PRODUCT MONOGRAPH

[Pr]TEVA-TENOFOVIR

tenofovir disoproxil fumarate tablets

300 mg

Antiretroviral Agent

Teva Canada Limited
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Toronto, Ontario
M1B 2K9

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PrTEVA-TENOFOVIR

Tenofovir Disoproxil Fumarate tablets 300 mg

PART I HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet / 300 mg	Colloidal anhydrous silica, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, FD&C Blue #2, carmine, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

INDICATIONS AND CLINICAL USE

HIV-1 Infection
TEVA-TENOFOVIR (tenofovir disoproxil fumarate) is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in patients 12 years of age and older.

Chronic Hepatitis B
TEVA-TENOFOVIR is indicated for the treatment of chronic hepatitis B infection in patients 18 years of age and older, with:

- Compensated liver disease, with evidence of active viral replication, with elevated serum alanine aminotransferase (ALT) levels or evidence of fibrosis (based on liver biopsy or a noninvasive procedure;
- Evidence of lamivudine-resistant hepatitis B virus; or
- Decompensated liver disease.

Geriatrics (≥ 65 years of age)
Clinical studies of tenofovir disoproxil fumarate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Pediatrics (12 to < 18 years of age)
The safety and efficacy of tenofovir disoproxil fumarate in adolescent patients aged 12 to <18 years is supported by data from one randomized study in which tenofovir disoproxil fumarate was administered to HIV-1 infected treatment experienced subjects. In this study, the pharmacokinetic profile of tenofovir disoproxil fumarate was similar to that found to be safe and effective in adult populations.

Safety and efficacy in pediatric patients less than 12 years of age have not been established.

CONTRAINDICATIONS

TEVA-TENOFOVIR (tenofovir disoproxil fumarate) is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product. For a complete listing, see the **DOSAGE FORMS**, **COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Lactic Acidosis and Severe Hepatomegaly with Steatosis**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including TEVA-TENOFOVIR, alone or in combination with other antiretrovirals (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

- **Post-Treatment Exacerbation of Hepatitis B**

Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including tenofovir disoproxil fumarate. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including TEVA-TENOFOVIR. If appropriate, resumption of anti-hepatitis B therapy may be warranted (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

- **Nephrotoxicity**

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) has been reported with the use of tenofovir disoproxil fumarate during clinical practice (see **WARNINGS AND PRECAUTIONS, Renal**).

General

For the effect of co-administered drugs, see **DRUG INTERACTIONS** section.

Clinical studies in HIV-infected patients 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 mutations 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.

TEVA-TENOFOVIR should not be used in combination with the followings:

- Products containing tenofovir disoproxil fumarate (ATRIPLA® (efavirenz/emtricitabine/tenofovir disoproxil fumarate), COMPLERA® (emtricitabine/rilpivirine/tenofovir disoproxil fumarate), STRIBILD® (elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate) or TRUVADA® (emtricitabine/tenofovir disoproxil fumarate)).

- Products containing tenofovir alafenamide (DESCOVY® (emtricitabine /tenofovir alafenamide) or GENVOYA ® (elvitegravir/ tenofovir alafenamide (as the hemifumarate)/emtricitabine/ cobicistat)), ODEFSEY™ (emtricitabine/rilpivirine/tenofovir alafenamide) or VEMLIDY™ (tenofovir alafenamide)).
- Adefovir dipivoxil (HEPSERA®).

Bone Effects

In HIV-infected patients treated with tenofovir disoproxil fumarate in Study 903 through 144 weeks, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both tenofovir disoproxil fumarate and stavudine treatment arms of the study and significantly greater decreases were seen in the lumbar spine measurement in the tenofovir disoproxil fumarate group relative to the stavudine group. Clinically relevant fractures were reported in both treatment groups. Increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) were observed, suggesting increased bone turnover. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range (see **ADVERSE REACTIONS, HIV-1 Infection, Study 903**). In a clinical study of HIV-1 infected adolescent subjects (Study 321), bone effects were similar to adult subjects. Under normal circumstances, BMD increases rapidly in adolescents. In this study, the mean rate of bone gain was less in the tenofovir disoproxil fumarate-treated group compared to the placebo group. Six tenofovir disoproxil fumarate treated adolescents and one placebo treated adolescent had significant (>4%) lumbar spine BMD loss in 48 weeks. Among 28 subjects receiving 96 weeks of tenofovir disoproxil fumarate, Z-scores declined by -0.341 for lumbar spine and -0.458 for total body. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in tenofovir disoproxil fumarate-treated adolescents increased bone turnover, consistent with the effects observed in adults. The effects of tenofovir disoproxil fumarate-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

Cases of osteomalacia (associated with proximal renal tubulopathy and infrequently contributing to fractures) have been reported in association with the use of tenofovir disoproxil fumarate (see **ADVERSE REACTIONS, Post Market Adverse Drug Reactions**).

Bone monitoring should be considered for patients who have a history of pathologic bone fracture or are at risk for osteopenia, such as subjects co-infected with HBV and HIV or subjects on extended corticosteroid therapy. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Tenofovir disoproxil fumarate did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumors, considered likely related to high local concentrations in the gastrointestinal tract at the high dose of 600 mg/kg/day. The mechanism of tumor formation in mice and potential relevance for humans are uncertain.

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

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered at 600 mg/kg/day to male rats for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats. A dose of 600 mg/kg/day is equivalent to 19 times the human dose based on body surface area comparisons.

Drug Interactions

Use with Certain HCV Regimens

Tenofovir exposure is increased when TEVA-TENOFOVIR is coadministered with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir. Patients receiving a regimen containing TEVA-TENOFOVIR concomitantly with ledipasvir/ sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir, particularly those at increased risk for renal dysfunction, should be monitored for tenofovir disoproxil fumarate-associated adverse reactions (see **DRUG INTERACTIONS**).

Use with Didanosine

Pharmacokinetic studies have shown that coadministration of didanosine and tenofovir disoproxil fumarate results in 40-60% increase in C_{max} and AUC of didanosine (see Table 12). The mechanism of this interaction is unknown. Increases in didanosine concentrations of this magnitude could potentiate didanosine-associated adverse events, including pancreatitis, lactic acidosis, and neuropathy. In addition, suppression of CD4 counts has been observed in patients receiving tenofovir DF with didanosine at a dose of 400 mg daily (see **DRUG INTERACTIONS**).

Endocrine and Metabolism

Serum Lipids and Blood Glucose

Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and life style changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders and blood glucose elevations should be managed as clinically appropriate.

Hepatic/Biliary/Pancreatic

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues, including tenofovir disoproxil fumarate, alone or in combination with other antiretrovirals in the treatment of HIV infection. A majority of these cases have been reported in women. Obesity and prolonged nucleoside exposure may be risk factors. Caution should be exercised when administering nucleoside analogs to any patient, and particularly

to those with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with TEVA-TENOFOVIR 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 levels).

Pancreatitis

Pancreatitis has occurred during therapy with combination regimens that included tenofovir disoproxil fumarate. Caution should be used when administering nucleoside analogues (including TEVA-TENOFOVIR) to patients with a history of pancreatitis or risk factors for the development of pancreatitis. Therapy should be suspended in patients with suspected pancreatitis.

Hepatic Impairment

Tenofovir and tenofovir disoproxil are not metabolized by liver enzymes. Clinically relevant pharmacokinetic changes in patients with hepatic impairment are not observed. Therefore, no dose adjustment is required in patients with hepatic impairment. The safety and efficacy of tenofovir disoproxil fumarate has not been established or specifically studied in patients with underlying liver disorders. Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Exacerbation of Hepatitis After Discontinuation of Treatment

Discontinuation of anti-HBV therapy, including TEVA-TENOFOVIR, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue TEVA-TENOFOVIR 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. In patients with advanced liver disease or cirrhosis, post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Therefore, in these patients, discontinuation of treatment without initiation of alternative anti-hepatitis B therapy is not recommended.

Immune

Immune Reconstitution Inflammatory Syndrome

During the initial phase of treatment, HIV-infected patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP, and TB), 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 and sometimes may be an atypical presentation.

Angioedema

Cases of angioedema have been reported in patients taking tenofovir disoproxil fumarate (see **ADVERSE REACTIONS, Post Market Adverse Drug Reactions**).

Renal

Nephrotoxicity

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 tenofovir disoproxil fumarate in clinical practice. The majority of these cases occurred in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents; however, some cases occurred in patients without identified risk factors (see **ADVERSE REACTIONS, Post Market Adverse Reactions and DRUG INTERACTIONS**).

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

Particular caution should be exercised when administering TEVA-TENOFOVIR to patients with known risk factors for renal disease and a history of renal dysfunction; however, cases of renal failure have also been reported in patients with no known risk factors. TEVA-TENOFOVIR should be avoided with concurrent or recent use of a nephrotoxic agent.

Dosing interval adjustment is required in all patients with creatinine clearance < 50 mL/min (see **DOSAGE AND ADMINISTRATION, Dose Adjustment for Renal Impairment**). The safety and efficacy of these dosing interval adjustment recommendations have not been clinically evaluated, therefore, clinical response to treatment and renal function should be closely monitored in these patients. The potential benefit of TEVA-TENOFOVIR therapy should be assessed against the potential risk for renal toxicity.

Special Populations

Patients with HIV and Hepatitis B Virus Coinfection

Due to the risk of development of HIV resistance, TEVA-TENOFOVIR should only be used in HIV and HBV co-infected patients as part of an appropriate antiretroviral combination therapy.

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

Pregnant Women

There are no adequate and well-controlled studies in pregnant women. Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. Reduced pup body weights, survival, and delay in sexual maturation was observed in a peri- and postnatal toxicity study in rats at the maternally toxic doses of 450 and 600 mg/kg (approximately 14 and 19 times the human dose based on body surface area comparisons). Because animal reproduction studies are not always predictive of human response, tenofovir disoproxil fumarate should be used in pregnant women only if the potential benefits outweigh the potential risks to the fetus.

Antiretroviral Pregnancy Registry

To monitor fetal outcomes of pregnant women exposed to ART including TEVA-TENOFOVIR, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling (800)-258-4263.

Nursing Women

HIV and HBV infected women should not breastfeed to avoid risking postnatal transmission of HIV-1 and HBV. In humans, samples of breast milk obtained from five HIV-1 infected mothers show that tenofovir is secreted in human milk at low levels (estimated neonatal concentrations 128 to 266 times lower than the tenofovir IC50). Tenofovir-associated risks, including the risk of developing viral resistance to tenofovir, in infants breastfed by mothers being treated with tenofovir disoproxil fumarate are unknown. **Mothers should be instructed not to breastfeed if they are receiving TEVA-TENOFOVIR because of both the potential for HIV-1 and HBV transmission and the potential for serious adverse reactions in nursing infants.**

Pediatrics

The safety and efficacy of tenofovir disoproxil fumarate in HIV adolescent patients aged 12 to <18 years is supported by data from one randomized study in which tenofovir disoproxil fumarate was administered to HIV-1 infected treatment experienced subjects. In this study, the pharmacokinetic profile of tenofovir disoproxil fumarate was similar to that found to be safe and effective in adult populations.

Safety and efficacy in patients less than 12 years of age have not been established.

Geriatric

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

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

HIV-1 Infection

Clinical Trials: More than 12,000 patients have been treated with tenofovir disoproxil fumarate alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in Phase 1-3 clinical trials and expanded access studies. A total of 1,544 patients have received tenofovir disoproxil fumarate 300 mg once daily in Phase 1-3 clinical trials; over 11,000 patients have received tenofovir disoproxil fumarate in expanded access studies.

Treatment-Experienced Adult Patients

Study 907 - Treatment-Emergent Adverse Events: The most common adverse events that occurred in patients receiving tenofovir disoproxil fumarate with other antiretroviral agents in clinical trials were mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting and flatulence. Less than 1% of patients discontinued participation in the clinical studies due to gastrointestinal adverse events (Study 907).

A summary of treatment-emergent adverse events that occurred during the first 48 weeks of Study 907 is provided in Table 1.

Table 1 Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥ 3% in Any Treatment Group in Study 907 (0–48 weeks)

	Tenofovir disoproxil fumarate (N = 368) (Week 0–24)	Placebo (N = 182) (Week 0–24)	Tenofovir disoproxil fumarate (N = 368) (Week 0–48)	Placebo Crossover to tenofovir disoproxil fumarate (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%

	Tenofovir disoproxil fumarate (N = 368) (Week 0–24)	Placebo (N = 182) (Week 0–24)	Tenofovir disoproxil fumarate (N = 368) (Week 0–48)	Placebo Crossover to tenofovir disoproxil fumarate (N = 170) (Week 24–48)
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[1]	3%	3%	5%	2%
Dizziness	1%	3%	3%	1%
Skin and Appendage				
Rash event[2]	5%	4%	7%	1%
Sweating	3%	2%	3%	1%
Musculoskeletal				
Myalgia	3%	3%	4%	1%
Metabolic				
Weight loss	2%	1%	4%	2%

1 Peripheral neuropathy includes peripheral neuritis and neuropathy
2 Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash

Laboratory Abnormalities: Laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir disoproxil fumarate and placebo-treated groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 2.

