VIREAD®

(tenofovir disoproxil fumarate) Tablets

℞ Only

WARNING: POSTTREATMENT ACUTE EXACERBATION OF HEPATITIS B

Severe acute exacerbations of hepatitis B virus (HBV) have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely in HBV-infected patients who discontinue VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted. *(5.1)*

1 INDICATIONS AND USAGE

1.1 HIV-1 Infection

VIREAD is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients 12 years of age and older.

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 DESCOVY®, GENVOYA®, STRIBILD®, TRUVADA® or other products containing tenofovir disoproxil fumarate (DF) or tenofovir alafenamide *[See Warnings and Precautions (5.4)]*.

1.2 Chronic Hepatitis B

VIREAD is indicated for the treatment of chronic hepatitis B virus (HBV) in adults and adolescents 12 to <18 years of age.

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

The indication in adults is based on safety and efficacy data from treatment of subjects who were nucleoside-treatment-naïve and subjects who were treatment-experienced with documented resistance to lamivudine. Subjects were adults with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease *[See Clinical Studies (13.2)].*

VIREAD was evaluated in a limited number of subjects with chronic hepatitis B and decompensated liver disease. *[See Adverse Reactions (6.1), Clinical Studies (13.2)]*

The numbers of subjects in clinical trials who had adefovir resistance-associated substitutions at baseline were too small to reach conclusions of efficacy *[See Microbiology (11.3), Clinical Studies (13.2)].*

VIREAD is indicated for the treatment of chronic hepatitis B in adolescents 12 to <18 years of age with:

Compensated liver disease and evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of VIREAD for Treatment of HIV-1 Infection or Chronic Hepatitis B

Prior to or when initiating VIREAD, test patients for HBV infection and HIV-1 infection. VIREAD alone should not be used in patients with HIV-1 infection *[see Warnings and Precautions (5.3)*].

Prior to initiation and during use of VIREAD, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus *[see Warnings and Precautions (5.2)]*.

2.2 Recommended Tablet Dosage in Adults and Pediatric Patients 12 Years of Age and Older (35 kg or more)

The recommended dosage of VIREAD in adults and pediatric patients weighing at least 35 kg is one 300 mg tablet taken orally, once daily without regard to food. The dosage for VIREAD is the same for both HIV and HBV indications.

In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown. Safety and efficacy in pediatric patients with chronic hepatitis B weighing less than 35 kg have not been established.

2.3 Dosage Adjustment in Patients with Renal Impairment

Significant increase in drug exposures occurred when VIREAD was administered to subjects with moderate to severe renal impairment (creatinine clearance below 50 mL/min)Table 1 provides dosage interval adjustment for patients with renal impairment. No dosage adjustment is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min) *[see Warnings and Precautions (5.2), Use in Specific Populations (8.5), and Clinical Pharmacology (11.2)]*.

Table 1 Dosage Interval Adjustment for Adult Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)[a]			
	50 or greater	**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 3 hemodialysis sessions a week of approximately 4 hours' duration. VIREAD should be administered following completion of dialysis.

No data are available to make dosage recommendations in patients with creatinine clearance below 10 mL/min who are not on hemodialysis.

No data are available to make dosage recommendations in pediatric patients 12 years of age and older with renal impairment.

3 DOSAGE FORMS AND STRENGTHS

VIREAD is available as tablets. Each tablet contains 300 mg of tenofovir DF, which is equivalent to 245 mg of tenofovir disoproxil. The tablets are almond-shaped, light blue, film-coated, debossed with "GILEAD" and "4331" on one side and with "300" on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Patients with HBV Infection

All patients should be tested for the presence of chronic hepatitis B virus (HBV) before or when initiating VIREAD *[see Dosage and Administration (2.1)]*.

Discontinuation of anti-HBV therapy, including VIREAD, may be associated with severe acute exacerbations of hepatitis B. 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, especially in patients with advanced liver disease or cirrhosis, since posttreatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

5.2 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)]*.

Prior to initiation and during use of VIREAD, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus.

Dosing interval adjustment of VIREAD and close monitoring of renal function are recommended in all patients with creatinine clearance below 50 mL/min *[see Dosage and Administration (2.3)]*. 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 (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs [NSAIDs]) *[see Drug Interactions (7.4)]*. Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on TDF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in patients at risk of renal dysfunction.

5.3 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.

5.4 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-1 infected patients treated with combination antiretroviral therapy, including VIREAD. During the initial phase of combination antiretroviral treatment, HIV-1 infected 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.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

5.5 Bone Loss and Mineralization Defects

Bone Mineral Density

In clinical trials in HIV-1 infected adults, VIREAD was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators [see Adverse Reactions (6.1)]. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving VIREAD.

Clinical trials evaluating VIREAD in pediatric subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects 2 years to less than 18 years of age, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the VIREAD-treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in chronic HBV-infected pediatric subjects 2 years to less than 18 years of age. In all pediatric trials, normal skeletal growth (height) was not affected for the duration of the clinical trials *[see Adverse Reactions (6.1)]*.

The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk in adults and pediatric subjects are unknown. The long-term effect of lower spine and total body BMD on skeletal growth in pediatric patients, and in particular, the effects of long-duration exposure in younger children is unknown.

Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial. Assessment of BMD should be considered for adult and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. If bone abnormalities are suspected, appropriate consultation should be obtained.

Mineralization Defects

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with VIREAD use *[see Adverse Reactions (6.2)]*. Arthralgia and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving TDF-containing products *[see Warnings and Precautions (5.5)]*.

5.6 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 TDF, alone or in combination with other antiretrovirals. 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).

5.7 Risk of Adverse Reactions Due to Drug Interactions

The concomitant use of VIREAD and other drugs may result in known or potentially significant drug interactions, some of which may lead to possible clinically significant adverse reactions from greater exposures of concomitant drugs *[see Drug Interactions (7.2)].*

See Table 12 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with VIREAD; review concomitant medications during therapy with VIREAD; and monitor for adverse reactions associated with the concomitant drugs.

