the nucleoside anti-HBV reverse transcriptase inhibitors emtricitabine, entecavir, lamivudine and telbivudine, no antagonistic activity was observed.

Resistance

Cumulative VIREAD genotypic resistance analysis of paired pre-treatment and on-treatment isolates was performed using an as-treated analysis. Subjects remaining viremic with HBV DNA >400 copies/mL at the last evaluable study visit after 96 weeks of cumulative treatment (16%[26/160] of HBeAg positive subjects in Study 103 and 3% [8/234] of HBeAg negative subjects in Study 102) were evaluated for genotypic resistance. These 34 subjects with viremia were primarily treatment-naïve and received VIREAD for up to 96 weeks; of these, 65% (17/26) of HBeAg-positive and 13% (1/8) of HBeAg-negative subjects had a baseline viral load of >9 log_{10} copies/mL.

In addition, 16 of the 84 HBeAg-positive subjects who received 48 weeks of HEPSERA and then switched to VIREAD for up to 48 weeks, and 18 of 53 Hepsera treatment-experienced subjects from an ongoing Phase 2 study who received up to 48 weeks of VIREAD monotherapy and who had plasma HBV DNA >400 copies/mL, were included in the resistance analysis. Subjects in the Phase 2 study were previously treated for 24

to 96 weeks with HEPSERA for chronic HBV infection and had plasma HBV DNA levels ≥ 1,000 copies/mL at screening.

In the three VIREAD-treatment studies, paired genotypic data were obtained for 55 of 68 viremic subjects. No specific amino acid substitutions in the HBV reverse transcriptase domain occurred at a sufficient frequency to be associated with resistance to VIREAD (genotypic or phenotypic analyses).

In the three VIREAD-treatment studies, prior to treatment with VIREAD, 13 and 10 subjects had HBV harboring adefovir resistance-associated substitutions (rtA181T/V and/or rtN236T) or lamivudine resistance-associated substitution (rtM204I/V), respectively. Following up to 96 weeks of VIREAD treatment, 11 of the 13 subjects with adefovir-resistant HBV and 8 of the 10 subjects with lamivudine-resistant HBV achieved virologic suppression (HBV DNA <400 copies/mL). Two of the 4 subjects harboring both the rtA181T/V and rtN236T substitutions remained viremic following 24 weeks of VIREAD monotherapy.

Cross Resistance

Cross-resistance has been observed among HBV 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. An HBV strain expressing rtL180M, rtT184G, rtS202I and rtM204V together had a 6.9-fold reduction in susceptibility to tenofovir.

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate 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.

Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse

micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate 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 disoproxil fumarate 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 Patients with HIV-1 Infection

Treatment-Naïve Patients

Study 903

Data through 144 weeks are reported for Study 903, a double-blind, active-controlled multicenter study comparing VIREAD (300 mg once daily) administered in combination with lamivudine and efavirenz versus stavudine (d4T), lamivudine, and efavirenz in 600 antiretroviral-naïve 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 14.

Table 14 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 study 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 study, 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 15.

Table 15 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 study 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 study. 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 Patients

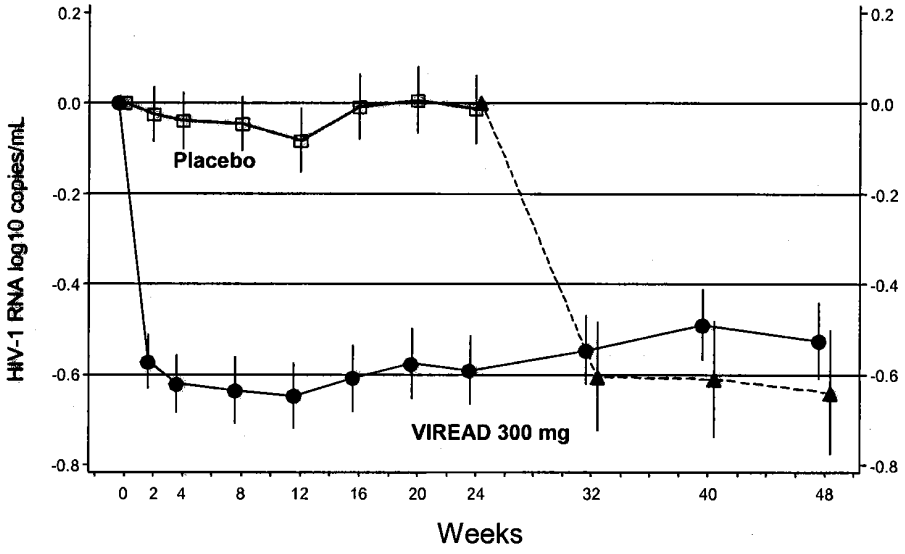
Study 907

Study 907 was a 24-week, double-blind placebo-controlled multicenter study of VIREAD added to a stable background regimen of antiretroviral agents in 550 treatment-

experienced subjects. After 24 weeks of blinded study treatment, all subjects continuing on study 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 and 69% were Caucasian, 17% Black and 12% Hispanic.