Table 2 Grade 3/4 Laboratory Abnormalities Reported in ≥ 1% of Tenofovir disoproxil fumarate-Treated Patients in Study 907 (0–48 weeks)

	Tenofovir disoproxil fumarate (N = 368) (Week 0–24) (%)	Placebo (N = 182) (Week 0–24) (%)	Tenofovir disoproxil fumarate (N = 368) (Week 0–48) (%)	Placebo Crossover to tenofovir disoproxil fumarate (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%
Urine Glucose (≥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%

Treatment-Naïve Adult Patients

Study 903 - Treatment-Emergent Adverse Events: The adverse reactions seen in a double-blind active-controlled study in which 600 treatment-naïve patients received tenofovir disoproxil fumarate (N = 299) or stavudine (N = 301) in combination with lamivudine and efavirenz for 144 weeks (Study 903) were generally consistent, with the addition of dizziness, with those seen in treatment-experienced patients (Table 3).

Mild adverse events (Grade 1) were common with a similar incidence in both arms and included dizziness, diarrhea and nausea.

Table 3 Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥ 5% in Any Treatment Group in Study 903 (0–144 Weeks)

	Tenofovir disoproxil fumarate + Lamivudine + EFV (Efavirenz) N = 299	**d4T (Stavudine) + Lamivudine + EFV (Efavirenz) N = 301**
Body as a Whole		
Headache	14%	17%
Pain	13%	12%
Back pain	9%	8%
Fever	8%	7%
Abdominal pain	7%	12%
Asthenia	6%	7%
Digestive System		
Diarrhea	11%	13%
Nausea	8%	9%
Vomiting	5%	9%
Dyspepsia	4%	5%
Metabolic Disorders		
Lipodystrophy	1%	8%
Musculoskeletal		
Arthralgia	5%	7%
Myalgia	3%	5%
Nervous System		
Depression	11%	10%
Anxiety	6%	6%
Insomnia	5%	8%
Dizziness	3%	6%
Peripheral neuropathy[1]	1%	5%
Respiratory		
Pneumonia	5%	5%
Skin and Appendages		
Rash event[2]	18%	12%

1 Peripheral neuropathy includes peripheral neuritis and neuropathy.

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

Laboratory Abnormalities: With the exception of triglyceride elevations that were more common in the stavudine group (14%) compared with tenofovir disoproxil fumarate (3%), laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir disoproxil fumarate and stavudine treatment arms. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 4.

Table 4 Grade 3/4 Laboratory Abnormalities Reported in ≥ 1% of Tenofovir disoproxil fumarate-Treated Patients in Study 903 (0–144 Weeks)

	Tenofovir disoproxil fumarate + Lamivudine + EFV N = 299	d4T (Stavudine) + Lamivudine + EFV 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%
Neutrophil (< 750/mm^3)	3%	1%
Fasting Triglyceride (> 750 mg/dL)	1%	9%

In Study 903 through 144 weeks, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients in the tenofovir disoproxil fumarate group compared with patients in the stavudine group (see Table 5). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through Week 144. Twenty-eight percent of tenofovir disoproxil fumarate-treated patients vs. 21% of the stavudine-treated patients 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 patients in the tenofovir disoproxil fumarate group and 6 patients in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) in the tenofovir disoproxil fumarate group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in the tenofovir disoproxil fumarate group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of tenofovir disoproxil fumarate-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

Table 5 Changes in Bone Mineral Density in Study 903

	Mean Percent Change (± SD) to Week 144 in BMD	
	Tenofovir disoproxil fumarate + Lamivudine+ EFV	d4T + Lamivudine +EFV
Lumbar Spine	–2.2% ± 3.9	–1.0% ± 4.6
Hip	–2.8% ± 3.5	–2.4% ± 4.5

Study 934 - Treatment Emergent Adverse Events: Study 934 was an open-label active-controlled study in which 511 antiretroviral-naïve patients received either tenofovir disoproxil fumarate +

emtricitabine administered in combination with efavirenz (N = 257) or lamivudine/zidovudine administered in combination with efavirenz (N = 254). Adverse events observed in this study were generally consistent with those seen in other studies in treatment-experienced or treatment-naïve patients (Table 6).

Table 6 Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥ 3% in Any Treatment Group in Study 934 (0–48 weeks)

	Tenofovir disoproxil fumarate + FTC (Emtricitabine) + EFV N = 257	**AZT (Zidovudine)/Lamivudine + EFV N = 254**
Blood and Lymphatic System Disorders		
Anemia	<1%	5%
Gastrointestinal Disorder		
Diarrhea	7%	4%
Nausea	8%	6%
Vomiting	1%	4%
General Disorders and Administration Site Condition		
Fatigue	7%	6%
Infections and Infestations		
Sinusitis	4%	2%
Upper respiratory tract infections	3%	3%
Nasopharyngitis	3%	1%
Nervous System Disorders		
Somnolence	3%	2%
Headache	5%	4%
Dizziness	8%	7%
Psychiatric Disorders		
Depression	4%	7%
Insomnia	4%	5%
Abnormal dreams	4%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	5%	4%

Patients who received treatment up to 144 weeks in Study 934 reported adverse events similar in nature and severity to those reported in the first 48 weeks.

Through 48 weeks, 7 patients in the emtricitabine + tenofovir disoproxil fumarate group and 5 patients in the lamivudine/zidovudine group experienced a new CDC Class C event (10 and 6 patients, respectively, through 144 weeks). Renal safety assessed by laboratory abnormalities was similar in the two groups and no patient discontinued study drug due to renal events. At Week 48 and 144, total limb fat (as measured by dual-energy x-ray absorptiometry) was significantly less in a subgroup of patients in the lamivudine/zidovudine group compared to the tenofovir/emtricitabine subgroup (see Table 7).

Table 7 Study 934: Total Limb Fat at Week 48 and 144 (Dual-Energy X-Ray Absorptiometry)

	Tenofovir disoproxil fumarate + FTC + EFV	**AZT/Lamivudine + EFV**
Week 48[1]	**N = 51**	**N = 49**
Total Limb Fat (kg) (Mean ± S.D.)	8.9 ± 5.4	6.9 ± 3.9
Week 144[2]	**N = 145**	**N = 124**
Total Limb Fat (kg) (Mean ± S.D.)	9.2 ± 5.4	6.5 ± 4.3

1 P = 0.03 for the comparison between arms
2 P < 0.001 for the comparison between arms

Laboratory Abnormalities: Laboratory Abnormalities observed in this study were generally consistent with those seen in other studies (Table 8).

Table 8 Grade 3/4 Laboratory Abnormalities Reported in ≥ 1% in Any Treatment Group in Study 934 (0–48 weeks)

	Emtricitabine + Tenofovir disoproxil fumarate + EFV N = 257	**AZT/Lamivudine+ EFV N = 254**
Any ≥ Grade 3 Laboratory Abnormality	25%	22%
Fasting Cholesterol (> 240 mg/dL)	15%	17%
Creatine Kinase (M: > 990 U/L) (F: > 845 U/L)	7%	6%
Serum Amylase (> 175 U/L)	7%	3%
Alkaline Phosphatase (> 550 U/L)	1%	0%
AST (M: > 180 U/L) (F: > 170 U/L)	3%	2%
ALT (M: > 215 U/L) (F: > 170 U/L)	2%	2%
Hemoglobin (< 8.0 mg/dL)	0%	3%
Hyperglycemia (> 250 mg/dl)	1%	1%
Hematuria (> 75 RBC/HPF)	2%	2%
Neutrophil (> 750/mm^3)	3%	4%
Fasting Triglycerides (> 750 mg/dL)	4%	2%

Laboratory abnormalities in patients who received treatment up to 144 weeks in Study 934 were consistent with those observed in the first 48 weeks of treatment.

Adolescent Patients with HIV-1 Infection
Assessment of adverse reactions is based on one randomized study (Study 321) in 87 HIV-1 infected adolescent patients (12 to <18 years of age) who received treatment with tenofovir disoproxil fumarate (N = 45) or placebo (N = 42) in combination with other antiretroviral agents for 48 weeks. The adverse reactions observed in adolescent patients who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical studies in adults.

Chronic Hepatitis B

Adult Patients

Patients with chronic hepatitis B and compensated liver function received double-blind treatment with tenofovir disoproxil fumarate (N = 426) or adefovir dipivoxil (N = 215) for 48 weeks in studies 0102 (HBeAg-) and 0103 (HBeAg+).

The most common adverse events in tenofovir disoproxil fumarate-treated patients (incidence ≥ 5%) identified during the 48-week double blind period of these studies, at any severity and regardless of causality, are presented in Table 9.

Table 9 Treatment-Emergent Adverse Events[a] (≥ 5% in tenofovir disoproxil fumarate treated patients) in Pooled Studies GS-US-174-0102 and GS-US-174-0103 (0-48 weeks)

	Tenofovir disoproxil fumarate (N = 426)	Adefovir dipivoxil (N = 215)
Body as a Whole		
Abdominal Pain Upper	7%	5%
Back Pain	7%	5%
Gastrointestinal Disorders		
Nausea	9%	3%
Diarrhea	7%	5%
General Disorders		
Fatigue	9%	7%
Infections and Infestations		
Nasopharyngitis	10%	11%
Nervous System Disorders		
Headache	13%	14%
Dizziness	6%	3%

a regardless of causality and severity

The adverse reactions observed with continued treatment for 288 weeks in Studies 0102 and 0103 were consistent with the safety profile of tenofovir disoproxil fumarate.

Adverse events observed in a double-blind, randomized, controlled study (Study 0106) in which 105 patients previously treated with adefovir dipivoxil were treated with tenofovir disoproxil fumarate for 48 weeks were similar in nature to those observed in Studies 0102 and 0103.

No new adverse events causally associated with tenofovir disoproxil fumarate were identified from a double-blind active controlled study (Study 0108) in which patients with decompensated liver disease received treatment containing tenofovir disoproxil fumarate (N = 90) for up to 48 weeks. This study was not large enough to detect rare or unexpected adverse events in this patient population. In this study, 7 of 90 patients (8%) receiving a tenofovir disoproxil fumarate-containing regimen, including 4 of 45 patients (9%) receiving tenofovir disoproxil fumarate, experienced a confirmed increase in serum creatinine of ≥ 0.5 mg/dL or confirmed decrease in serum phosphorus of <2 mg/dL through Week 48 **(see CLINICAL TRIALS for additional safety information regarding tenofovir disoproxil fumarate).**

No new adverse reactions to tenofovir disoproxil fumarate were identified from a randomized, double-blind study (Study 0121) in which lamivudine-resistant patients received treatment containing tenofovir disoproxil fumarate (N = 280) for 96 weeks.

Laboratory Abnormalities: In Studies 0102 and 0103, the most frequently occurring Grade 3 or 4 laboratory abnormality during the 48-week double-blind period in the tenofovir disoproxil fumarate treatment group was ALT increased. All patients with treatment-emergent Grade 3 or 4 ALT increases had elevated ALT at baseline. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 10.

Table 10 Grade 3/4 Laboratory Abnormalities Reported in ≥ 1% in Any Treatment Group in Pooled Studies GS-US-174-0102 and GS-US-174-0103 (0–48 weeks)

	Tenofovir disoproxil fumarate N = 426	**Adefovir dipivoxil N = 215**
Any ≥ Grade 3 Laboratory Abnormality	19%	13%
ALT (> 5.00 x ULN)	10%	6%
AST (> 5.00 x ULN)	4%	4%
Serum Amylase (> 2.0 x ULN)	4%	1%
Urine Glucose (≥ 3+)	3%	1%
Creatine Kinase (≥ 10.0 x ULN)	2%	3%
Hyperglycemia (> 250 mg/dl)	1%	2%

Grade 3/4 laboratory abnormalities were similar in nature and frequency in patients continuing treatment for up to 288 weeks in these studies. Overall, the following Grade 3–4 laboratory abnormalities were reported in ≥ 1% of subjects during open-label tenofovir disoproxil fumarate treatment (Weeks 48-288 of Studies 0102 and 0103): urine glucose (5%), AST (4%), prothrombin time (4%), ALT (3%), serum amylase (3%), creatine kinase (3%), serum lipase (2%) and hyperglycemia (2%).

Post Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of tenofovir disoproxil fumarate. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been considered possible adverse reactions due to a combination of their seriousness, frequency of reporting or potential causal relationship with tenofovir disoproxil fumarate.

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
Blood and lymphatic system:	Thrombocytopenia
Hepatobiliary disorders:	Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT, GGT)
Skin and Subcutaneous Tissue Disorders:	Rash
Musculoskeletal and Connective Tissue Disorders:	Rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing 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, sometimes appeared to be concurrent with proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalemia, muscular weakness, myopathy, hypophosphatemia.

There have been three post marketing reports of acute renal failure in patients on concomitant NSAIDS therapy where a relationship to tenofovir disoproxil fumarate could not be excluded. These events mostly occurred in medically complex patients, where underlying disease processes confound interpretation.

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy an inflammatory reaction to infectious pathogens (active or inactive) may arise (see **WARNINGS and PRECAUTIONS**).

In HBV infected patients, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of HBV therapy (see **WARNINGS AND PRECAUTIONS, Exacerbations of Hepatitis after Discontinuation of Treatment**).

DRUG INTERACTIONS

Drug-Drug Interactions

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

Established and Other Potentially Significant Drug Interactions

The drug interactions described are based on studies conducted with tenofovir disoproxil fumarate as an individual agent and/or in combination, or are potential drug interactions that may occur with tenofovir disoproxil fumarate.