5.8 Early Virologic Failure

Clinical trials 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.

5.9 HBV Patients with Decompensated Liver Disease

There are limited data on the safety and efficacy of tenofovir DF in HBV infected patients with decompensated liver disease and who have a Child-Pugh-Turcotte (CPT) score > 9. These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population.

6 ADVERSE REACTIONS

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

- Severe Acute Exacerbation of Hepatitis B in Patients with HBV Infection *[see Warnings and Precautions (5.1)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.2)].*
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.4)]*.
- Bone Loss and Mineralization Defects *[see Warnings and Precautions (5.5)]*.
- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[see Warnings and Precautions (5.6)]*.

6.1 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.

Adverse Reactions from Clinical Trials Experience in HIV-1 Infected Adults

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 programs. 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 programs.

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

Clinical Trials in Treatment-Naïve HIV-1 Infected Adult Subjects

In Trial 903, 600 antiretroviral-naïve subjects received VIREAD (N=299) or stavudine (d4T) (N=301) administered in combination with lamivudine (3TC) and efavirenz (EFV) for 144 weeks. The most common adverse reactions 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. Table 2 provides the treatment-emergent adverse reactions (Grades 2-4) occurring in greater than or equal to 5% of subjects treated in any treatment group.

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

	VIREAD + 3TC + EFV	d4T + 3TC + EFV
	N=299	N=301
Rash event[b]	18%	12%
Headache	14%	17%
Pain	13%	12%
Diarrhea	11%	13%
Depression	11%	10%
Back pain	9%	8%
Nausea	8%	9%
Fever	8%	7%
Abdominal pain	7%	12%
Asthenia	6%	7%
Anxiety	6%	6%
Vomiting	5%	9%
Insomnia	5%	8%
Arthralgia	5%	7%
Pneumonia	5%	5%
Dyspepsia	4%	5%
Dizziness	3%	6%
Myalgia	3%	5%
Lipodystrophy[c]	1%	8%
Peripheral neuropathy[d]	1%	5%

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

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

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

d. Peripheral neuropathy includes peripheral neuritis and neuropathy.

Laboratory Abnormalities: Table 3 provides a list of laboratory abnormalities (Grades 3-4) observed in Trial 903. With the exception of fasting cholesterol and fasting triglyceride elevations that were more common in the d4T group (40% and 9%) compared with the VIREAD group (19% and 1%), respectively, laboratory abnormalities observed in this trial occurred with similar frequency in the VIREAD and d4T treatment arms.

Table 3 Grades 3-4 Laboratory Abnormalities Reported in ≥1% of VIREAD-Treated Subjects in Trial 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%

Changes in Bone Mineral Density:

In HIV-1 infected adult subjects in Trial 903, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving VIREAD + 3TC+EFV (−2.2% ± 3.9) compared with subjects receiving d4T + 3TC + EFV (−1.0% ± 4.6) through 144 weeks. 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 d4T group). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the trial and this reduction was sustained through Week 144. Twenty-eight percent of VIREAD-treated subjects vs. 21% of d4T-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 d4T 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) and higher serum parathyroid hormone levels and 1,25 Vitamin D levels in the VIREAD group relative to the d4T group; however, except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range *[see Warnings and Precautions (5.5)]*.

In Trial 934, 511 antiretroviral-naïve subjects received efavirenz (EFV) administered in combination with either emtricitabine (FTC) + VIREAD (N=257) or zidovudine (AZT)/lamivudine (3TC) (N=254) for 144 weeks. The most common adverse reactions (incidence greater than or equal to 10%, all grades) included diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. Table 4 provides the treatment-emergent adverse reactions (Grades 2−4) occurring in greater than or equal to 5% of subjects treated in any treatment group.

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

	VIREAD[b] + FTC + EFV	AZT/3TC + EFV
	N=257	N=254
Fatigue	9%	8%
Depression	9%	7%
Nausea	9%	7%
Diarrhea	9%	5%
Dizziness	8%	7%
Sinusitis	8%	4%
Rash event[c]	7%	9%
Headache	6%	5%
Insomnia	5%	7%
Nasopharyngitis	5%	3%
Vomiting	2%	5%

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 trial, subjects received TRUVADA® with EFV in place of VIREAD + FTC with EFV.

c. Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculopapular, rash pruritic, and rash vesicular.

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

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

	VIREAD + FTC + EFV[a]	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 trial, subjects received TRUVADA with EFV in place of VIREAD + FTC with EFV.

Clinical Trials in Treatment-Experienced HIV-1 Infected Adult Subjects

In Trial 907, the adverse reactions seen in HIV-1 infected 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 trials due to gastrointestinal adverse reactions. Table 6 provides the treatment-emergent adverse reactions (Grades 2–4) occurring in greater than or equal to 3% of subjects treated in any treatment group.

Table 6 Selected Adverse Reactions[a] (Grades 2–4) Reported in ≥3% in Any Treatment Group in Trial 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: Table 7 provides a list of Grade 3-4 laboratory abnormalities observed in Trial 907. Laboratory abnormalities occurred with similar frequency in the VIREAD and placebo groups.

Table 7 Grades 3-4 Laboratory Abnormalities Reported in ≥1% of VIREAD-Treated Subjects in Trial 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: >990 U/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%

Adverse Reactions from Clinical Trials Experience in HIV-1 Infected Pediatric Subjects 12 Years and Older

Assessment of adverse reactions is based on two randomized trials (Trials 352 and 321) in 184 HIV-1 infected pediatric subjects (2 years to less than 18 years of age) who received treatment with VIREAD (N=93) or placebo/active comparator (N=91) in combination with other antiretroviral agents for 48 weeks *[see Clinical Studies (13.3)]*. The adverse reactions observed in subjects who received treatment with VIREAD were consistent with those observed in clinical trials in adults.