Changes from baseline in log_{10} copies/mL plasma HIV-1 RNA levels over time up to Week 48 are presented below in Figure 1.

Figure 1 **Mean Change from Baseline in Plasma HIV-1 RNA (log_{10} copies/mL) Through Week 48 (Study 907; All Available Data)†**



VIREAD (N=)	368	335	358	353	354	353	347	346	346	336	327
Placebo (N=)	182	170	179	175	175	173	173	172			
Placebo->VIREAD (N=)								170	167	162	160

† Patients on placebo after 24 weeks received VIREAD.

The percent of subjects with HIV-1 RNA <400 copies/mL and outcomes of subjects through 48 weeks are summarized in Table 16.

Table 16 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 Patients with Chronic Hepatitis B

HBeAg-Negative Chronic Hepatitis B

Study 0102 was a Phase 3, randomized, double-blind, active-controlled study 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 study 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 studies was complete response to treatment defined as HBV DNA <400 copies/mL and Knodell necroinflammatory score improvement of at least 2 points, without worsening in Knodell fibrosis at Week 48 (Table 17).

Table 17 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 rolled over with no interruption in treatment to open-label VIREAD through Week 96 after receiving double-blind treatment for 48 weeks (either VIREAD or HEPSERA). At Week 72 or thereafter, emtricitabine could be added to VIREAD in subjects who had detectable HBV DNA.

In Study 0102, 90% of subjects who were randomized to VIREAD completed 96 weeks of treatment. Among subjects randomized to VIREAD followed by open-label treatment with VIREAD, 89% had undetectable HBV DNA (< 400 copies/mL), and 71% had ALT normalization at Week 96. In the group of subjects randomized to HEPSERA followed by open-label treatment with VIREAD, 88% completed 96 weeks of treatment; 96% of this cohort had undetectable HBV DNA (< 400 copies/mL) and 71% had ALT normalization at Week 96. Emtricitabine was added to VIREAD in 2 (<1%) subjects initially randomized to VIREAD and none of those randomized to HEPSERA. No subject in either treatment group experienced HBsAg loss/seroconversion through Week 96.

In Study 0103, 82% of subjects randomized to VIREAD completed 96 weeks of treatment. Among subjects randomized to VIREAD, 81% had undetectable HBV DNA (< 400 copies/mL), 64% had ALT normalization, 27% had HBeAg loss (23% seroconversion to anti-HBe antibody), and 5% had HBsAg loss (4% seroconversion to anti-HBs antibody) through Week 96. Among subjects randomized to HEPSERA followed by up to 48 weeks of open-label treatment with VIREAD, 92% of subjects completed 96 weeks of treatment; 76% had undetectable HBV DNA (< 400 copies/mL), 67% had ALT normalization, 24% had HBeAg loss (21% seroconversion to anti-HBe antibody), and 6% experienced HBsAg loss (5% seroconversion to anti-HBs antibody) through Week 96. Emtricitabine was added to VIREAD in 15 (9%) subjects randomized to VIREAD, and in 13 (14%) subjects randomized to HEPSERA.

Across the combined HBV treatment studies, the number of subjects with lamivudine- or adefovir-resistance associated substitutions at baseline was too small to establish efficacy in this subgroup.

16 HOW SUPPLIED/STORAGE AND HANDLING

The almond-shaped, light blue, film-coated tablets contain 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil, are debossed with "GILEAD" and "4331" on one side and with "300" on the other side, and are available in unit of use bottles (containing a desiccant [silica gel canister or sachet] and closed with a child-resistant closure) of:

- 30 tablets (NDC 61958–0401–1)

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

Do not use if seal over bottle opening is broken or missing.

17 PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling

Information for Patients

Patients should be advised 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.