Table 11 Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiretroviral Agents:		
Didanosine	↑ didanosine	Pharmacokinetic studies have shown that co-administration of didanosine and tenofovir disoproxil fumarate results in 40–60% increase in C_{max} and AUC of didanosine (see Table 12). The mechanism of this interaction is unknown. Increases in didanosine concentrations of this magnitude could potentiate didanosine-associated adverse events, including pancreatitis, lactic acidosis, and neuropathy. In addition, suppression of CD4 counts has been observed in patients receiving tenofovir disoproxil fumarate with didanosine at a dose of 400 mg daily. A reduced dose of didanosine is recommended when co-administered with tenofovir disoproxil fumarate. When co-administered with tenofovir disoproxil fumarate, the didanosine Product Monograph recommends a reduced dose of 250 mg didanosine for HIV-infected adults with body weight ≥ 60 kg and creatinine clearance ≥ 60 mL/min. For adult patients with body weight < 60 kg, and creatinine clearance ≥ 60 mL/min, the recommended dose of didanosine is 200 mg. Data are not available to recommend a dose adjustment for patients with creatinine clearance < 60mL/min or for the buffered tablet formulation of didanosine. Caution should be used when co-administering reduced-dose didanosine, tenofovir, and an NNRTI in treatment-naïve patients with high viral loads at baseline since such use has been associated with reports of a high rate of virologic failure and emergence of resistance at an early stage. All patients receiving tenofovir disoproxil fumarate and didanosine concomitantly should be closely monitored for didanosine-related adverse events and clinical response
Atazanavir/ritonavir Darunavir/ritonavir Lopinavir/ritonavir	↑ tenofovir	Atazanavir/ritonavir, darunavir/ritonavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations (see Table 13). The mechanism of this interaction is unknown. Higher tenofovir concentrations could potentiate tenofovir disoproxil fumarate-associated adverse events, including renal disorders. Patients should be monitored for tenofovir disoproxil fumarate-associated adverse events when receiving atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir in combination with tenofovir disoproxil fumarate.
Atazanavir	↓ atazanavir	Tenofovir decreases atazanavir concentrations (see Table 14). Although safety and efficacy data are limited, it is recommended that atazanavir, without ritonavir, should not be coadministered with tenofovir DF. The recommended regimen is atazanavir 300 mg given with ritonavir 100 mg when used in combination with tenofovir DF 300 mg (all as a single daily dose with food).
Hepatitis C Virus Antiviral Agents:		
Ledipasvir/sofosbuvir Sofosbuvir/velpatasvir Sofosbuvir/velpatasvir/ voxilaprevir	↑ tenofovir	Co-administration of tenofovir disoproxil fumarate and ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir has been shown to increase tenofovir exposure (see Table 13). Patients receiving a regimen containing tenofovir disoproxil fumarate concomitantly with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir should be monitored for adverse reactions associated with tenofovir disoproxil fumarate.

[a] This table is not all inclusive.

[b] ↑ = increase, ↓ = decrease

Drugs Affecting Renal Function

Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Co-administration of tenofovir disoproxil fumarate with drugs that are eliminated by active tubular secretion may increase serum concentrations of either tenofovir or the co-administered drug, due to competition for this elimination pathway. Some examples include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir. Drugs that decrease renal function may also increase serum concentrations of tenofovir.

TEVA-TENOFOVIR should not be administered in combination with adefovir dipivoxil (see **WARNINGS AND PRECAUTIONS, General**).

Drugs without Clinically Significant Interactions with TEVA-TENOFOVIR

There were no clinically significant drug interactions observed when tenofovir disoproxil fumarate was co-administered with abacavir, efavirenz, emtricitabine, entecavir, indinavir, lamivudine, methadone, nelfinavir, oral contraceptives, ribavirin, rifampicin, saquinavir/ritonavir, sofosbuvir and tacrolimus (see Table 13 and Table 14).

Assessment of Drug Interactions

Drug-drug interaction studies were conducted with tenofovir disoproxil fumarate as an individual agent and/or in combination with emtricitabine. The effects of didanosine in the presence of tenofovir disoproxil fumarate are shown in Table 12.

The effects of coadministered drugs on the exposure of tenofovir disoproxil fumarate are shown in Table 13.

The effects of tenofovir disoproxil fumarate on the exposure of coadministered drugs are shown in Table 14.

Table 12 Drug Interactions: Pharmacokinetic Parameters for Didanosine in the Presence of tenofovir disoproxil fumarate

Didanosine[1] Dose (mg) / Method of Administration[2]	Tenofovir Disoproxil Fumarate Method of Administration[2]	N	% Difference (90% CI) vs. Didanosine 400 mg Alone, Fasted[3]	
			C_{max}	AUC
Buffered tablets				
400 once daily[4] x 7 days	Fasted 1 hour after didanosine	14	↑ 27 (↑ 8 to ↑ 46)	↑ 43 (↑ 30 to ↑ 57)
Enteric Coated capsules				
400 once, fasted	With food, 2 hr after didanosine	26	↑ 48 (↑ 25 to ↑ 76)	↑ 48 (↑ 31 to ↑ 67)
400 once, with food	Simultaneously with didanosine	26	↑ 64 (↑ 41 to ↑ 89)	↑ 60 (↑ 44 to ↑ 79)
250 once, fasted	With food, 2 hr after didanosine	28	↓ 10 (↓ 22 to ↑ 3)	0 (↓ 11 to ↑ 12)
250 once, fasted	Simultaneously with didanosine	28	↓ 8 (↓ 19 to ↑ 5)	↑ 14 (0 to ↑ 31)
250 once, with food	Simultaneously with	28	↓ 29	↓ 11

Didanosine[1] Dose (mg) / Method of Administration[2]	Tenofovir Disoproxil Fumarate Method of Administration[2]	N	% Difference (90% CI) vs. Didanosine 400 mg Alone, Fasted[3]	
			C_{max}	AUC
	didanosine		(↓ 39 to ↓ 18)	(↓ 23 to ↑ 2)

1 See PRECAUTIONS regarding use of didanoside with TEVA-TENOFOVIR
2 Administration with food was with a light meal (~ 373 kcal, 20% fat)
3 Increase = ↑; Decrease = ↓
4 Includes 4 subjects weighing < 60 kg receiving didanosine 250 mg

Table 13 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[1] in the Presence of the Co-administered Drug

Co-administered Drug	Dose of Co-administered Drug (mg)	N	Mean % Change of Tenofovir Pharmacokinetic Parameters[2] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↓ 8 (↓ 24 to ↑ 12)	↑ 4 (↓ 14 to ↑ 26)	NC
Atazanavir sulfate[3]	400 once daily x 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Atazanavir/Ritonavir[3]	300/100 once daily	12	↑ 34 (↑ 20 to ↑ 51)	↑ 37 (↑ 30 to ↑ 45)	↑ 29 (↑ 21 to ↑ 36)
Darunavir/Ritonavir[4]	300/100 twice daily	12	↑ 24 (↑ 8 to ↑ 42)	↑ 22 (↑ 10 to ↑ 35)	↑ 37 (↑ 19 to ↑ 57)
Didanosine (enteric-coated)	400 once	25	↓ 2 (↓ 7 to ↑ 4)	↑ 2 (↓ 2 to ↑ 5)	NC
Didanosine (buffered)[4]	250 or 400 once daily x 7 days[5]	14	↑ 1 (↓ 12 to ↑ 14)	↓ 5 (↓ 14 to ↑ 4)	↓ 22 (↓ 36 to ↓ 7)
Efavirenz	600 once daily x 14 days	29	↑ 7 (↓ 4 to ↑ 17)	↓ 2 (↓ 8 to ↑ 3)	↑ 2 (↓ 9 to ↑ 12)
Emtricitabine	200 once daily x 7 days	17	↑ 3 (↓ 5 to ↑ 11)	0 (↓ 8 to ↑ 9)	↑ 2 (↓ 8 to ↑ 13)
Entecavir	1 mg once daily x 10 days	28	NA	NA	NA
Indinavir	800 three times daily x 7 days	13	↑ 14 (↓ 3 to ↑ 31)	↑ 7 (↓ 5 to ↑ 19)	↑ 8 (↓ 7 to ↑ 22)
Lamivudine	150 twice daily x 7 days	15	↑ 2 (↓ 4 to ↑ 9)	↓ 3 (↓ 15 to ↑ 19)	↓ 8 (↓ 33 to ↑ 18)
Ledipasvir/Sofosbuvir[6,7]	90/400 once daily x 10 days	24	↑ 47 (↑ 37 to ↑ 58)	↑ 35 (↑ 29 to ↑ 42)	↑ 47 (↑ 38 to ↑ 57)
Ledipasvir/Sofosbuvir[6,8]		23	↑ 64 (↑ 54 to ↑ 74)	↑ 50 (↑ 42 to ↑ 59)	↑ 59 (↑ 49 to ↑ 70)
Ledipasvir/Sofosbuvir[9]	90/400 once daily x 10 days	15	↑ 79 (↑ 56 to ↑ 104)	↑ 98 (↑ 77 to ↑ 123)	↑ 163 (↑ 132 to ↑ 197)
Ledipasvir/Sofosbuvir[10]		14	↑ 32 (↑ 25 to ↑ 39)	↑ 40 (↑ 31 to ↑ 50)	↑ 91 (↑ 74 to ↑ 110)
Ledipasvir/ Sofosbuvir[11]	90/400 once daily x 10 days	29	↑ 61 (↑ 51 to ↑ 72)	↑ 65 (↑ 59 to ↑ 71)	↑ 115 (↑ 105 to ↑ 126)
Lopinavir/Ritonavir	400/100 twice daily x 14 days	24	↑ 33 (↑ 17 to ↑ 49)	↑ 32 (↑ 25 to ↑ 40)	↑ 28 (↑ 7 to ↑ 49)
Nelfinavir	1250 twice daily x 14 days	29	↓ 2 (↓ 9 to ↑ 5)	↑ 1 (↓ 5 to ↑ 7)	↑ 9 (↑ 2 to ↑ 17)
Saquinavir/Ritonavir	1000/100 twice daily x 14 days	35	↑ 15 (↑ 7 to ↑ 22)	↑ 14 (↑ 9 to ↑ 19)	↑ 23 (↑ 16 to ↑ 30)
Sofosbuvir[12]	400 once daily	16	↑ 25	↓ 2	↓ 1

Co-administered Drug	Dose of Co-administered Drug (mg)	N	Mean % Change of Tenofovir Pharmacokinetic Parameters[2] (90% CI)		
			C_{max}	AUC	C_{min}
			(↑ 8 to ↑ 45)	(↓ 9 to ↑ 5)	(↓ 9 to ↑ 7)
Sofosbuvir/Velpatasvir[13]	400/100 once daily	24	↑ 55 (↑ 43 to ↑ 68)	↑ 30 (↑ 24 to ↑ 36)	↑ 39 (↑ 31 to ↑ 48)
Sofosbuvir/Velpatasvir[14]		29	↑ 55 (↑ 45 to ↑ 66)	↑ 39 (↑ 33 to ↑ 44)	↑ 52 (↑ 45 to ↑ 59)
Sofosbuvir/Velpatasvir[15]		15	↑ 77 (↑ 53 to ↑ 104)	↑ 81 (↑ 68 to ↑ 94)	↑ 121 (↑ 100 to ↑ 143)
Sofosbuvir/Velpatasvir[16]		24	↑ 44 (↑ 33 to ↑ 55)	↑ 40 (↑ 34 to ↑ 46)	↑ 84 (↑ 76 to ↑ 92)
Sofosbuvir/Velpatasvir[17]		24	↑ 36 (↑ 25 to ↑ 47)	↑ 35 (↑ 29 to ↑ 42)	↑ 45 (↑ 39 to ↑ 51)
Sofosbuvir/Velpatasvir[18]		30	↑ 46 (↑ 39 to ↑ 54)	↑ 40 (↑ 34 to ↑ 45)	↑ 70 (↑ 61 to ↑ 79)
Sofosbuvir/ Velpatasvir/ Voxilaprevir[19]	400/100/100 + voxilaprevir[20] 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)	↑ 6 (↓ 1 to ↑ 13)	↑ 11 (↑ 4 to ↑ 18)

1 Patients received tenofovir disoproxil fumarate 300 mg once daily
2 Increase = ↑; Decrease = ↓; NA = Not Available; NC = Not calculated
3 Reyataz Prescribing Information (Bristol-Myers Squibb)
4 Includes 4 subjects weighing < 60 kg receiving didanosine 250 mg
5 Weight < 60 kg: 250 mg, ≥ 60 kg more: 400 mg
6 Data generated from simultaneous dosing with ledipasvir/sofosbuvir. Staggered administration (12 hours apart) provides similar results.
7 Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate coadministered with ledipasvir/sofosbuvir
8 Comparison based on exposure when administered as darunavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate coadministered with ledipasvir/sofosbuvir
9 Study conducted with efavirenz/emtricitabine/tenofovir disoproxil fumarate coadministered with ledipasvir/ sofosbuvir
10 Study conducted with emtricitabine/rilpivirine/tenofovir disoproxil fumarate coadministered with ledipasvir/ sofosbuvir
11 Study conducted with efavirenz/emtricitabine/tenofovir disoproxil fumarate + dolutegravir coadministered with ledipasvir/sofosbuvir
12 Study conducted with efavirenz/emtricitabine/tenofovir disoproxil fumarate coadministered with sofosbuvir
13. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate coadministered with sofosbuvir/velpatasvir
14 Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate coadministered with sofosbuvir/velpatasvir
15 Study conducted with efavirenz/emtricitabine/tenofovir disoproxil fumarate coadministered with sofosbuvir/velparasvir
16 Study conducted with efavirenz/rilpivirine/tenofovir disoproxil fumarate coadministered with sofosbuvir/velparasvir
17 Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate coadministered with sofosbuvir/velparasvir
18 Administered as raltegravir + efavirenz/emtricitabine/tenofovir disoproxil fumarate coadministered with sofosbuvir/velparasvir
19 Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/TDF.
20 Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Table 14 Drug Interactions: Changes in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Tenofovir Disoproxil Fumarate