Changes in Bone Mineral Density:

In Trial 321 (12 years to less than 18 years of age), the mean rate of BMD gain at Week 48 was less in the VIREAD group compared to the placebo group. Six VIREAD treated subjects and one placebo treated subject had significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline BMD Z-scores were −0.341 for lumbar spine and −0.458 for total body in the 28 subjects who were treated with VIREAD for 96 weeks. Skeletal growth (height) appeared to be unaffected for the duration of the clinical trials *[See Warnings and Precautions (5.5)]*.

Adverse Reactions from Clinical Trials Experience in HBV-Infected Adults

Clinical Trials in Adult Subjects with Chronic Hepatitis B and Compensated Liver Disease

In controlled clinical trials in 641 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 more than 5% of subjects treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain and skin rash.

In Trials 0102 and 0103, during the open-label phase of treatment with VIREAD (weeks 48-384), 2% of subjects (13/585) experienced a confirmed increase in serum creatinine of 0.5 mg/dL from baseline. No significant change in the tolerability profile was observed with continued treatment for up to 384 weeks.

Laboratory Abnormalities: Table 8 provides a list of Grade 3- 4 laboratory abnormalities through Week 48. Grades 3-4 laboratory abnormalities were similar in subjects continuing VIREAD treatment for up to 384 weeks in these trials.

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

	VIREAD N=426	**HEPSERA N=215**
Any ≥ Grade 3 Laboratory Abnormality	19%	13%
Creatine Kinase (M: >990 U/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 flares (defined as serum ALT greater than 2 × baseline and greater than 10 × ULN, with or without associated symptoms) was similar between VIREAD (2.6%) and HEPSERA (2%). ALT flares generally occurred within the first 4 to 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.

The adverse reactions observed in subjects with chronic hepatitis B and lamivudine resistance who received treatment with VIREAD were consistent with those observed in other HBV clinical trials in adults.

Clinical Trials in Adult Subjects with Chronic Hepatitis B and Decompensated Liver Disease

In Trial 0108, a small randomized, double-blind, active-controlled trial, subjects with chronic HBV and decompensated liver disease received treatment with VIREAD or other antiviral drugs for up to 48 weeks *[see Clinical Studies (13.2)]*. Among the 45 subjects receiving VIREAD, the most frequently reported treatment-emergent adverse reactions of any severity were abdominal pain (22%), nausea (20%), insomnia (18%), pruritus (16%), vomiting (13%), dizziness (13%), and pyrexia (11%). Two of 45 (4%) subjects died through Week 48 of the trial due to progression of liver disease. Three of 45 (7%) subjects discontinued treatment due to an adverse event. Four of 45 (9%) subjects experienced a confirmed increase in serum creatinine of 0.5 mg/dL (1 subject also had a confirmed serum phosphorus less than 2 mg/dL through Week 48). Three of these subjects (each of whom had a Child-Pugh score greater than or equal to 10 and MELD score greater than or equal to 14 at entry) developed renal failure. Because both VIREAD and decompensated liver disease may have an impact on renal function, the contribution of VIREAD to renal impairment in this population is difficult to ascertain.

One of 45 subjects experienced an on-treatment hepatic flare during the 48 week trial.

Adverse Reactions from Clinical Trials Experience in HBV-Infected Pediatric Subjects 12 Years of Age and Older

Assessment of adverse reactions is based on one randomized study (Study GS-US-174-0115) in 106 pediatric subjects (12 to less than 18 years of age) infected with chronic hepatitis B receiving treatment with VIREAD (N = 52) or placebo (N = 54) for 72 weeks. The adverse reactions observed in pediatric subjects who received treatment with VIREAD were consistent with those observed in clinical trials of VIREAD in adults.

In this study, both the VIREAD and placebo treatment arms experienced an overall increase in mean lumbar spine BMD over 72 weeks, as expected for an adolescent population. The BMD gains from baseline to Week 72 in lumbar spine and total body BMD in VIREAD-treated subjects (+5% and +3%, respectively) were less than the BMD gains observed in placebo-treated subjects (+8% and +5%, respectively). Three subjects in the VIREAD group and two subjects in the placebo group had significant (greater than 4%) lumbar spine BMD loss at Week 72. At baseline, mean BMD Z-scores in subjects randomized to VIREAD were −0.43 for lumbar spine and −0.20 for total body, and mean BMD Z-scores in subjects randomized to placebo were −0.28 for lumbar spine and −0.26 for total body. In subjects receiving VIREAD for 72 weeks, the mean change in BMD Z-score was −0.05 for lumbar spine and −0.15 for total body compared to +0.07 and +0.06, respectively, in subjects receiving placebo. As observed in pediatric studies of HIV-infected patients, skeletal growth (height) appeared to be unaffected *[See Warnings and Precautions (5.5)]*.

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

7.1 Drugs Affecting Renal Function

Tenofovir is primarily eliminated by the kidneys *[see Clinical Pharmacology (11.2)]*. Coadministration of VIREAD with drugs that are eliminated by active tubular secretion may increase concentrations of tenofovir and/or the coadministered drug. Some examples include, but are not limited to acyclovir, cidofovir, ganciclovir,valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[see Warnings and Precautions (5.2)].* Drugs that decrease renal function may increase concentrations of tenofovir.

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

7.2 Established and Significant Interactions

Table 9 provides a listing of established or clinically significant drug interactions. The drug interactions described are based on studies conducted with TDF *[see Clinical Pharmacology (11.3)]*.