- The use of VIREAD has not been shown to reduce the risk of transmission of HIV-1 or HBV to others through sexual contact or blood contamination. Patients should be advised to continue to practice safer sex and to use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Patients should be advised never to re-use or share needles.
- The long term effects of VIREAD are unknown.
- VIREAD Tablets 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.
- 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 (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) *[See Warnings and Precautions (5.1)]*.
- Patients with HIV-1 should be tested for Hepatitis B virus (HBV) before initiating antiretroviral therapy *[See Warnings and Precautions (5.5)]*.
- 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 (5.2)]*.
- In patients with chronic hepatitis B, it is important to obtain HIV antibody testing prior to initiating VIREAD *[See Warnings and Precautions (5.5)]*.
- 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 *[See Warnings and Precautions (5.3)]*. Dosing interval of VIREAD may need adjustment in patients with renal impairment *[See Dosage and Administration (2.2)]*.
- VIREAD should not be coadministered with the fixed-dose combination products TRUVADA and ATRIPLA since it is a component of these products *[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 in patients with HIV. 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 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.

FDA-Approved Patient Labeling

VIREAD® (VEER ee ad) Tablets

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

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

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

• **Some people who have taken medicine like VIREAD (nucleoside analogs) have developed a serious condition called lactic acidosis** (build up of an acid in the blood). Lactic acidosis can be a medical emergency and may need to be treated in the hospital. **Call your healthcare provider right away if you get the following signs or symptoms of lactic acidosis.**

- You feel very weak or tired.
- You have unusual (not normal) muscle pain.
- You have trouble breathing.
- You have stomach pain with nausea and vomiting.
- You feel cold, especially in your arms and legs.
- You feel dizzy or lightheaded.
- You have a fast or irregular heartbeat.

• **Some people who have taken medicines like VIREAD have developed serious liver problems called hepatotoxicity**, with liver enlargement (hepatomegaly) and fat in the liver (steatosis). **Call your healthcare provider right away if you get the following signs or symptoms of liver problems.**

- Your skin or the white part of your eyes turns yellow (jaundice).
- Your urine turns dark.
- Your bowel movements (stools) turn light in color.
- You don't feel like eating food for several days or longer.
- You feel sick to your stomach (nausea).
- You have lower stomach area (abdominal) pain.

•**You may be more likely to get lactic acidosis or liver problems** if you are female, very overweight (obese), or have been taking nucleoside analog medicines, like VIREAD, for a long time.

If you are infected with the Hepatitis B Virus (HBV), you need close medical follow-up for several months after stopping treatment with VIREAD. Follow-up includes medical exams and blood tests to check for HBV that could be getting worse. **Patients with Hepatitis B Virus infection, who take VIREAD and then stop it, may get "flare-ups" of their**

hepatitis. A "flare-up" is when the disease suddenly returns in a worse way than before.

What is VIREAD and how does it work?

VIREAD is a type of medicine called an HIV nucleotide analog reverse transcriptase inhibitor (NRTI) and an HBV polymerase inhibitor.

Use in the Treatment of HIV-1 Infection:

VIREAD is a treatment for Human Immunodeficiency Virus (HIV) infection in adults age 18 years and older. VIREAD is always used in combination with other anti-HIV-1 medicines to treat people with HIV-1 infection.

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

VIREAD helps to block HIV-1 reverse transcriptase, a chemical in your body (enzyme) that is needed for HIV-1 to multiply. VIREAD lowers the amount of HIV-1 in the blood (called viral load) and may help to increase the number of T cells (called $CD4^+$ cells). Lowering the amount of HIV-1 in the blood lowers the chance of death or infections that happen when your immune system is weak (opportunistic infections).

Use in the Treatment of Chronic Hepatitis B:

VIREAD is also used to treat chronic hepatitis B (an infection with hepatitis B virus [HBV]) in adults age 18 years and older. VIREAD works by interfering with the normal working of an enzyme (HBV DNA polymerase) that is essential for the HBV virus to reproduce itself. VIREAD may help lower the amount of hepatitis B virus in your body by lowering the ability of the virus to multiply and infect new liver cells.

We do not know how long VIREAD may help your hepatitis. Sometimes viruses change in your body and medicines no longer work. This is called drug resistance.

Viread may improve the condition of your liver; but we do not know if VIREAD will reduce your chances of getting liver damage (cirrhosis) or liver cancer from chronic hepatitis B.

Does VIREAD cure HIV-1 or AIDS?

VIREAD does not cure HIV-1 infection or AIDS. The long-term effects of VIREAD are not known at this time. People taking VIREAD may still get opportunistic infections or other conditions that happen with HIV-1 infection. Opportunistic infections are infections that develop because the immune system is weak. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infections.

Does VIREAD reduce the risk of passing HIV-1 or HBV to others?