Co-administered Drug	Dose of Co-administered Drug (mg)	N	Mean % Change of Co-administered Drug Pharmacokinetic Parameters[1] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	↑ 11 (↑ 4 to ↑ 19)	NC
Atazanavir	400 once daily x 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir[2]	Atazanavir/ritonavir 300/100 once daily x 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25[3] (↓ 42 to ↓ 3)	↓ 23[3] (↓ 46 to ↑ 10)
Efavirenz	600 once daily x 14 days	30	↓ 4 (↓ 9 to ↑ 5)	↓ 3 (↓ 7 to 0)	↓ 7 (↓ 13 to ↓ 1)
Emtricitabine	200 once daily x 7 days	17	↓ 4 (↓ 13 to ↑ 6)	↑ 7 (0 to ↑ 4)	↑ 20 (↑ 12 to ↑ 29)
Entecavir	1 mg once daily x 10 days	28	NA	↑ 13 (↑ 11 to ↑ 15)	NA
Indinavir	800 three times daily x 7 days	12	↓ 6 (↓ 23 to ↑ 10)	↓ 2 (↓ 12 to ↑ 8)	↑ 43 (↓ 45 to ↑ 130)
Lamivudine	150 twice daily x 7 days	15	↓ 29 (↓ 39 to ↓ 19)	↓ 10 (↓ 17 to ↓ 3)	↑ 17 (↑ 3 to ↑ 32)
Ledipasvir	Ledipasvir/ Sofosbuvir 90/400 once daily x 10 days[9,10]	24	↑ 68 (↑ 54 to ↑ 84)	↑ 96 (↑ 74 to ↑ 121)	↑ 118 (↑ 91 to ↑ 150)
Sofosbuvir			↑ 1 (↓ 12 to ↑ 15)	↑ 11 (↑ 2 to ↑ 21)	NC
GS-331007[8]			↑ 17 (↑ 12 to ↑ 23)	↑ 31 (↑ 25 to ↑36)	↑ 42 (↑ 34 to ↑ 49)
Ledipasvir	Ledipasvir/ Sofosbuvir 90/400 once daily x 10 days[9,11]	23	↑ 11 (↓ 1 to ↑ 23)	↑ 12 (0 to ↑ 25)	↑ 17 (↑ 4 to ↑ 31)
Sofosbuvir			↓ 37 (↓ 48 to ↓25)	↓ 27 (↓ 35 to ↓ 18)	NC
GS-331007[8]			↑ 10 (↑ 4 to ↑ 16)	↑ 20 (↑ 16 to ↑ 24)	↑ 26 (↑ 20 to ↑ 32)
Ledipasvir	Ledipasvir/ Sofosbuvir 90/400 once daily x 10 days[12]	15	↓ 34 (↓ 41 to ↓ 25)	↓ 34 (↓ 41 to ↓ 25)	↓ 34 (↓ 43 to ↓ 24)
Sofosbuvir			↑ 3 (↓ 13 to ↑ 23)	↓ 6 (↓ 19 to ↑ 10)	NC
GS-331007[8]			↓ 14 (↓ 24 to ↓ 4)	↓ 10 (↓ 17 to ↓ 3)	↑ 7 (↑ 2 to ↑ 13)
Ledipasvir	Ledipasvir/ Sofosbuvir 90/400 once daily x 10 days[13]	14	↑ 1 (↓ 5 to ↑ 7)	↑ 8 (↑ 2 to ↑ 15)	↑ 16 (↑ 8 to ↑ 25)
Sofosbuvir			↑ 5 (↓ 7 to↑ 20)	↑ 10 (↑ 1 to ↑ 21)	NC
GS-331007[8]			↑ 6 (↑ 1 to ↑ 11)	↑ 15 (↑ 11 to ↑ 19)	↑ 18 (↑ 13 to ↑ 23)
Sofosbuvir	400/100 once daily[14]	24	↑ 12 (↓ 3 to↑ 29)	↑ 22 (↑ 12 to ↑ 33)	NC
GS-331007[8]			↑ 21 (↑ 12 to ↑ 29)	↑ 32 (↑ 27 to ↑ 36)	↑ 42 (↑ 37 to ↑ 49)
Velpatasvir			↑ 55 (↑ 41 to ↑ 71)	↑ 142 (↑ 123 to ↑ 164)	↑ 301 (↑ 257 to ↑ 350)
Sofosbuvir	400/100 once daily[15]	29	↓ 38 (↓ 46 to ↓ 29)	↓ 28 (↓ 34 to ↓ 20)	NC

Co-administered Drug	Dose of Co-administered Drug (mg)	N	Mean % Change of Co-administered Drug Pharmacokinetic Parameters[1] (90% CI)		
			C_{max}	AUC	C_{min}
GS-331007[8]			↑ 4 (↓ 1 to ↑ 8)	↑ 13 (↑ 8 to ↑ 18)	↑ 13 (↑ 6 to ↑ 19)
Velpatasvir			↓ 24 (↓ 35 to ↓ 11)	↓ 16 (↓ 28 to ↓ 2)	↑ 1 (↓ 13 to ↑ 18)
Sofosbuvir	400/100 once daily[16]		↑ 38 (↑ 14 to ↑ 67)	↓ 3 (↓ 17 to ↑ 14)	NC
GS-331007[8]			↓ 14 (↓ 20 to ↓ 7)	↓ 10 (↓ 15 to ↓ 4)	↑ 1 (↓ 5 to ↑ 7)
Velpatasvir			↓ 47 (↓ 57 to ↓ 36)	↓ 53 (↓ 61 to ↓ 43)	↓ 57 (↓ 64 to ↓ 48)
Sofosbuvir	400/100 once daily[17]		↑ 9 (↓ 5 to ↑ 25)	↑ 16 (↑ 9 to ↑ 24)	NC
GS-331007[8]			↓ 4 (↓ 10 to ↑ 1)	↑ 21 (0 to ↑ 7)	↑ 12 (↑ 7 to ↑ 17)
Velpatasvir			↓ 4 (↓ 5 to ↑ 10)	↓ 1 (↓ 12 to ↑ 11)	↑ 2 (↓ 9 to ↑ 15)
Sofosbuvir	400/100 once daily[18]		↑ 1 (↓ 15 to↑ 19)	↑ 24 (↑ 13 to ↑ 37)	NC
GS-331007[8]			↑ 13 (↑ 7 to ↑ 8)	↑ 35 (↑ 30 to ↑ 40)	↑ 45 (↑ 38 to ↑ 52)
Velpatasvir			↑ 5 (↓ 7 to↑ 19)	↑ 19 (↑ 7 to ↑ 34)	↑ 37 (↑ 22 to ↑ 54)
Sofosbuvir	400/100 once daily[19]		↑ 9 (↓ 3 to↑ 23)	↑ 16 (↑ 7 to ↑ 25)	NC
GS-331007[8]			↓ 5 (↓ 9 to ↓ 2)	↑ 21 (0 to ↑ 6)	↑ 8 (↑ 4 to ↑ 13)
Velpatasvir			↓ 3 (↓ 13 to ↑ 8)	↓ 2 (↓ 12 to ↑ 10)	↓ 3 (↓ 13 to ↑ 7)
Sofosbuvir	400/100/100 + voxilaprevir[21] 100 once daily	29	↓ 30 (↓ 38 to ↓ 22)[22]	↓ 22 (↓ 27 to ↓ 17)[22]	NA
GS-331007[8]			↑ 6 (↑ 1 to ↑ 10)[22]	↑ 15 (↑ 12 to ↑ 19)[22]	NA
Velpatasvir			↓ 22 (↓ 27 to ↓ 16)[22]	↓ 5 (↓ 12 to ↑ 2)[22]	↑ 16 (↑ 7 to ↑ 26)[22]
Voxilaprevir			↑ 72 (↑ 51 to ↑ 97)[22]	↑ 143 (↑ 115 to ↑ 175)[22]	↑ 300 (↑ 244 to ↑ 365)[22]
Lopinavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24	↓ 14 (↓ 23 to ↓ 4)	↓ 12 (↓ 20 to ↓ 5)	↓ 11 (↓ 22 to ↑ 1)
Ritonavir			↓ 24 (↓ 46 to ↓ 3)	↓ 22 (↓ 34 to↓ 9)	↓ 15 (↓ 32 to ↑ 2)
Methadone[4]	40-110 once daily x 14 days[5]	13	↑ 5 (↓ 3 to ↑ 14)	↑ 5 (↓ 2 to ↑ 13)	↑ 6 (↓ 3 to ↑ 15)
Nelfinavir	1250 twice daily x 14 days	29	↓ 8 (↓ 15 to ↓ 1)	↓ 7 (↓15 to ↑ 2)	↑ 1 (↓ 15 to ↑ 19)
M8 metabolite			↓ 8 (↓ 16 to 0)	↓ 7 (↓ 17 to ↑ 5)	↓ 2 (↓ 16 to ↑ 15)
Norgestimate[6]	Ethinyl Estradiol/ Norgestimate Once daily x 7 days	20	↓ 6 (↓ 13 to ↑ 1)	↓ 5 (↓ 9 to ↓ 1)	↓ 4 (↓ 8 to ↑ 1)
Ethinyl Estradiol			↓ 6 (↓ 12 to 0)	↓ 4 (↓ 9 to ↑ 1)	↓ 2 (↓ 9 to ↑ 6)
Ribavirin	600 once	22	↓ 5 (↓ 11 to ↑ 1)	↑ 12 (↑ 6 to ↑ 17)	NC

Co-administered Drug	Dose of Co-administered Drug (mg)	N	Mean % Change of Co-administered Drug Pharmacokinetic Parameters[1] (90% CI)		
			C_{max}	AUC	C_{min}
Saquinavir	1000/100 twice daily x 14 days	32	↑ 22 (↑ 6 to ↑ 41)	↑ 29[7] (↑ 12 to ↑ 48)	↑ 47[7] (↑ 23 to ↑ 76)
Ritonavir			↑ 10 (↓ 5 to ↑ 28)	↑ 11 (0 to ↑ 22)	↑ 23 (↑ 3 to ↑ 46)
Sofosbuvir	Sofosbuvir 400 once daily x 10 days[20]	16	↓ 19 (↓ 40 to ↑ 10)	↓ 6 (↓ 24 to ↑ 16)	NC
GS-331007[8]			↓ 23 (↓ 30 to ↓ 16)	↓ 16 (↓ 24 to ↓ 8)	NC
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↑ 3 (↓ 3 to ↑ 9)	↑ 4 (↓ 3 to ↑ 11)	↑ 10 (↑ 2 to ↑ 17)

1 Increase = ↑; Decrease = ↓; NA = Not Available; NC = Not Calculated
2 Reyataz Prescribing Information (Bristol-Myers Squibb)
3 In HIV-infected patients, addition of tenofovir disoproxil fumarate to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and Cmin values of atazanavir that were 2.3 and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.
4 R-(active), S-and total methadone exposures were equivalent when dosed alone or with tenofovir disoproxil fumarate
5 Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
6 Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir disoproxil fumarate.
7 Increase in AUC and Cmin are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir disoproxil fumarate and ritonavir-boosted saquinavir are coadministered.
8 The predominant circulating nucleoside metabolite of sofosbuvir
9 Data generated from simultaneous dosing with ledipasvir/sofosbuvir. Staggered administration (12 hours apart) provides similar results.
10 Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate coadministered with ledipasir/sofosbuvir.
11 Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate coadministered with ledipasir/sofosbuvir.
12 Study conducted with efavirenz/emtricitabine/tenofovir disoproxil fumarate coadministered with ledipasvir/ sofosbuvir.
13 Study conducted with emtricitabine/rilpivirine/tenofovir disoproxil fumarate coadministered with ledipasvir/ sofosbuvir
14 Comparison based on exposures when administered as atazanavir /ritonavir + emtricitabine/tenofovir disoproxil fumarate coadministered with sofosbuvir/velpatasvir.
15 Comparison based on exposures when administered as darunavir /ritonavir + emtricitabine/tenofovir disoproxil fumarate coadministered with sofosbuvir/velpatasvir.
16 Study conducted with efavirenz/emtricitabine/tenofovir disoproxil fumarate coadministered with sofosbuvir/velpatasvir.
17 Study conducted with emtricitabine/rilpivirine/tenofovir disoproxil fumarate coadministered with sofosbuvir/velpatasvir.
18 Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate coadministered with sofosbuvir/velpatasvir.
19 Comparison based on exposures when administered as raltegravir + efavirenz/emtricitabine/tenofovir disoproxil fumarate coadministered with sofosbuvir/velpatasvir.
20 Study conducted with efavirenz/emtricitabine/tenofovir disoproxil fumarate coadministered with sofosbuvir
21 Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.
22 Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/ tenofovir disoproxil fumarate.

Drug-Food Interactions

TEVA-TENOFOVIR can be taken with or without food. Administration of tenofovir disoproxil fumarate following a high-fat meal (~700 to 1000 kcal containing 40–50% 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% (see **ACTION AND CLINICAL PHARMACOLOGY, Effect of Food on Absorption**).

Drug-Herb Interactions

Interactions of TEVA-TENOFOVIR with herbs have not been established.

Drug-Laboratory Interactions

Interactions of TEVA-TENOFOVIR with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Adults

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

In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown. TEVA-TENOFOVIR may be discontinued if there is HBsAg loss or HBsAg seroconversion.