Table 9 Established and Significant[a] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Trials

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
NRTI: didanosine	↑ didanosine	Patients receiving VIREAD and didanosine should be monitored closely for didanosine-associated adverse reactions. Discontinue didanosine in patients who develop didanosine-associated adverse reactions. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving VIREAD with didanosine 400 mg daily. In patients weighing greater than 60 kg, reduce the didanosine dose to 250 mg when it is coadministered with VIREAD. In patients weighing less than 60 kg, reduce the didanosine dose to 200 mg when it is coadministered with VIREAD. When coadministered, VIREAD and didanosine EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).
HIV-1 Protease Inhibitors: atazanavir	↓ atazanavir	When coadministered with VIREAD, atazanavir 300 mg should be given with ritonavir 100 mg.
lopinavir/ritonavir atazanavir/ritonavir darunavir/ritonavir	↑ tenofovir	Monitor patients receiving VIREAD concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir for TDF-associated adverse reactions. Discontinue VIREAD in patients who develop TDF-associated adverse reactions.
Hepatitis C Antiviral Agents: sofosbuvir/velpatasvir sofosbuvir/velpatasvir/voxilaprevir	↑ tenofovir	Monitor patients receiving VIREAD concomitantly with EPCLUSA® (sofosbuvir/velpatasvir) for adverse reactions associated with TDF.
ledipasvir/sofosbuvir		Monitor patients receiving VIREAD concomitantly with HARVONI® (ledipasvir/sofosbuvir) without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination for adverse reactions associated with TDF. In patients receiving VIREAD concomitantly with HARVONI and an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, consider an alternative HCV or antiretroviral therapy, as the safety of increased tenofovir concentrations in this setting has not been established. If coadministration is necessary, monitor for adverse reactions associated with TDF.

a. This table is not all inclusive.
b. ↑=Increase, ↓=Decrease

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are 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.

Animal Data

TDF was administered orally to pregnant rats (at 0, 50, 150, or 450 mg/kg/day) and rabbits (at 0, 30, 100, or 300 mg/kg/day) through organogenesis (on gestation days 7 through 17, and 6 through 18, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with TDF in rats at doses up to 14 times the human dose based on body surface area comparisons and in rabbits at doses up to 19 times the human dose based on body surface area comparisons. In a pre/postnatal development study in rats, TDF was administered orally through lactation at doses up to 600 mg/kg/day; no adverse effects were observed in the offspring at tenofovir exposures of approximately 2.7 times higher than human exposures at the recommended daily dose of VIREAD.

8.2 Lactation

Risk Summary

Based on published data, tenofovir has been shown to be present in human breast milk *(see Data).* It is not known if tenofovir affects milk production or has effects on the breastfed child.

Treatment of HIV-1 infection:

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.

Because of the potential for: (1) HIV transmission (in HIV-negative infants); (2) developing viral resistance (in HIV-positive infants); and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breast-feed if they are taking VIREAD for the treatment of HIV-1.

Treatment of HBV infection:

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VIREAD and any potential adverse effects on the breastfed infant from VIREAD or from the underlying maternal condition.

Data

In a study of 50 HIV-uninfected, breastfeeding women on a tenofovir-containing regimen initiated between 1 and 24 weeks postpartum (median 13 weeks) tenofovir was

undetectable in the plasma of most infants after 7 days of treatment in mothers. There were no serious adverse events in mothers or infants.

8.3 Pediatric Use

Pediatric Patients 12 Years of Age and Older with HIV-1 Infection

The safety of VIREAD in pediatric patients aged 12 to less than 18 years is supported by data from one randomized trial in which VIREAD was administered to HIV-1 infected treatment-experienced subjects. In addition, the pharmacokinetic profile of tenofovir in patients 12 to less than 18 years of age at the recommended doses was similar to that found to be safe and effective in adult clinical trials *[See Clinical Pharmacology (11.2)]*

Trial 321 was a placebo-controlled trial in 87 HIV-1 treatment-experienced subjects 12 to less than 18 years of age who were treated with VIREAD (N=45) or placebo (N=42) in combination with an optimized background regimen (OBR) for 48 weeks. Overall, the trial failed to show a difference in virologic response between the VIREAD and placebo treatment groups. Subgroup analyses suggest the lack of difference in virologic response may be attributable to imbalances between treatment arms in baseline viral susceptibility to VIREAD and OBR *[see Adverse Reactions (6.1) and Clinical Studies (13.3)]*.

Although changes in HIV-1 RNA in these highly treatment-experienced subjects were less than anticipated, the pharmacokinetic profile of tenofovir in patients 12 years to less than 18 years of age at the recommended doses was similar to that found to be safe and effective in adult clinical trials *[see Clinical Pharmacology (11.3)]*.

The effects of VIREAD associated changes in BMD and biochemical markers on long-term bone health and future fracture risk in HIV-1 pediatric patients 12 years of age and older are unknown. The long-term effect of lower spine and total body BMD on skeletal growth in pediatric patients 12 years and older, and in particular, the effects of long-duration exposure in younger children is unknown *[see Warnings and Precautions (5.5), Adverse Reactions (6.1)].*

Safety and effectiveness of VIREAD in pediatric patients younger than 12 years of age with HIV-1 infection have not been established.

Pediatric Patients 12 Years of Age and Older with Chronic Hepatitis B

In Trial 115, 106 HBeAg negative (9%) and positive (91%) subjects 12 years to less than 18 years of age with chronic HBV infection were randomized to receive blinded treatment with VIREAD or placebo for 72 weeks. At Week 72, 88% of subjects in the VIREAD group and 0% of subjects in the placebo group had HBV DNA <400 copies/mL (69 IU/mL).

The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk in chronic HBV-infected pediatric patients 12 years and older are unknown. The long-term effect of lower spine and total body BMD on skeletal growth in pediatric patients 12 years and older, and in particular, the effects of long-duration exposure in younger children is unknown *[see Warnings and Precautions (5.5), Adverse Reactions (6.1)]*.

Safety and effectiveness of VIREAD in chronic HBV-infected pediatric patients younger than 12 years of age or less than 35 kg with chronic hepatitis B have not been established.

8.4 Geriatric Use

Clinical trials 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.

8.5 Renal Impairment

The dosing interval for VIREAD should be modified in adult patients with estimated creatinine clearance below 50 mL/min or in patients with end stage renal disease requiring dialysis *[see Dosage and Administration (*2.3*) and Clinical Pharmacology (11.2)]*.