VIREAD does not reduce the risk of passing HIV-1 or HBV to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles. Do not share personal items that can have blood or body fluids on them

like toothbrushes or razor blades. A shot (vaccine) is available to protect people at risk for becoming infected with HBV.

Who should not take VIREAD?

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

Do not take VIREAD if

- you are allergic to VIREAD or any of its ingredients
- you are already taking TRUVADA® or ATRIPLA® because VIREAD is one of the active ingredients in TRUVADA and ATRIPLA
- you are currently taking HEPSERA®

What should I tell my healthcare provider before taking VIREAD?

Tell your healthcare provider

- *If you are pregnant or planning to become pregnant:* The effects of VIREAD on pregnant women or their unborn babies are not known. You and your healthcare provider will need to decide if VIREAD is right for you. If you use VIREAD while you are pregnant, talk to your healthcare provider about how you can be on the VIREAD Antiviral Pregnancy Registry.
- *If you are breast-feeding:* You should not breastfeed if you are taking VIREAD. It is not known whether VIREAD is passed to the infant in breast milk; and whether it could harm your baby. Do not breast-feed if you have HIV. If your baby does not already have HIV, there is a chance that the baby can get HIV through breast-feeding. Talk with your healthcare provider about the best way to feed your baby.
- **If you have kidney or bone problems**
- **If you have liver problems including Hepatitis B Virus infection**
- **If you have HIV-1 Infection**
- **Tell your healthcare provider about all your medical conditions**

TELL YOUR HEALTHCARE PROVIDER ABOUT ALL THE MEDICINES YOU TAKE, INCLUDING PRESCRIPTION AND NON-PRESCRIPTION MEDICINES AND DIETARY SUPPLEMENTS. ESPECIALLY TELL YOUR HEALTHCARE PROVIDER IF YOU TAKE:

- VIDEX, VIDEX EC (DIDANOSINE). VIREAD MAY INCREASE THE AMOUNT OF VIDEX IN YOUR BLOOD. YOU MAY NEED TO BE FOLLOWED MORE CAREFULLY IF YOU ARE TAKING VIDEX AND VIREAD TOGETHER. IF YOU ARE TAKING VIDEX AND VIREAD TOGETHER YOUR HEALTHCARE PROVIDER MAY NEED TO REDUCE YOUR DOSE OF VIDEX.
- REYATAZ (ATAZANAVIR SULFATE) OR KALETRA (LOPINAVIR/RITONAVIR). THESE MEDICINES MAY INCREASE THE AMOUNT OF VIREAD IN YOUR

BLOOD, WHICH COULD RESULT IN MORE SIDE EFFECTS. YOU MAY NEED TO BE FOLLOWED MORE CAREFULLY IF YOU ARE TAKING VIREAD AND REYATAZ OR KALETRA TOGETHER. VIREAD MAY DECREASE THE AMOUNT OF REYATAZ IN YOUR BLOOD. IF YOU ARE TAKING VIREAD AND REYATAZ TOGETHER YOU SHOULD ALSO BE TAKING NORVIR (RITONAVIR).

KEEP A COMPLETE LIST OF ALL THE MEDICINES THAT YOU TAKE. MAKE A NEW LIST WHEN MEDICINES ARE ADDED OR STOPPED. GIVE COPIES OF THIS LIST TO ALL OF YOUR HEALTHCARE PROVIDERS **EVERY** TIME YOU VISIT YOUR HEALTHCARE PROVIDER OR FILL A PRESCRIPTION.

How should I take VIREAD?

- Stay under a healthcare provider's care when taking VIREAD. Do not change your treatment or stop treatment without first talking with your healthcare provider.
- Take VIREAD exactly as your healthcare provider prescribed it. Follow the directions from your healthcare provider, exactly as written on the label. Set up a dosing schedule and follow it carefully.
- If you are taking VIREAD to treat your HIV or if you have both HIV and HBV infection and are taking VIREAD, always take VIREAD in combination with other anti-HIV medicines. VIREAD and other products like VIREAD may be less likely to work in the future if you are not taking VIREAD with other anti-HIV medicines because you may develop resistance to those medicines.
- Talk to your doctor about taking an HIV test before you start treatment with VIREAD for chronic hepatitis B.
- The usual dose of VIREAD is 1 tablet once a day. If you have kidney problems, your healthcare provider may recommend that you take VIREAD less frequently.
- VIREAD may be taken with or without a meal.
- When your VIREAD supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to VIREAD and become harder to treat.
- Only take medicine that has been prescribed specifically for you. Do not give VIREAD to others or take medicine prescribed for someone else.