Adolescent Patients with HIV-1 Infection (12 Years of Age and Over)

Body weight ≥35 kg (≥77 lb): Take one 300 mg TEVA-TENOFOVIR tablet once daily orally, without regard to food.

Dose Adjustment for Renal Impairment

Significantly increased drug exposures occurred when tenofovir disoproxil fumarate was administered to patients with moderate to severe renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency**). Therefore, the dosing interval of TEVA-TENOFOVIR should be adjusted in patients with baseline creatinine clearance < 50 mL/min using the recommendations in Table 15. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis. The safety and efficacy of these dosing interval adjustment recommendations have not been clinically evaluated in moderate to severe renal impairment, therefore, clinical response to treatment and renal function should be closely monitored in these patients.

No dose adjustment of TEVA-TENOFOVIR tablets (300 mg) is necessary in patients with mild renal impairment (creatinine clearance 50−80 mL/min). Routine monitoring of calculated creatinine clearance, serum phosphorus, urine glucose and urine protein should be performed in patients with mild renal impairment (see **WARNINGS and PRECAUTIONS**).

Table 15 Dosage Recommendations for Patients with Altered Creatinine Clearance

Creatinine Clearance (mL/min)[1]				Hemodialysis Patients
	≥ 50	**30-49**	**10-29**	
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[2]

1 Calculated using ideal (lean) body weight.
2 Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. TEVA-TENOFOVIR should be administered following completion of dialysis.

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

No data are available to make dose recommendations in adolescent patients with renal impairment.

Missed Dose

If a patient misses a dose at the regularly scheduled time, but then remembers it that same day, the patient should take the missed dose immediately. The next dose should be taken at the regularly scheduled time the following day. The patient should not take two doses of tenofovir disoproxil fumarate at once to make up for missing a dose.

OVERDOSAGE

For management of a suspected drug overdose, please contact your Regional Poison Control Centre immediately.

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

If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug.

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

ACTION AND CLINICAL PHARMACOLOGY

Tenofovir disoproxil fumarate is an acyclic nucleotide diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis (by non-specific esterases in blood

and tissues) for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV reverse transcriptase and HBV polymerase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination.

Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Tenofovir disoproxil fumarate is a water soluble diester prodrug of the active ingredient tenofovir. Following oral administration of a single dose of tenofovir disoproxil fumarate 300 mg to HIV-infected patients in the fasted state, maximum serum concentrations (C_{max}) of tenofovir are achieved in 1.0 ± 0.4 hours. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients is approximately 25%. Administration of tenofovir disoproxil fumarate following a high-fat meal increases the oral bioavailability, with an increase in tenofovir AUC_{∞} of approximately 40% and an increase in C_{max} of approximately 14% (see **DOSAGE AND ADMINISTRATION**).

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

Pharmacodynamics

Activity in HIV-1

The in vitro 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 IC_{50} values for tenofovir were in the range of 0.04-8.5 µM. In drug combination studies of tenofovir with integrase strand transfer inhibitors (elvitegravir or raltegravir), nucleoside reverse transcriptase inhibitors (abacavir, didanosine, emtricitabine, lamivudine, stavudine, zalcitabine or zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine or rilpivirine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir or saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Tenofovir displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, G, and O (IC_{50} values ranged from 0.5-2.2 µM).

The antiviral effects of tenofovir disoproxil fumarate monotherapy in reducing HIV-1 viral load and the relationship with dose were assessed in clinical phase 1 studies in treatment-naive and treatment-experienced HIV-infected patients. Doses of tenofovir disoproxil fumarate ranging from 75 mg to 600 mg once daily resulted in statistically significant decreases in plasma HIV-1 RNA levels compared with placebo. In a mixed population of treatment-naive and treatment-experienced patients who received 28 days of repeat daily dosing with tenofovir disoproxil fumarate 300 mg QD (Study GS-97-901) the median decrease in plasma $\log_{10}$ HIV-1 RNA level was 1.22 $\log_{10}$ copies/mL.

Activity in HBV

The in vitro antiviral activity of tenofovir against HBV was assessed in the HepG2 2.2.15 cell line. The EC_{50} values for tenofovir were in the range of 0.14 to 1.5 µM, with CC_{50} (50% cytotoxicity concentration) values > 100 µM. Tenofovir diphosphate inhibits recombinant HBV polymerase with a Ki (inhibition constant) of 0.18 µM. In in vitro drug combination studies of tenofovir with

nucleoside anti-HBV reverse transcriptase inhibitors lamivudine, telbivudine, and entecavir, additive anti-HBV activity was observed. Additive to slightly synergistic effects were observed with the combination of tenofovir and emtricitabine.

Pharmacokinetics

Pharmacokinetics of intravenous tenofovir were evaluated in Study GS-96-701 (N = 16). Following intravenous administration of tenofovir 1.0 and 3.0 mg/kg, pharmacokinetics were dose-proportional with the exception of the estimated terminal half-life (5.3 and 7.8 hours, respectively). The pharmacokinetics of tenofovir were not affected by repeated dosing in the 1.0 mg/kg/day group, with the exception of half-life (5.3 on Day 1 vs. 7.7 on Day 14) and volume of distribution (763 vs. 1320 mL/kg). At the 3.0 mg/kg/day, there was an approximate 27% decrease in serum clearance of tenofovir following 7 days of once daily administration; renal clearance and estimated terminal half-life were also significantly different.

The pharmacokinetics of tenofovir following administration of tenofovir disoproxil fumarate were evaluated in the fasted state in Study GS-97-901 (HIV-infected patients) and Study GS-00-914 (healthy volunteers). The pharmacokinetics in HIV-infected patients and healthy volunteers were similar. The estimated terminal half-life in HIV-infected patients measured over 24 hours was ~12-13 hr. The terminal elimination half-life in healthy subjects assessed over 48 hours was ~17 hours. There were no significant differences in the dose-normalized steady-state pharmacokinetics of tenofovir over the dose range of 75 to 600 mg. Tenofovir exposure following 8 and 28 days was slightly higher than those observed following the first dose.

Absorption

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

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 0.01-25 µg/mL. The volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following intravenous administration of tenofovir 1.0 mg/kg and 3.0 mg/kg.

Metabolism

In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP450 enzymes.

Following IV administration of tenofovir, approximately 70-80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. After multiple oral doses of tenofovir

disoproxil fumarate 300 mg once daily (under fed conditions), 32 ± 0% of the administered dose is recovered in urine over 24 hours.

Excretion

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 tenofovir disoproxil fumarate following a high-fat meal (~700 to 1000 kcal containing 40-50% fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40% and an increase in C_{max} of approximately 14%. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 326 ± 119 ng/mL and 3324 ± 1370 ng•hr/mL following multiple doses of tenofovir disoproxil fumarate 300 mg once daily in the fed state, when meal content was not controlled.

Special Populations and Conditions

Pediatric Patients

Steady-state pharmacokinetics of tenofovir were evaluated in 8 HIV-1 infected adolescent patients (12 to <18 years). All pediatric patients were receiving tenofovir disoproxil fumarate with a ritonavir-boosted protease inhibitor. 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 adolescent patients receiving oral daily doses of tenofovir disoproxil fumarate 300 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil fumarate 300 mg.

Geriatrics

Pharmacokinetic studies have not been performed in the elderly.

Race

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

Gender

Limited data on the pharmacokinetics of tenofovir in women indicate no major gender effect.

Hepatic Insufficiency

The pharmacokinetics of tenofovir following a 300 mg single dose of tenofovir disoproxil fumarate have been studied in 8 non-HIV, non-HBV infected subjects with moderate hepatic impairment and 8 non-HIV infected subjects with severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects. No change in TEVA-TENOFOVIR dosing is required in patients with hepatic impairment.

Renal Insufficiency

The pharmacokinetics of tenofovir are altered in subjects with renal impairment (see **WARNINGS, Nephrotoxicity**). In non-HIV, non-HBV infected subjects with creatinine clearance < 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, and $AUC_{0-\infty}$ of tenofovir were increased (Table 16). It is recommended that the dosing interval for tenofovir disoproxil fumarate be modified in patients with creatinine clearance < 50 mL/min or in patients with ESRD who require dialysis (see **DOSAGE AND ADMINISTRATION**).

Table 16 Pharmacokinetic Parameters (Mean ± SD) of Tenofovir* in Patients 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} (ng/mL)	335.5 ± 31.8	330.4 ± 61.0	372.1 ± 156.1	601.6 ± 185.3
AUC_{∞} (ng•hr/mL)	2184.5 ± 257.4	3063.8 ± 927.0	6008.5 ± 2504.7	15984.7 ± 7223.0
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

* 300 mg, single dose of tenofovir disoproxil fumarate

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

STORAGE AND STABILITY

Store between 15°C and 30°C.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-TENOFOVIR is available as tablets. Each tablet contains 300 mg of tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil), as active ingredients. The tablets also include the following inactive ingredients: colloidal anhydrous silica, lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. The tablets are coated with Opadry II 85F205009 Blue, which contains FD&C Blue #2, carmine, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

The tablets are light blue to blue, modified capsule-shaped film-coated tablets debossed with “93” on one side and with “7104” on the other side. Each bottle contains 30 tablets and a child-resistant cap with desiccant silica gel (3 gm.) sorbit canister.

PART II SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

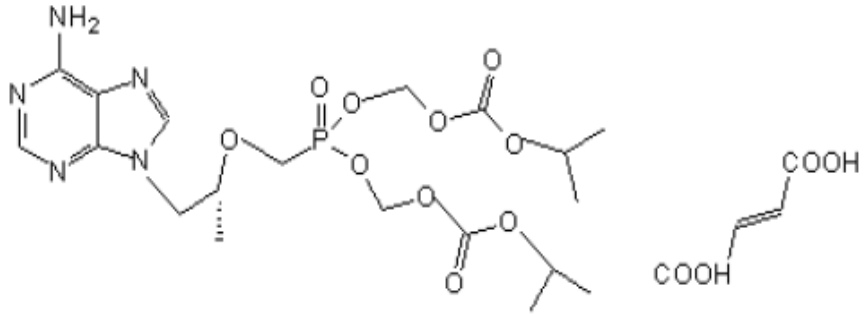
Common Name: Tenofovir disoproxil fumarate

Chemical Name: 9-[(R)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]-methoxy]propyl] adenine Fumarate

Empirical Formula: $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$

Molecular Weight: 635.52 g/mol

Structural Formula:



Physicochemical Properties: Tenofovir disoproxil fumarate is a white to off-white crystalline powder. It is freely soluble in methanol, sparingly soluble in acetone and ethanol, practically insoluble in diethyl ether and water. The partition coefficient (log P) for Tenofovir disoproxil fumarate is 1.25 at 25ºC and the pKa is 3.75.

CLINICAL TRIALS

Comparative Bioavailability Studies

A single-dose, randomized, two-period, two-sequence, two-treatment, crossover comparative bioavailability study between Tenofovir disoproxil fumarate 300 mg Tablets (Teva Canada Limited) and Viread® 300 mg Tablets (Gilead Sciences Canada Inc., Canada) in twenty three (23) healthy subjects (11 males and 12 females) under fasting conditions.

Tenofovir (1 x 300 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**Confidence Interval, 90%**
AUC_{0-t} (ng*h/mL)	1963.44 2030.03 (26.47)	2281.76 2315.92 (18.59)	86.05	80.57 – 91.90
AUC_{0-inf} (ng*h/mL)	2090.36 2167.47 (27.76)	2416.09 2459.13 (20.00)	86.52	81.20 – 92.18
C_{max} (ng/mL)	269.66 282.66 (30.79)	299.99 307.21 (23.14)	89.89	81.12 – 99.61
T_{max}§ (h)	0.986 (60.38)	0.877 (43.53)		
$T_{½}$§ (h)	19.19 (19.60)	18.49 (16.33)		

* Tenofovir disoproxil fumarate 300 mg Tablets

† Viread® 300 mg Tablets (Gilead Sciences Canada Inc., Canada), purchased in Canada

§ Expressed as the arithmetic mean (CV%) only

Clinical Efficacy in Patients with HIV

Study Demographics and Trial Design

Treatment-Experienced Adult Patients

Study 907 – Tenofovir disoproxil fumarate + Standard Background Therapy (SBT) Compared to Placebo + SBT: Study 907 was a 24-week, double-blind placebo-controlled multicenter study of tenofovir disoproxil fumarate added to a stable background regimen of antiretroviral agents in 550 treatment-experienced patients. After 24 weeks of blinded study treatment, all patients continuing on study were offered open-label tenofovir disoproxil fumarate for an additional 24 weeks. Patients had a mean baseline CD4 cell count of 427 cells/mm^3 (range 23-1385), median baseline plasma HIV RNA of 2340 (range 50-75,000) copies/mL, and mean duration of prior HIV treatment was 5.4 years. Mean age of the patients was 42 years, 85% were male and 69% were Caucasian, 17% Black and 12% Hispanic.

Table 17 Study 907: Tenofovir Disoproxil Fumarate + Standard Background Therapy (SBD) Compared to Placebo + SBD

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subject (N =550)	Mean Age (Range)	Gender
GS-99-907	Randomized (2:1), Double-Blind, Placebo-Controlled	**Arm 1**: tenofovir disoproxil fumarate 300 mg QD oral **Arm 2**: placebo QD Added to stable background regimen for 24 weeks followed by open label tenofovir for all patients for an additional 24 weeks.	Patients on stable antiretroviral therapy with early virologic failure. (N = 550)	42 years (22-70)	Male: 85% Female: 15%

Treatment-Naïve Adult Patients

Study 903 – Tenofovir disoproxil fumarate + Lamivudine + Efavirenz Compared to Stavudine + Lamivudine + Efavirenz: Data through 144 weeks are reported for Study 903, a double-blind, active-controlled multicenter study comparing tenofovir disoproxil fumarate (300 mg QD) administered in combination with lamivudine and efavirenz versus stavudine, lamivudine, and efavirenz in 600 antiretroviral-naïve patients. Patients 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). Patients were stratified by baseline HIV-1 RNA and CD4 count. Forty-three percent of patients had baseline viral loads > 100,000 copies/mL and 39% had CD4 cell counts < 200 cells/mL.