9 OVERDOSAGE

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

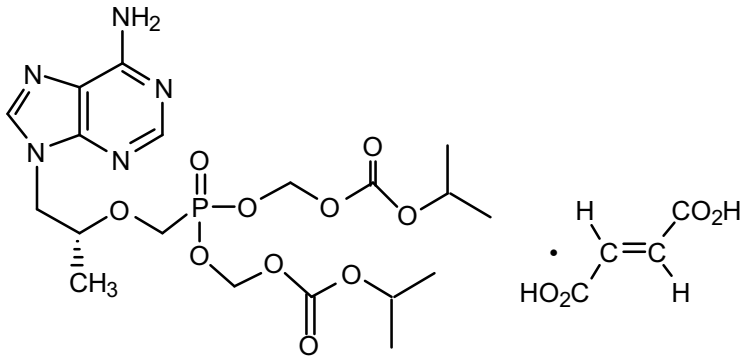
Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of VIREAD, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

10 DESCRIPTION

VIREAD is the brand name for tenofovir disoproxil fumarate (TDF) (a prodrug of tenofovir) which is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. TDF is converted in vivo to tenofovir, an acyclic nucleoside

phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir exhibits activity against HIV-1 reverse transcriptase.

The chemical name of TDF 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 TDF, 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, hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin.

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

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

TDF is an antiviral drug *[see Microbiology (11.3)].*

11.2 Pharmacokinetics

The pharmacokinetics of TDF 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 $\pm$ 0.4 hrs. C_{max} and AUC values are 0.30 $\pm$ 0.09 μg/mL and 2.29 $\pm$ 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 $\pm$ 0.6 L/kg and 1.2 $\pm$ 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 $\pm$ 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 1,000 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.

Specific 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 Patients 12 Years of Age and Older: Steady-state pharmacokinetics of tenofovir were evaluated in 8 HIV-1 infected pediatric subjects (12 to less than 18 years). Mean (± SD) C_{max} and AUC_{tau} are 0.38 ± 0.13 μg/mL and 3.39 ± 1.22 μg·hr/mL, respectively. Tenofovir exposure achieved in these pediatric subjects receiving oral daily doses of VIREAD 300 mg was similar to exposures achieved in adults receiving once-daily doses of VIREAD 300 mg.

Tenofovir exposures in HBV-infected pediatric subjects (12 years to less than 18 years of age) receiving oral once-daily doses of VIREAD 300 mg tablet were comparable to exposures achieved in HIV-1-infected adults and adolescents receiving once-daily doses of 300 mg.

Geriatric Patients: Pharmacokinetic trials have not been performed in the elderly (65 years and older).

Patients with Renal Impairment: The pharmacokinetics of tenofovir are altered in subjects with renal impairment *[see Warnings and Precautions (5.2)]*. In subjects with creatinine clearance below 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, and $AUC_{0-\infty}$ of tenofovir were increased (Table 10).

Table 10 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

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.

VIREAD has been evaluated in healthy volunteers in combination with other antiretroviral and potential concomitant drugs. Tables 11 and 12 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of VIREAD on the pharmacokinetics of coadministered drug.

TDF is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters. When TDF is coadministered with an inhibitor of these transporters, an increase in absorption may be observed.

No clinically significant drug interactions have been observed between VIREAD and efavirenz, methadone, nelfinavir, oral contraceptives, ribavirin, or sofosbuvir.

Table 11 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}
Atazanavir[c]	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Atazanavir/ Ritonavir[c]	300/100 once daily	12	↑ 34 (↑ 20 to ↑ 51)	↑ 37 (↑ 30 to ↑ 45)	↑ 29 (↑ 21 to ↑ 36)
Darunavir/ Ritonavir[d]	300/100 twice daily	12	↑ 24 (↑ 8 to ↑ 42)	↑ 22 (↑ 10 to ↑ 35)	↑ 37 (↑ 19 to ↑ 57)
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Ledipasvir/ Sofosbuvir[e,f]	90/400 once daily x 10 days	24	↑ 47 (↑ 37 to ↑ 58)	↑ 35 (↑ 29 to ↑ 42)	↑ 47 (↑ 38 to ↑ 57)
Ledipasvir/ Sofosbuvir[e,g]		23	↑ 64 (↑ 54 to ↑ 74)	↑ 50 (↑ 42 to ↑ 59)	↑ 59 (↑ 49 to ↑ 70)
Ledipasvir/ Sofosbuvir[h]	90/400 once x 14 days	15	↑ 79 (↑ 56 to ↑ 104)	↑ 98 (↑ 77 to ↑ 123)	↑ 163 (↑ 132 to↑197)
Lopinavir/ Ritonavir	400/100 twice daily × 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Saquinavir/ Ritonavir	1000/100 twice daily × 14 days	35	⇔	⇔	↑ 23 (↑ 16 to ↑ 30)
Sofosbuvir[i]	400 single dose	16	↑ 25 (↑ 8 to ↑ 45)	⇔	⇔
Sofosbuvir/ Velpatasvir[j]	400/100 once daily	24	↑ 44 (↑ 33 to ↑ 55)	↑ 40 (↑ 34 to ↑ 46)	↑ 84 (↑ 76 to ↑ 92)
Sofosbuvir/ Velpatasvir[k]	400/100 once daily	30	↑ 46 (↑ 39 to ↑ 54)	↑ 40 (↑ 34 to ↑ 45)	↑ 70 (↑ 61 to ↑ 79)
Sofosbuvir/ Velpatasvir/ Voxilaprevir[r]	400/100/100 + Voxilaprevir[s] 100 once daily	29	↑ 48 (↑ 36 to ↑ 61)	↑ 39 (↑ 32 to↑ 46)	↑ 47 (↑ 38 to ↑ 56)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↑ 13 (↑ 1 to ↑ 27)	⇔	⇔
Tipranavir/ Ritonavir[n]	500/100 twice daily	22	↓ 23 (↓ 32 to ↓ 13)	↓ 2 (↓ 9 to ↑ 5)	↑ 7 (↓ 2 to ↑ 17)
	750/200 twice daily (23 doses)	20	↓ 38 (↓ 46 to ↓ 29)	↑ 2 (↓ 6 to ↑ 10)	↑ 14 (↑ 1 to ↑ 27)

a. Subjects received VIREAD 300 mg once daily.