What should I do if I miss a dose of VIREAD?

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

What happens if I take too much VIREAD?

If you suspect that you took more than the prescribed dose of VIREAD, contact your local poison control center or emergency room right away.

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

What should I avoid while taking VIREAD?

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

What are the possible side effects of VIREAD? (see also "What is the most important information I should know about VIREAD")

- Clinical studies in patients with HIV-1: The most common side effects of VIREAD are: rash, headache, pain, diarrhea, depression, weakness, and nausea. Less common side effects include vomiting, dizziness, and intestinal gas.

  Clinical studies in patients with chronic hepatitis B: The most common side effect of VIREAD is nausea. Less common side effects include abdominal pain, diarrhea, headache, dizziness, fatigue, common cold symptoms such as sore throat and runny nose, back pain, and skin rash.

- Marketing experience: Other side effects reported since VIREAD has been marketed include: lactic acidosis, kidney problems (including decline or failure of kidney function), inflammation of the pancreas, inflammation of the liver, allergic reactions (including itching, or swelling of the face, lips, tongue or throat), shortness of breath, stomach pain, and high volume of urine and thirst caused by kidney problems. Muscle pain and muscle weakness, bone pain, and softening of the bone (which may contribute to fractures) as a consequence of kidney problems have been reported.
- Some patients treated with VIREAD have had kidney problems. If you have had kidney problems in the past or need to take another drug that can cause kidney problems, your healthcare provider may need to perform additional blood tests.
- Laboratory tests show changes in the bones of patients treated with VIREAD. Some HIV patients treated with VIREAD developed thinning of the bones (osteopenia) which could lead to fractures. If you have had bone problems in the past, your healthcare provider may need to perform additional tests or may suggest additional medication. Additionally, bone pain and softening of the bone (which may contribute to fractures) may occur as a consequence of kidney problems.
- Changes in body fat have been seen in some patients taking anti-HIV-1 medicine. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms and face may also happen. The cause and long term health effects of these conditions are not known at this time.
- In some patients with advanced HIV infection (AIDS), 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. If you notice any symptoms of infection, please inform your doctor immediately.

- After stopping treatment with VIREAD, some patients with HBV have had symptoms or blood tests showing that their hepatitis has gotten worse ("flare-ups"). Therefore, your doctor should check your health, which may include blood tests, for at least several months after stopping treatment with VIREAD. Tell your doctor right away about any new or unusual symptoms that you notice after stopping treatment.
- If you have HBV infection or HIV and HBV infection together, you may have a "flare-up" of Hepatitis B, in which the disease suddenly returns in a worse way than before if you stop taking VIREAD. Do not stop taking VIREAD without your doctor's advice. After stopping VIREAD, tell your doctor immediately about any new, unusual, or worsening symptoms that you notice after stopping treatment. After you stop taking VIREAD, your doctor will still need to check your health and take blood tests to check your liver for several months.
- There have been other side effects in patients taking VIREAD. However, these side effects may have been due to other medicines that patients were taking or to the illness itself. Some of these side effects can be serious.
- This list of side effects is **not** complete. If you have questions about side effects, ask your healthcare provider. You should report any new or continuing symptoms to your healthcare provider right away. Your healthcare provider may be able to help you manage these side effects.

How do I store VIREAD?

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

General advice about prescription medicines:

TALK TO YOUR HEALTHCARE PROVIDER IF YOU HAVE ANY QUESTIONS ABOUT THIS MEDICINE OR YOUR CONDITION. MEDICINES ARE SOMETIMES PRESCRIBED FOR PURPOSES OTHER THAN THOSE LISTED IN A PATIENT INFORMATION LEAFLET. IF YOU HAVE ANY CONCERNS ABOUT THIS MEDICINE, ASK YOUR HEALTHCARE PROVIDER. YOUR HEALTHCARE PROVIDER OR PHARMACIST CAN GIVE YOU INFORMATION ABOUT THIS MEDICINE THAT WAS WRITTEN FOR HEALTH CARE PROFESSIONALS. DO NOT USE THIS MEDICINE FOR A CONDITION FOR WHICH IT WAS NOT PRESCRIBED. DO NOT SHARE THIS MEDICINE WITH OTHER PEOPLE.

DO NOT USE IF SEAL OVER BOTTLE OPENING IS BROKEN OR MISSING.

What are the ingredients of VIREAD?

Active Ingredient: tenofovir disoproxil fumarate

Inactive Ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The tablets are coated with Opadry II Y–30–10671–A, which contains FD&C blue #2 aluminum lake, hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide, and triacetin.

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