Table 18 Study 903: Tenofovir Disoproxil Fumarate + Lamivudine + Efavirenz Compared with Stavudine + Lamivudine + Efavirenz

Study Number	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N = 600)	Mean Age(Range)	Gender
GS-99-903	Randomized (1:1), double-blind, active-controlled, equivalence study. **Arm 1:** tenofovir DF + lamivudine + efavirenz **Arm 2:** stavudine + lamivudine + efavirenz	**Arm 1:** tenofovir disoproxil fumarate 300 mg tablets QD, stavudine placebo capsules BID, lamivudine 150 mg tablets BID, efavirenz 600 mg QD **Arm 2:** tenofovir disoproxil fumarate placebo tablets QD, stavudine[1] capsules 40/30 mg BID, lamivudine 150 mg tablets BID, efavirenz 600 mg QD All for oral (PO)	Treatment-naïve (HIV-1 RNA > 5,000 copies/mL) (N = 600)	36 years (18-64)	Male: 74% Female: 26%

Study Number	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N = 600)	Mean Age(Range)	Gender
		administration for 144 weeks double-blind phase followed by 192-week open-label phase. (Nevirapine 200 mg BID could replace efavirenz in the event of efavirenz-associated central nervous system toxicity or rash.)			

1 Stavudine/placebo capsules 20/15 mg BID as need for dose reduction.

Study 934 - Tenofovir disoproxil fumarate + Emtricitabine+ Efavirenz Compared with Lamivudine/Zidovudine + Efavirenz: Data through 144 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter study comparing tenofovir disoproxil fumarate (300 mg QD) + emtricitabine (200 mg QD) administered in combination with efavirenz (600 mg QD) versus lamivudine 150 mg/ zidovudine 300 mg BID administered in combination with efavirenz (600 mg QD) in 511 antiretroviral-naïve patients. From weeks 96 to 144 of the study, patients randomized to tenofovir disoproxil fumarate + emtricitabine received emtricitabine/tenofovir with efavirenz in place of emtricitabine + tenofovir disoproxil fumarate. Patients 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). Patients were stratified by baseline CD4 count (< or ≥ 200 cells/mm^3); 41% had CD4 cell counts < 200 cells/mm^3 and 51% of patients had baseline viral loads > 100,000 copies/mL.

Table 19 Study 934: Emtricitabine + Tenofovir Disoproxil Fumarate + Efavirenz Compared with Lamivudine/Zidovudine + Efavirenz

Study Number	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N = 511	Mean Age	Gender
GS-01-934	Randomized, open-label, parallel, multicenter, active controlled Arm 1: emtricitabine+ tenofovir disoproxil fumarate + efavirenz Arm 2: lamivudine/zidovudine + efavirenz	Arm 1[1]: Efavirenz 600 mg once daily for oral administration, emtricitabine 200 mg once and tenofovir disoproxil fumarate 300 mg once daily Arm 2: Efavirenz 600 mg once daily for oral administration and lamivudine/zidovudine 150/300 mg twice daily). 144 weeks	Antiretroviral naïve patients (HIV-1 RNA > 10,000 copies/mL)	Mean 38 years Range 18-80	Male: 86% Female: 14%

1 From weeks 96 to 144 of the study, patients received emtricitabine/tenofovir with efavirenz in place of emtricitabine + tenofovir disoproxil fumarate

Study Results

Study 907 – Tenofovir Disoproxil Fumarate + Standard Background Therapy (SBT) Compared to Placebo + SBT: Changes from baseline in log_{10} copies/mL plasma HIV-1 RNA levels through Week 48 are presented in Table 20.

Table 20 Mean Change from Baseline in Plasma HIV-1 RNA (log_{10} copies/mL): Study 907 (48 weeks)

Study Week	HIV-1 RNA log_{10} copies/mL	
	Tenofovir disoproxil fumarate (N = 368)	**Placebo (N = 182)**
Week 12	-0.65 (n = 354)	-0.08 (n = 175)
Week 24	-0.59 (n = 346)	-0.01 (n = 172)
	Tenofovir disoproxil fumarate (N = 368)	**Placebo Crossover to tenofovir disoproxil fumarate[1] (N =170)**
Week 32	-0.55 (n = 346)	-0.61 (n = 167)
Week 40	-0.49 (n = 336)	-0.61 (n = 162)
Week 48	-0.53 (n = 327)	-0.64 (n = 160)

1 For Placebo Crossover to tenofovir disoproxil fumarate, baseline HIV-1 RNA was reset at Week 24

The percent of patients with HIV-1 RNA < 400 copies/mL and outcomes of patients through 48 weeks are summarized in Table 21.

Table 21 Outcomes of Randomized Treatment (Study 907)

Outcomes	0-24 weeks		0-48 weeks	21-48 weeks
	Tenofovir disoproxil fumarate (N = 368) %	**Placebo (N =182) %**	**Tenofovir disoproxil fumarate (N = 368) %**	**Placebo Crossover to tenofovir disoproxil fumarate (N = 170) %**
HIV-1 RNA < 400 copies/mL[1]	40%	11%	28%	30%
Virologic failure[2]	53%	84%	61%	64%
Discontinued due to adverse event	3%	3%	5%	5%
Discontinued for other reasons[3]	3%	3%	5%	1%

1 Patients with HIV-1 RNA < 400 copies/mL and no prior study drug discontinuation at Week 24 and 48 respectively.
2 Patients with HIV-1 RNA ≥ 400 copies/mL efficacy failure or missing HIV-1 RNA at Week 24 and 48 respectively.
3 Includes lost to follow-up, patient withdrawal, noncompliance, protocol violation and other reasons.

At 24 weeks of therapy, there was a higher proportion of patients in the tenofovir disoproxil fumarate arm compared to the placebo arm with HIV-1 RNA < 50 copies/mL (22% and 1%, respectively). Mean change in absolute CD4 counts by Week 24 was +12 cells/mm^3 for the tenofovir disoproxil fumarate group and -5 cells/mm^3 for the placebo group. Mean change in absolute CD4 counts by Week 48 was +4 cells/mm^3 for the tenofovir disoproxil fumarate group.

Through Week 24, one patient in the tenofovir disoproxil fumarate group and no patients in the placebo arm experienced a new CDC Class C event.

Study 903 - Tenofovir Disoproxil Fumarate + Lamivudine + Efavirenz Compared to Stavudine + Lamivudine + Efavirenz: Treatment outcomes through 144 weeks are presented in Table 22.

Table 22 Outcomes of Randomized Treatment (Study 903)

	At Week 48		At Week 144	
Outcomes	**Tenofovir disoproxil fumarate + Lamivudine + EFV (N = 299) %**	**Stavudine + Lamivudine + EFV (N = 301) %**	**Tenofovir disoproxil fumarate + Lamivudine + EFV (N = 299) %**	**Stavudine + Lamivudine + EFV (N = 301) %**
Responder[1]	79%	82%	68%	62%
Virologic failure[2]	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[3]	8%	7%	14%	15%

1 Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 144.
2 Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL through Week 144.
3 Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation and other reasons.

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

Through 144 weeks, 12 patients in the tenofovir disoproxil fumarate group and 9 patients in the stavudine group experienced a new CDC Class C event.

The proportion of patients who achieved and maintained confirmed HIV RNA < 400 copies/mL using intent-to-treat analysis at Weeks 24, 48, 96 and 144 in Study 903 are presented in Table 23.

Table 23 Virologic Response Through Week 144, Study 903[*†]

Study Week	**Proportion of Patients with HIV-1 RNA < 400 copies/mL (%)**	
	Tenofovir disoproxil fumarate + Lamivudine + EFV (N = 299)	**Stavudine + Lamivudine + EFV (N = 301)**
Week 24	86	86

Study Week	Proportion of Patients with HIV-1 RNA < 400 copies/mL (%)	
	Tenofovir disoproxil fumarate + Lamivudine + EFV (N = 299)	Stavudine + Lamivudine + EFV (N = 301)
Week 48	79	82
Week 96	74	70
Week 144	68	62

* Roche Amplicor HIV-1 Monitor Test

† Responders at each visit are patients who had achieved and maintained HIV-1 RNA < 400 copies/mL without discontinuation by that visit

Study 934 – Tenofovir Disoproxil Fumarate + Emtricitabine + Efavirenz Compared with Lamivudine/Zidovudine + Efavirenz: Treatment outcomes through 48 and 144 weeks for those patients who did not have efavirenz resistance at baseline are presented in Table 24.

Table 24 Outcomes of Randomized Treatment at Weeks 48 and 144 (Study 934)

Outcomes	At Week 48		At Week 144[1]	
	Tenofovir disoproxil fumarate + FTC + EFV (N = 244)	Lamivudine/AZT + EFV (N = 243)	Tenofovir disoproxil fumarate + FTC + EFV (N = 227)	Lamivudine/AZT + EFV (N = 229)
Responder[2]	84%	73%	71%	58%
Virologic failure[3]	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[4]	10%	14%	20%	22%

1 Patients who were responders at Week 48 or Week 96 but did not consent to continue study after Week 48 or Week 96 were excluded from analysis.

2 Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 48.

3 Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL through Week 48.

4 Includes lost to follow-up, patient withdrawal, non-compliance, protocol violation and other reasons.

In this study, tenofovir disoproxil fumarate + emtricitabine in combination with efavirenz showed statistically significant superiority over lamivudine/zidovudine in combination with efavirenz in achieving and maintaining HIV-1 RNA < 400 copies/mL through 48 weeks and 144 weeks (Table 24). The difference in the percentages of responders, stratified by baseline CD4 cell count (< or ≥ 200 cells/mm^3), between the tenofovir disoproxil fumarate + emtricitabine group and the lamivudine/zidovudine group was 11.4%, and the 95% CI was 4.3% to 18.6% (p = 0.002) at Week 48 and was 13% at Week 144, 95% CI = 4% to 22% (p = 0.004). Through 48 weeks of therapy, 80% and 70% of patients in the tenofovir disoproxil fumarate + emtricitabine and the lamivudine/ zidovudine arms, respectively, achieved and maintained HIV-1 RNA < 50 copies/mL (64% and 56%, respectively, through Week 144). The difference in the percentages of responders, stratified by baseline CD4 cell count (< or ≥ 200 cells/mm^3), between the tenofovir disoproxil fumarate + emtricitabine group and the lamivudine/zidovudine group was 9.1%, and the 95% CI was 1.6% to

16.6% (p = 0.021) at Week 48 and was 8% at Week 144, 95% CI = -1% to 17% (p = 0.082). The mean increase from baseline in CD4 cell count was 190 cells/mm^3 for the tenofovir disoproxil fumarate + emtricitabine + efavirenz arm, and 158 cells/mm3 for the lamivudine/zidovudine + efavirenz arm (p = 0.002) at Week 48 (312 and 271 cells/mm^3, respectively, at Week 144, p = 0.089). Through 48 weeks, 7 patients in the tenofovir disoproxil fumarate + emtricitabine group and 5 patients in the lamivudine/zidovudine group experienced a new CDC Class C event (10 and 6 patients, respectively, through 144 weeks).

The difference in the proportion of patients who achieved and maintained HIV-1 RNA < 400 copies/mL through 48 weeks largely results from the higher number of discontinuations due to adverse events and other reasons in the zidovudine/lamivudine group in this open label study.

Adolescent Patients

In Study 321, 87 treatment-experienced patients 12 to <18 years of age were treated with tenofovir disoproxil fumarate (N = 45) or placebo (N = 42) in combination with an optimized background regimen (OBR) for 48 weeks. The mean baseline CD4 cell count was 374 cells/mm^3 and the mean baseline plasma HIV-1 RNA was 4.6 $\log_{10}$ copies/mL. The median time-weighted average changes from baseline in plasma HIV-1 RNA at Weeks 24 ($DAVG_{24}$) and 48 ($DAVG_{48}$) were −1.58 and −1.42 $\log_{10}$ copies/mL for the tenofovir disoproxil fumarate group compared to −1.55 and −1.35 $\log_{10}$ copies/mL for the placebo group, at Weeks 24 and 48, respectively. The lack of difference in virological response between the two groups was primarily attributable to greater activity of the OBR in the placebo group compared to the tenofovir disoproxil fumarate group.

Genotypic Analyses of Tenofovir Disoproxil Fumarate in Patients with Previous Antiretroviral Therapy (Studies 902 and 907)

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

Several exploratory analyses were conducted to evaluate the effect of specific mutations and mutational patterns on virologic outcome.

Reduced responses to tenofovir disoproxil fumarate were observed in patients with pre-existing zidovudine-associated mutations and appeared to depend on the number of specific mutations. Tenofovir disoproxil fumarate-treated patients whose HIV expressed 3 or more zidovudine-associated mutations that included either the M41L or L210W reverse transcriptase mutation showed reduced responses to tenofovir disoproxil fumarate therapy; however, these responses were still improved compared with placebo. The presence of the D67N, K70R, T215Y/F, or K219Q/E/N mutation did not appear to affect responses to tenofovir disoproxil fumarate therapy.