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

c. Reyataz Prescribing Information

d. Prezista Prescribing Information

e. Data generated from simultaneous dosing with HARVONI (ledipasvir/sofosbuvir). Staggered administration (12 hours apart) provided similar results.

f. Comparison based on exposures when administered as atazanavir/ritonavir + FTC/TDF.

g. Comparison based on exposures when administered as darunavir/ritonavir + FTC/TDF.

h. Study conducted with ATRIPLA® (EFV/FTC/TDF) coadministered with HARVONI; coadministration with HARVONI also results in comparable increases in tenofovir exposure when TDF is administered as COMPLERA® (FTC/rilpivirine/TDF) or TRUVADA + dolutegravir.

i. Study conducted with ATRIPLA coadministered with SOVALDI® (sofosbuvir).

j. Study conducted with COMPLERA coadministered with EPCLUSA; coadministration with EPCLUSA also results in comparable increases in tenofovir exposures when TDF is administered as ATRIPLA, STRIBILD® (elvitegravir/cobicistat/FTC/TDF), TRUVADA + atazanavir/ritonavir, or TRUVADA + daruvanir/ritonavir.

k. Administered as raltegravir + FTC/TDF.

l. Comparison based on exposures when administered as darunavir+ritonavir + FTC/TDF.

m. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients

n. Aptivus Prescribing Information

No effect on the pharmacokinetic parameters of the following coadministered drugs was observed with VIREAD: abacavir, didanosine (buffered tablets), emtricitabine, entecavir, and lamivudine.

Table 12 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)
Darunavir[d]	Darunavir/Ritonavir 300/100 once daily	12	↑ 16 (↓ 6 to ↑ 42)	↑ 21 (↓ 5 to ↑ 54)	↑ 24 (↓ 10 to ↑ 69)
Didanosine[e]	250 once, simultaneously with VIREAD and a light meal[f]	33	↓ 20[g] (↓ 32 to ↓ 7)	⇔[g]	NA
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 Ritonavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	⇔ ⇔	⇔ ⇔	⇔ ⇔
Saquinavir Ritonavir	Saquinavir/Ritonavir 1000/100 twice daily × 14 days	32	↑ 22 (↑ 6 to ↑ 41) ⇔	↑ 29[h] (↑ 12 to ↑ 48) ⇔	↑ 47[h] (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	⇔	⇔	⇔
Tipranavir[i]	Tipranavir/Ritonavir 500/100 twice daily	22	↓ 17 (↓ 26 to ↓ 6)	↓ 18 (↓ 25 to ↓ 9)	↓ 21 (↓ 30 to ↓ 10)
	Tipranavir/Ritonavir 750/200 twice daily (23 doses)	20	↓ 11 (↓ 16 to ↓ 4)	↓ 9 (↓ 15 to ↓ 3)	↓ 12 (↓ 22 to 0)

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

b. Reyataz Prescribing Information.

c. In HIV-infected subjects, addition of TDF 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. Prezista Prescribing Information.

e. Videx EC Prescribing Information. Subjects received didanosine enteric-coated capsules.

f. 373 kcal, 8.2 g fat

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

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

i. Aptivus Prescribing Information

11.3 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 (TFV-DP), an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) and HBV RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Activity against HIV

Antiviral Activity

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

Resistance

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

In Trial 903 of treatment-naïve subjects (VIREAD + 3TC + EFV versus d4T+3TC+EFV) *[see Clinical Studies (13.1)]*, genotypic analyses of isolates from subjects with virologic failure through Week 144 showed development of EFV and 3TC resistance-associated substitutions to occur most frequently and with no difference between the treatment arms. The K65R substitution occurred in 8/47 (17%) of analyzed patient isolates in the VIREAD arm and in 2/49 (4%) of analyzed patient isolates in the d4T arm. Of the 8 subjects whose virus developed K65R in the VIREAD arm through 144 weeks, 7 occurred in the first 48 weeks of treatment and one at Week 96. One patient in the

VIREAD arm developed the K70E substitution in the virus. Other substitutions resulting in resistance to VIREAD were not identified in this trial.

In Trial 934 of treatment-naïve subjects (VIREAD + FTC+EFV versus AZT)/3TC + EFV) *[see Clinical Studies (13.1)]*, 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 EFV resistance-associated substitutions occurred most frequently and was similar between the two treatment arms. The M184V substitution, associated with resistance to FTC and 3TC, was observed in 2/19 of analyzed subject isolates in the VIREAD + FTC group and in 10/29 of analyzed subject isolates in the AZT/3TC group. Through 144 weeks of Trial 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 HIV-1 NRTIs has been recognized. The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1 infected subjects treated with abacavir or didanosine. HIV-1 isolates with this substitution also show reduced susceptibility to FTC and 3TC. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors the K65R or K70E substitution. HIV-1 isolates from subjects (N=20) whose HIV-1 expressed a mean of three AZT-associated RT substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N), showed a 3.1-fold decrease in the susceptibility to tenofovir.

In Trials 902 and 907 conducted in treatment-experienced subjects (VIREAD + Standard Background Therapy (SBT) compared to placebo + SBT) *[see Clinical Studies (13.1)]*, 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 RT gene.

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

Several exploratory analyses were conducted to evaluate the effect of specific substitutions and substitutional patterns on virologic outcome. Because of the large number of potential comparisons, statistical testing was not conducted. Varying degrees of cross-resistance of VIREAD to pre-existing AZT resistance-associated substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) were observed and appeared to depend on the type and number of specific substitutions. VIREAD-treated subjects whose HIV-1 expressed 3 or more AZT resistance-associated substitutions that included either the M41L or L210W RT 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 AZT 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/FTC/3TC resistance-associated M184V substitution. HIV-1 RNA responses among these subjects were durable through Week 48.

Trials 902 and 907 Phenotypic Analyses

Phenotypic analysis of baseline HIV-1 from treatment-experienced subjects (N=100) demonstrated a correlation between baseline susceptibility to VIREAD and response to VIREAD therapy. Table 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 HBV NRTIs entecavir, lamivudine, and telbivudine, and with the HIV-1 NRTI emtricitabine, no antagonistic activity was observed.