In the protocol defined analyses, virologic response to tenofovir disoproxil fumarate was not reduced in patients with HIV that expressed the lamivudine/abacavir-associated M184V mutation. In the absence of zidovudine-associated mutations, patients with the M184V mutation receiving tenofovir disoproxil fumarate showed a -0.84 $\log_{10}$ copies/mL decrease in their HIV-1 RNA relative to placebo. In the presence of zidovudine-associated mutations, the M184V mutation did not affect the mean HIV RNA responses to tenofovir disoproxil fumarate treatment. HIV-1 RNA responses among these patients were durable through Week 48.

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

The presence of at least one HIV protease inhibitor or non-nucleoside reverse transcriptase inhibitor mutation at baseline did not appear to affect the virologic response to tenofovir disoproxil fumarate. Cross-resistance between tenofovir disoproxil fumarate and HIV-1 protease inhibitors is unlikely because of the different enzyme targets involved.

In treatment-experienced patients, 14/304 (4.6%, studies 902 and 907) isolates from patients failing tenofovir disoproxil fumarate at 96 weeks showed > 1.4 fold (median 2.7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution.

Phenotypic Analyses of Tenofovir Disoproxil Fumarate in Patients with Previous Antiretroviral Therapy (Studies 902 and 907)

The virologic response to tenofovir disoproxil fumarate therapy has been evaluated with respect to baseline phenotype (N = 100) in treatment-experienced patients participating in trials 902 and 907. Phenotypic analysis of baseline HIV from patients in Studies 902 and 907 demonstrated a correlation between baseline susceptibility to tenofovir disoproxil fumarate and response to tenofovir disoproxil fumarate therapy. Table 25 summarizes the HIV-1 RNA response by baseline tenofovir disoproxil fumarate susceptibility.

Table 25 HIV-1 RNA Response at Week 24 by Baseline Tenofovir Disoproxil Fumarate Susceptibility (Intent-To-Treat)[1]

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

1 Tenofovir susceptibility was determined by recombinant phenotypic Antivirogram™ assay (Virco).
2 Fold change in susceptibility from wild-type.
3 Average HIV-1 RNA change from baseline through Week 24 (DAVG24) in log10 copies/mL.

Genotypic Analyses of Tenofovir Disoproxil Fumarate in Antiretroviral-Naïve Patients

Genotypic analyses of patients with virologic failure showed development of efavirenz-associated and lamivudine-associated mutations to occur most frequently and with no difference between the treatment arms (Study 903). The K65R mutation occurred in 8 patients on the tenofovir disoproxil fumarate arm and in 2 patients on the stavudine arm. Of the 8 patients who developed K65R in the tenofovir disoproxil fumarate arm through 144 weeks, 7 of these occurred in the first 48 weeks of treatment and one at Week 96. One patient in the tenofovir disoproxil fumarate arm developed the K70E substitution in their virus. Among these patients, 5/8 patients subsequently gained full virologic control (< 50 copies/mL) upon switching to new regimens that included a protease inhibitor in combination with nucleoside reverse transcriptase inhibitors through a median of 155 weeks of follow-up. From both genotypic and phenotypic analyses there was no evidence for other pathways of resistance to tenofovir disoproxil fumarate.

In Study 934 (tenofovir disoproxil fumarate + emtricitabine + efavirenz compared with lamivudine/zidovudine + efavirenz), resistance analysis was performed on HIV isolates from all patients with > 400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation. Genotypic resistance to efavirenz, predominantly the K103N substitution, was the most common form of resistance that developed. Resistance to efavirenz occurred in 13 of 19 (68%) analyzed patients in the tenofovir disoproxil fumarate + emtricitabine group and in 21 of 29 (72%) analyzed patients in the lamivudine/zidovudine group. The M184V substitution, associated with resistance to emtricitabine and lamivudine, was observed in 2 of 19(11%) analyzed patients in the tenofovir disoproxil fumarate + emtricitabine group and in 10 of 29 (34%) analyzed patients in the lamivudine/zidovudine group.

In treatment-naïve patients treated with tenofovir disoproxil fumarate + emtricitabine + efavirenz, none of the HIV isolates from 19 patients analyzed for resistance showed reduced susceptibility to tenofovir or the presence of the K65R or K70E substitution.

In Study 321 (adolescent patients 12 to <18 years) (see **CLINICAL TRIALS**), HIV-1 isolates from 43 patients who had plasma HIV-1 RNA ≥ 400 copies/mL were evaluated for tenofovir resistance-associated substitutions. One patient developed the K65R substitution by Week 48.

<u>Clinical Efficacy in Patient with HBV</u>

Study Demographics and Trial Design

HBeAg-Negative Chronic Hepatitis B: Study 0102 was a Phase 3, randomized, double-blind, active-controlled study of tenofovir disoproxil fumarate 300 mg compared to adefovir dipivoxil 10 mg in 375 HBeAg- (anti-HBe+) patients, the majority of whom were nucleoside-naïve. The mean age of patients 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, patients had a mean Knodell necroinflammatory score of 7.8; mean plasma HBV DNA was 6.9 $\log_{10}$ copies/mL; and mean serum ALT was 140 U/L.

HBeAg-Positive Chronic Hepatitis B: Study 0103 was a Phase 3, randomized, double-blind, active-controlled study of tenofovir disoproxil fumarate 300 mg compared to adefovir dipivoxil 10 mg in 266 (HBeAg+) nucleoside-naïve patients. The mean age of patients was 34 years, 69% were

male, 36% were Asian, 52% were Caucasian, and 16% had previously received alpha-interferon therapy. At baseline, patients 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 patients reached 48 weeks of treatment.

Table 26 Studies 0102 and 0103: Tenofovir Disoproxil Fumarate Compared to Adefovir Dipivoxil

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subjects	Mean Age (Range)	Gender
GS-US-174 -0102	Randomized (2:1), Double-Blind, Parallel group	**Arm 1**: tenofovir disoproxil fumarate 300 mg QD oral **Arm 2**: adefovir dipivoxil 10 mg QD oral Double-blind phase up to Week 48 After double-blind phase, eligible patients were allowed to rollover to open-label tenofovir disoproxil fumarate up to Week 384 (8 years)	N = 250 N = 125 HBeAg-; nucleoside-naïve and nucleoside-experienced; HBV DNA > 10^5 copies/mL	44 years (18–69)	Male: 77% Female:23%
GS-US-174 -0103	Randomized (2:1), Double-Blind, Parallel group	**Arm 1**: tenofovir disoproxil fumarate 300 mg QD oral **Arm 2**: adefovir dipivoxil 10 mg QD oral Double blind phase up to Week 48 After double-blind phase, eligible patients were allowed to rollover to open-label tenofovir disoproxil fumarate up to Week 384 (8 years)	N = 176 N = 90 $HBeAg^+$; nucleoside-naïve HBV DNA > 10^6 copies/mL	34 (18–64)	Male: 69% Female:31%

Study Results

Experience in Patients with Compensated Liver Disease at 48 weeks: In HBeAg- and HBeAg + patients tenofovir disoproxil fumarate was shown to be statistically superior with respect to the primary efficacy endpoint (complete response to treatment). Tenofovir disoproxil fumarate was associated with significantly greater proportions of patients with HBV DNA < 400 copies/mL when compared to adefovir dipivoxil as shown in Table 27.

In study 0103, a significantly greater proportion of patients in the tenofovir disoproxil fumarate group had normalized ALT and achieved HBsAg loss, when compared to adefovir dipivoxil.

Table 27 Histological, Virological, Biochemical and Serological Response at Week 48 (Studies 0102 and 0103)

	0102 (HBeAg-)		0103 (HBeAg+)	
	Tenofovir disoproxil fumarate (n = 250)	**Adefovir dipivoxil (n = 125)**	**Tenofovir disoproxil fumarate (n = 176)**	**Adefovir dipivoxil (n = 90)**
Complete Response (%)[a]	71*	49	67*	12
Histology Histological Response (%)[b]	72	69	74	68
HBV DNA (%) < 400 copies/mL (< 69 IU/mL)	93*	63	76*	13
ALT(%) Normalized ALT[c]	76	77	68**	54
Serology (%) HBeAg Loss/ Seroconversion	NA	NA	22/21	18/18
HBsAg Loss/ Seroconversion	0/0	0/0	3**/1	0/0

* p value vs adefovir dipivoxil < 0.001, **p value vs adefovir dipivoxil < 0.05,

a Complete response defined as HBV DNA levels < 400 copies/ml and Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis,

b Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis,

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

Tenofovir disoproxil fumarate was associated with significantly greater proportions of patients with undetectable HBV DNA (< 169 copies/mL[< 29 IU/mL]; the limit of quantification of the Roche Cobas Taqman HBV assay), when compared to adefovir dipivoxil (study 0102; 91%, 56%, $p < 0.001$ and Study 0103; 69%, 9%, $p < 0.001$), respectively.

Response to treatment with tenofovir disoproxil fumarate was comparable in nucleoside-experienced (N = 51) and nucleoside-naive (N = 375) patients and in patients with normal ALT (n = 21) and abnormal ALT (N = 405) at baseline when studies 0102 and 0103 were combined. Forty-nine of the 51 nucleoside-experienced patients were previously treated with lamivudine. Seventy-three percent of nucleoside-experienced and 69% of nucleoside-naive patients achieved complete response to treatment; 90% of nucleoside-experienced and 88% of nucleoside-naive patients achieved HBV DNA suppression < 400 copies/mL. All patients with normal ALT at baseline and 88% of patients with abnormal ALT at baseline achieved HBV DNA suppression < 400 copies/mL.

In Study ACTG 5127, a randomized, 48-week double-blind, controlled trial of tenofovir disoproxil fumarate 300 mg in patients co-infected with HIV-1 and chronic hepatitis B with prior lamivudine experience (90% of patients were lamivudine resistant), the mean serum HBV DNA level at baseline in patients randomized to the tenofovir disoproxil fumarate arm was 9.45 log10 copies/mL (N = 27). Treatment with tenofovir disoproxil fumarate was associated with a mean change in serum HBV

DNA from baseline, in the patients for whom there was 48 week data, of -5.74 log10 copies/mL (N = 18). In addition, 61% of patients had normal ALT at Week 48.

Experience in Patients with Persistent Viral Replication at 48 weeks: Study 0106 was a double-blind, randomized study in which 53 nucleoside-experienced patients with persistent viral replication after receiving 24-96 weeks of treatment with adefovir dipivoxil were randomized to tenofovir disoproxil fumarate monotherapy. Of these, 81% had HBV DNA < 400 copies/mL, 75% had undetectable DNA (< 169 copies/mL [< 29 IU/mL]) and 41% had ALT normalization at Week 48.

Experience in Patients with Decompensated Liver Disease at 48 weeks: Study 0108 was a randomized, double-blind, active-controlled study evaluating the safety and efficacy of tenofovir disoproxil fumarate (N = 45) in patients with decompensated liver disease. Patients had a mean Child-Pugh-Turcotte (CPT) score of 7, mean HBV DNA of 5.8 log10 copies/mL and mean serum ALT of 61 U/L at baseline. Forty-two percent (19/45) of patients had at least 6 months of prior lamivudine experience and 9 of 45 patients (20%) had lamivudine and/or adefovir resistance substitutions at baseline.

The coprimary safety endpoints were discontinuation due to an adverse event and confirmed increase in serum creatinine ≥0.5 mg/dL or confirmed decrease in serum phosphorus of < 2 mg/dL.

In the tenofovir disoproxil fumarate treatment arm, 3 of 45 patients (7%) discontinued treatment due to an adverse event; 4 of 45 patients (9%) experienced a confirmed increase in serum creatinine of ≥ 0.5 mg/dL or confirmed decrease in serum phosphorus of <2 mg/dL through Week 48. HBV DNA < 400 copies/mL and normal ALT were observed in 31 of 44 patients (70%) and 25 of 44 patients (57%), respectively. The mean change from baseline in CPT score was -1; the mean absolute CPT score was 6 at Week 48.

Experience Beyond 48 weeks: In Studies 0102 and 0103 patients who completed 48 weeks of double-blind treatment with either tenofovir disoproxil fumarate or adefovir dipivoxil rolled over with no interruption in treatment to open-label tenofovir disoproxil fumarate. In Studies 0102 and 0103, 93% and 89% of the randomized and treated patients entered the open-label study, respectively. In Study 0102, 90% and 88% of patients who were randomized to tenofovir disoproxil fumarate and adefovir dipivoxil, respectively, completed 96 weeks of treatment and in Study 0103, 82% and 92% of patients who were randomized to tenofovir disoproxil fumarate and adefovir dipivoxil, respectively, completed 96 weeks of treatment. In Studies 0102 and 0103, 84% and 73% of patients who entered the open-label phase continued in the study through to Week 288, respectively. At both Week 96 and Week 288, viral suppression, biochemical and serological responses were in general maintained with continued tenofovir disoproxil fumarate treatment. In patients rolling over from adefovir dipivoxil to tenofovir disoproxil fumarate at Week 48, HBV DNA rapidly declined in adefovir dipivoxil nonresponders (HBV DNA ≥ 400 copies/ml at Week 48) and was maintained below 400 copies/ml in adefovir dipivoxil responders (HBV DNA < 400 copies/ml at Week 48) (see Table 28).