Resistance

Cumulative VIREAD genotypic resistance has been evaluated annually for up to 384 weeks in Trials 0102, 0103, 0106, 0108, and 0121 *[see Clinical Studies (13.4)]* with the paired HBV RT amino acid sequences of the pretreatment and on-treatment isolates from subjects who received at least 24 weeks of VIREAD monotherapy and remained viremic with HBV DNA ≥ 400 copies/mL (69 IU/mL) at the end of each study year (or at discontinuation of VIREAD monotherapy) using an as-treated analysis. In the nucleotide-naïve population from Trials 0102 and 0103, HBeAg-positive subjects had a higher baseline viral load than HBeAg-negative subjects and a significantly higher

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

HBV isolates from these subjects who remained viremic showed treatment-emergent substitutions (Table 14); however, no specific substitutions occurred at a sufficient frequency to be associated with resistance to VIREAD (genotypic and phenotypic analyses).

Table 14 Amino Acid Substitutions in Viremic Subjects across HBV Trials of VIREAD

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

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

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

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

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

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

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

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

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

Cross-Resistance

Cross-resistance has been observed between HBV NrtIs.

In cell based assays, HBV strains expressing the rtV173L, rtL180M, and rtM204I/V substitutions associated with resistance to lamivudine (3TC) and telbivudine showed a susceptibility to tenofovir ranging from 0.7- to 3.4-fold that of wild type virus. The rtL180M and rtM204I/V double substitutions conferred 3.4-fold reduced susceptibility to tenofovir.

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

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

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

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

Tenofovir 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, TDF was negative when administered to male mice.

Impairment of Fertility

There were no effects on fertility, mating performance or early embryonic development when TDF 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.

12.2 Animal Toxicology and/or Pharmacology

Tenofovir and TDF 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.

13 CLINICAL STUDIES

13.1 Overview of Clinical Trials

The efficacy and safety of VIREAD in adults and adolescent subjects were evaluated in the trials summarized in Table 15.

Table 15 Trials Conducted with VIREAD in Adults and Adolescents Subjects for HIV-1 Treatment and Chronic HBV Treatment

Trial	Population	Study Arms (N)[a]	Timepoint (Week)
Trial 903[b] (NCT00158821)	HIV-1 treatment-naïve adults	VIREAD+lamivudine+efavirenz (299) stavudine+lamivudine+efavirenz (301)	144
Trial 934[c] (NCT00112047)		emtricitabine+VIREAD+efavirenz (257) zidovudine/lamivudine+efavirenz (254)	144
Trial 907[d] (NCT00002450)	HIV-1 treatment-experienced adults	VIREAD (368) Placebo (182)	24
Trial 0102[b] (NCT00117676)	HBeAg-negative adults with chronic HBV	VIREAD (250) HEPSERA (125)	48
Trial 0103[b] (NCT00116805)	HBeAg-positive adults with chronic HBV	VIREAD (176) HEPSERA (90)	48
Trial 121[b] (NCT00737568)	Adults with lamivudine-resistant chronic HBV	VIREAD (141)	96
Trial 0108[b] (NCT00298363)	Adults with chronic HBV and decompensated liver disease	VIREAD (45)	48
Trial 321[d] (NCT00352053)	HIV-1 treatment-experienced pediatric subjects 12 years to <18 years	VIREAD (45) Placebo (42)	48
Trial 115[d] (NCT00734162)	Pediatric subjects 12 years to <18 years with chronic HBV	VIREAD (52) Placebo (54)	72

a. Randomized and dosed.
b. Randomized, double-blind, active-controlled trial.

c. Randomized, open-label active-controlled trial.
d. Randomized, double-blind, placebo-controlled trial.

13.2 Clinical Trial Results in Adults with HIV-1 Infection

Treatment-Naïve Adult Patients

Study 903

Data through 144 weeks are reported for Trial 903, a double-blind, active-controlled multicenter trial comparing VIREAD (300 mg once daily) administered in combination with lamivudine (3TC) and efavirenz (EFV) versus stavudine (d4T), 3TC, and EFV 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. Table 16 provides treatment outcomes through 48 and 144 weeks.

Table 16 Outcomes of Randomized Treatment at Week 48 and 144 (Trial 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 < 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 d4T 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 d4T arm.

Through 144 weeks, 11 subjects in the VIREAD group and 9 subjects in the d4T group experienced a new CDC Class C event.

Trial 934

Data through 144 weeks are reported for Trial 934, a randomized, open-label, active-controlled multicenter trial comparing emtricitabine (FTC) + VIREAD administered in combination with efavirenz (EFV) versus zidovudine (AZT)/lamivudine (3TC) fixed-dose combination administered in combination with EFV in 511 antiretroviral-naïve subjects. From Weeks 96 to 144 of the trial, subjects received a fixed-dose combination of FTC and TDF with EFV in place of FTC + VIREAD with EFV. 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. Table 17 provides treatment outcomes through 48 and 144 weeks for those subjects who did not have EFV resistance at baseline.

Table 17 Outcomes of Randomized Treatment at Week 48 and 144 (Trial 934)

Outcomes	At Week 48		At Week 144	
	FTC +VIREAD +EFV (N=244)	AZT/3TC +EFV (N=243)	FTC +VIREAD +EFV (N=227)[a]	AZT/3TC +EFV (N=229)[a]
Responder[b]	84%	73%	71%	58%
Virologic failure[c]	2%	4%	3%	6%
Rebound	1%	3%	2%	5%
Never suppressed	0%	0%	0%	0%
Change in antiretroviral regimen	1%	1%	1%	1%
Death	<1%	1%	1%	1%
Discontinued due to adverse event	4%	9%	5%	12%
Discontinued for other reasons[d]	10%	14%	20%	22%

a. Subjects who were responders at Week 48 or Week 96 (HIV-1 RNA <400 copies/mL) but did not consent to continue the trial after Week 48 or Week 96 were excluded from analysis.

b. Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Weeks 48 and 144.

c. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Weeks 48 and 144.

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

Through Week 48, 84% and 73% of subjects in the FTC + VIREAD group and the AZT/3TC 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 AZT/3TC group in this open-label trial. In addition, 80% and 70% of subjects in the FTC + VIREAD group and the AZT/3TC 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 FTC + VIREAD group and 158 cells/mm^3 in the AZT/3TC group at Week 48 (312 and 271 cells/mm^3 at Week 144).

Through 48 weeks, 7 subjects in the FTC + VIREAD group and 5 subjects in the AZT/3TC group experienced a new CDC Class C event (10 and 6 subjects through 144 weeks).

Treatment-Experienced Adult Patients

Trial 907

Trial 907 was a 24-week, double-blind placebo-controlled multicenter trial of VIREAD added to a stable background regimen of antiretroviral agents in 550 treatment-experienced subjects. After 24 weeks of blinded trial treatment, all subjects continuing on trial were offered open-label VIREAD for an additional 24 weeks. Subjects had a mean baseline $CD4^+$ cell count of 427 cells/mm^3 (range 23–1,385), median baseline plasma HIV-1 RNA of 2,340 (range 50–75,000) copies/mL, and mean duration of prior HIV-1 treatment was 5.4 years. Mean age of the subjects was 42 years; 85% were male , 69% Caucasian, 17% Black and 12% Hispanic.

Table 18 provides the percent of subjects with HIV-1 RNA <400 copies/mL and outcomes of subjects through 48 weeks.

Table 18 Outcomes of Randomized Treatment (Trial 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 group experienced a new CDC Class C event.

13.2 Clinical Efficacy in Adults with Chronic Hepatitis B

HBeAg-Negative Chronic HBV Subjects: Trial 0102

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

HBeAg-Positive Chronic HBV Subjects: Trial 0103

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

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

The primary efficacy endpoint in both trials was complete response to treatment defined as HBV DNA <400 copies/mL (69 IU/mL) and Knodell necroinflammatory score improvement of at least 2 points, without worsening in Knodell fibrosis at Week 48 (see Table 19).

Table 19 Histological, Virological, Biochemical, and Serological Response at Week 48 (Trials 0102 and 0103)

	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: Trials 0102 and 0103

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

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

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

initially randomized to VIREAD and 12% and 10%, respectively, in subjects initially randomized to HEPSERA.

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

Lamivudine-Resistant Chronic HBV Subjects: Trial 121

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

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

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

Chronic HBV and Decompensated Liver Disease Subjects: Trial 0108

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

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

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

13.3 Clinical Trial Results in Pediatric Subjects 12 Years to less than 18 Years of Age with Chronic Hepatitis B

In Trial 115, 106 HBeAg negative (9%) and positive (91%) subjects aged 12 to less than 18 years with chronic HBV infection were randomized to receive blinded treatment with VIREAD 300 mg (N=52) or placebo (N=54) for 72 weeks. At trial entry, the mean HBV DNA was 8.1 $\log_{10}$ copies/mL and mean ALT was 101 U/L. Of 52 subjects treated with VIREAD, 20 subjects were nucleos(t)ide-naïve and 32 subjects were nucleos(t)ide-experienced. Thirty-one of the 32 nucleos(t)ide-experienced subjects had prior lamivudine experience. At Week 72, 88% (46/52) of subjects in the VIREAD group and 0% (0/54) of subjects in the placebo group had HBV DNA <400 copies/mL (69 IU/mL). Among subjects with abnormal ALT at baseline, 74% (26/35) of subjects receiving VIREAD had normalized ALT at Week 72 compared to 31% (13/42) in the placebo group. One VIREAD-treated subject experienced sustained HBsAg-loss and seroconversion to anti-HBs during the first 72 weeks of trial participation.

14 HOW SUPPLIED/STORAGE AND HANDLING

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

Store below 30 °C

Keep the bottle tightly closed. Dispense only in original container. Do not use if seal over bottle opening is broken or missing.

15 PATIENT COUNSELING INFORMATION

Severe Acute Exacerbation of Hepatitis B in Patients Infected with HBV

Inform patients that severe acute exacerbations of hepatitis B have been reported in patients infected with hepatitis B virus (HBV) and have discontinued VIREAD. Advise

patients not to discontinue VIREAD without first informing their healthcare provider. All patients should be tested for HBV infection before or when starting VIREAD and those who are infected with HBV need close medical follow-up for several months after stopping VIREAD to monitor for exacerbations of hepatitis *[see Warnings and Precautions (5.1)]*.

New Onset or Worsening Renal Impairment

Inform patients that renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported in association with the use of VIREAD. Advise patients to avoid VIREAD with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) *[see Warnings and Precautions (5.2)]*. The dosing interval of VIREAD may need adjustment in HIV-1 infected patients with renal impairment.

Immune Reconstitution Syndrome

Inform patients that 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. Advise patients to inform their healthcare provider immediately of any symptoms of infection *[see Warnings and Precautions (5.4)].*

Bone Loss and Mineralization Defects

Inform patients that decreases in bone mineral density have been observed with the use of VIREAD. Consider bone monitoring in patients who have a history of pathologic bone fracture or at risk for osteopenia *[see Warnings and Precautions (5.5)]*.

Lactic Acidosis and Severe Hepatomegaly

Inform patients that lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with VIREAD should be suspended in any patient who develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.6)]*.

Drug Interactions

Advise patients that VIREAD may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other medication, including other HIV drugs and drugs for treatment of hepatitis C virus *[see Warnings and Precautions (5.7) and Drug Interactions (7)].*

Dosing Recommendations

Inform patients that it is important to take VIREAD on a regular dosing schedule with or without food and to avoid missing doses as it can result in development of resistance [see Dosage and Administration (2)].

Lactation

Instruct mothers not to breastfeed if they are taking VIREAD for the treatment of HIV-1 infection because of the risk of passing the HIV-1 virus to the baby *[see Use in Specific Populations (8.2)].*

Treatment Duration

Advise patients that 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.

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