Table 28 Virological, Biochemical and Serological Response at Week 96 and Week 288 (Studies 0102 and 0103)

Outcomes[a]	0102 (HBeAg-)				0103 (HBeAg+)			
	Tenofovir disoproxil fumarate[f] (N = 250)		Adefovir dipivoxil Rollover to Tenofovir disoproxil fumarate[f] (N = 125)		Tenofovir disoproxil fumarate[f] (N = 176)		Adefovir dipivoxil Rollover to Tenofovir disoproxil fumarate[f] (N = 90)	
	96 weeks[b]	288 weeks[d]	96 weeks[c]	288 weeks[e]	96 weeks[b]	288 weeks[d]	96 weeks[c]	288 weeks[e]
HBV DNA < 400 copies/mL [< 69 IU/mL]	91%	81%	89%	84%	78%	69%	78%	78%
Week 48 Adefovir dipivoxil Responder[g]	-	-	100%	100%	-	-	100%	100%
Week 48 Adefovir dipivoxil Non-responder[h]	-	-	100%	100%	-	-	82%	100%
HBV DNA < 169 copies/mL [< 29 IU/mL]	90%	81%	89%	84%	74%	68%	76%	78%
ALT Normalized ALT[i]	72%	70%	68%	74%	65%	52%	74%	70%
Serology HBeAg Loss/ Seroconversion	NA	NA	NA	NA	26%/ 23%	38%/ 27%	26%/ 22%	41%/ 33%
HBsAg Loss/ Seroconversion	0/0	0/0	0/0	1/1[j]	5%/ 4%	11%/ 8%[k]	6%/ 5%	10%/ 8%[k]

a Based on Long-Term Evaluation algorithim (LTE-ITT Analysis) - patients who discontinued the study at any time prior to Week 288 due to a protocol defined endpoint, as well as those completing Week 288, are included in the denominator. The LTE-ITT Analysis includes data for subjects who added FTC 200 mg once daily to their open-label tenofovir disoproxil fumarate regimen at or beyond Week 72.
b 48 weeks double-blind tenofovir disoproxil fumarate followed by up to 48 weeks open-label tenofovir disoproxil fumarate.
c 48 weeks double-blind adefovir dipivoxil followed by up to 48 weeks open-label tenofovir disoproxil fumarate.
d 48 weeks double-blind tenofovir disoproxil fumarate followed by up to 240 weeks open-label tenofovir disoproxil fumarate.
e 48 weeks double-blind adefovir dipivoxil followed by up to 240 weeks open-label tenofovir disoproxil fumarate.
f At the discretion of the clinician, patients with HBV DNA ≥ 400 copies/mL at Week 72 or later could receive intensification therapy with open label tenofovir disoproxil fumarate + 200 mg emtricitabine (administered as fixed dose combination emtricitabine/tenofovir disoproxil fumarate).
g Patients treated with adefovir dipivoxil for 48 weeks whose HBV DNA < 400 copies/mL based on observed (missing = excluded) data (Study 0102, N = 68; Study 0103, N = 7)
h Patients treated with adefovir dipivoxil for 48 weeks whose HBV DNA ≥ 400 copies/mL based on observed (missing = excluded) data (Study 0102, N = 29; Study 0103, N = 56)
i The population used for analysis of ALT normalization included only patients with ALT above ULN at baseline.
j One patient had confirmed HBsAg loss through Week 288 and remains in the treatment-free follow-up period.
k Cumulative percentages based upon a Kaplan Meier analysis (KM-ITT)
NA = Not Applicable

Paired baseline and Week 240 liver biopsy data were available for 348/489 patients who remained in Studies 0102 and 0103 (Table 29). Ninety-five percent (240/252) of patients without cirrhosis at baseline and 99% (95/96) of patients with cirrhosis at baseline had either no change or an improvement in fibrosis (Ishak fibrosis score). Of the 96 patients with cirrhosis at baseline (Ishak fibrosis score 5-6), 25% (24) experienced no change in Ishak fibrosis score and 73% (70) experienced regression of cirrhosis by Week 240 with a reduction in Ishak fibrosis score of at least 2 points.

Table 29 Histological Response (%) in Compensated HBeAg Negative and HBeAg Positive Subjects at Week 240 Compared to Baseline

	Study 0102 (HBeAg-)		Study 0103 (HBeAg+)	
	Tenofovir disoproxil fumarate n = 250[c]	Adefovir dipivoxil Rollover to Tenofovir disoproxil fumarate N = 125[d]	Tenofovir disoproxil fumarate N = 176[c]	Adefovir dipivoxil Rollover to Tenofovir disoproxil fumarate n = 90[d]
Histological Response[a,b] (%)	87 [131/150]	85 [63/74]	88 [67/76]	90 [43/48]

a The population used for analysis of histology included only patients with available liver biopsy data (Missing = Excluded) by Week 240. Response after addition of emtricitabine is included (total of 17 subjects across both studies).
b Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis score.
c 48 weeks double-blind tenofovir disoproxil fumarate followed by up to 192 weeks open-label tenofovir disoproxil fumarate.
d. 48 weeks double-blind adefovir dipivoxil followed by up to 192 weeks open-label tenofovir disoproxil fumarate.

Patients with Lamivudine-Resistant Chronic Hepatitis B: Study GS-US-174-0121 explored the safety and efficacy of tenofovir disoproxil fumarate (300 mg) compared to an unapproved antiviral regimen (emtricitabine 200 mg / tenofovir disoproxil funarate 300 mg) in subjects with CHB, viremia (HBV DNA ≥ 1,000 IU/mL), and genotypic evidence of lamivudine resistance (rtM204I/V +/- rtL180M).

After 96 weeks of treatment, 126 of 141 subjects (89%) and 120 of 139 subjects (86.3%) randomized to tenofovir disoproxil fumarate and to the comparator, respectively, had HBV DNA < 400 copies/mL, and 49 of 79 subjects (62%) randomized to tenofovir disoproxil fumarate had ALT normalization. Among the HBeAg-positive subjects randomized to tenofovir disoproxil fumarate, 10 of 65 subjects (15%) experienced HBeAg loss, and 7 of 65 subjects (11%) experienced anti-HBe seroconversion through Week 96.

Genotypic Analyses of Tenofovir Disoproxil Fumarate in Patients with HBV (Studies 0102, 0103, 0106 and 0108)

A cumulative genotypic resistance analysis of subjects in Studies GS-US-174-0102 and GS-US-174-0103 who received at least 24 weeks of tenofovir disoproxil fumarate monotherapy and remained viremic (HBV DNA ≥ 400 copies/mL) at the last evaluable study visit on tenofovir disoproxil fumarate monotherapy was performed. Of the 612 subjects who received at least 24 weeks of tenofovir disoproxil fumarate monotherapy, 57 (9.3%) were viremic with up to 288 weeks of cumulative treatment with tenofovir disoproxil fumarate monotherapy. Overall, no amino acid substitutions in the HBV polymerase were associated with resistance to tenofovir disoproxil fumarate (genotypic or phenotypic analyses). Genotypic data from paired baseline and on-treatment isolates were available for 49/57 subjects. The majority of subjects (33 of 57, 58%) had no change in their HBV polymerase compared to the baseline isolate, 12 of 57 (21%) had polymorphic site changes, and 4 of 57 (7%) had conserved site changes.

In Study 0106, 53 patients (including 15 patients with adefovir or lamivudine resistance substitutions at baseline) received tenofovir disoproxil fumarate for 48 weeks. Genotypic data from paired baseline and on treatment HBV isolates were available for 15/17 patients with HBV DNA > 400 copies/mL at Week 48. No amino acid substitutions associated with resistance to tenofovir disoproxil fumarate were identified in these isolates.

In Study 0108, 45 patients (including 9 patients with lamivudine and/or adefovir resistance substitutions at baseline) received tenofovir disoproxil fumarate for up to 48 weeks. Genotypic data from paired baseline and on treatment HBV isolates were available for 6/8 patients with HBV DNA > 400 copies/mL. No amino acid substitutions associated with resistance to tenofovir disoproxil fumarate were identified in these isolates.

In study 0121, 141 patients with lamivudine resistance substitutions at screening received treatment with tenofovir disoproxil fumarate for up to 96 weeks. Genotypic data from paired baseline and on treatment HBV isolates were available for 6 of 9 patients with HBV DNA > 400 copies/mL at their last time point on tenofovir disoproxil fumarate. No amino acid substitutions associated with resistance to tenofovir disoproxil fumarate were identified in these isolates.

VIROLOGY (MICROBIOLOGY)

Activity in HIV-1

Tenofovir diphosphate inhibits the activity of HIV reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Anti-HIV Activity In Vitro

The in vitro antiviral activity of tenofovir against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC_{50} (50% inhibitory concentrations) for tenofovir was in the range of 0.04 µM to 8.5 µM. In drug combination studies of tenofovir with nucleoside and non-nucleoside analog inhibitors of HIV reverse transcriptase, and protease inhibitors, additive to synergistic effects were observed. In addition, tenofovir has also been shown to be active in vitro against HIV-2, with similar potency as observed against HIV-1.

In Vitro Resistance

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

In Vitro Cross-Resistance

Cross-resistance among certain reverse transcriptase inhibitors has been recognized. The K65R and K70E substitutions results in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir. The in vitro activity of tenofovir against HIV-1 strains with zidovudine-associated reverse transcriptase mutations (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) was evaluated. Zidovudine-associated mutations may also confer reductions in susceptibility to other nucleoside reverse transcriptase inhibitors (NRTIs) and these mutations have been reported to emerge during combination therapy with stavudine and didanosine. In 20 samples that had multiple zidovudine-associated mutations (mean 3.3), a mean 3.1-fold increase of the IC_{50} of tenofovir was observed (range 0.8–8.4). Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir. Tenofovir showed slightly increased activity against HIV-1 expressing the M184V resistance mutation.

Activity in HBV

Anti-Hepatitis B Virus Activity In Vitro

The in vitro antiviral activity of tenofovir against HBV was assessed in the HepG2 2.2.15 cell line. The EC_{50} values for tenofovir were in the range of 0.14 to 1.5 µM, with CC_{50} (50% cytotoxicity concentration) values > 100 µM. Tenofovir diphosphate inhibits recombinant HBV polymerase with a Ki (inhibition constant) of 0.18 µM. In in vitro drug combination studies of tenofovir with nucleoside anti-HBV reverse transcriptase inhibitors lamivudine, telbivudine, and entecavir, additive anti-HBV activity was observed. Additive to slightly synergistic effects were observed with the combination of tenofovir and emtricitabine.

In Vitro Cross-Resistance

Cross-resistance has been observed among HBV reverse transcriptase inhibitors.

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

HBV strains expressing the rtL180M, rtT184G, rtS202G/I, rtM204V and rtM250V mutations 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-associated resistance mutations rtA181V and rtN236T showed a susceptibility to tenofovir ranging from 2.9 to 10-fold that of wild type virus.

Viruses containing the rtA181T mutation remained susceptible to tenofovir with EC_{50} values 1.5-fold that of wild type virus.

NON-CLINICAL TOXICOLOGY

The nonclinical safety profile of tenofovir disoproxil fumarate has been studied in mice, rats, guinea pigs, rabbits, dogs, and monkeys. In all species, tenofovir disoproxil fumarate was hydrolyzed to tenofovir following absorption. Tenofovir was cleared exclusively by renal elimination, without further metabolic changes, by a combination of glomerular filtration and tubular secretion.

Single Dose Toxicity

Following single doses, the no-effect-level (NOEL) in rats was 1500 mg/kg. Following single doses in dogs (270 mg/kg), mild renal tubular karyomegaly and/or basophilia were the only effects observed. Single oral doses of tenofovir disoproxil fumarate had no adverse effects on the central nervous system (male rats, 50 or 500 mg/kg) or on cardiovascular and respiratory function (conscious male dogs, 30 mg/kg). An assessment of effects on renal function demonstrated increased urinary electrolyte excretion and urine volume in rats administered tenofovir disoproxil fumarate 500 mg/kg; no effect was observed at 50 mg/kg. When rats were administered tenofovir disoproxil fumarate (0, 50, or 500 mg/kg) to evaluate effects on the gastrointestinal transit of a charcoal meal, there was reduced gastric emptying at 500 mg/kg/day, but no effect at 50 mg/kg/day.

Subacute and Chronic Toxicity

The target organs of toxicity identified in the preclinical program were the gastrointestinal tract, renal tubular epithelium, and bone.

Gastrointestinal Tract

Gastrointestinal (GI) toxicity, observed primarily in rats, was dose related, reversible, and characterized by inflammation of the stomach and intestines, epithelial cytomegaly in the duodenum and jejunum, and villous atrophy of the ileum in rodents.

Kidney

Renal tubular epithelial karyomegaly, a morphologic change without pathologic consequence, was the most sensitive histological indicator of an effect on the kidney and was observed in rats, dogs, and monkeys. In dogs, the species most sensitive to effects on the kidney, additional microscopic alterations reported following chronic administration of tenofovir disoproxil fumarate (≥10 mg/kg/day for 42 weeks) included individual cell necrosis, tubular dilatation, degeneration/ regeneration, pigment accumulation, and interstitial nephritis. Associated biochemical changes in dogs administered tenofovir disoproxil fumarate 30 mg/kg/day were a slight elevation in serum creatinine, glucosuria, proteinuria, and increased urine volume. The incidence and severity of nephrotoxicity was dose related.

Bone

Chronic administration of high doses of tenofovir or tenofovir disoproxil fumarate in laboratory animals resulted in bone alterations. Minimal decreases in bone mineral density and content were observed in rats and dogs following oral administration of tenofovir disoproxil fumarate at the doses of 300 and 30 mg/kg/day, respectively (6 and 10x human exposure, respectively). In juvenile

monkeys pathologic osteomalacia and hypophosphatemia was observed following subcutaneous administration of tenofovir at the dose of 30 mg/kg/day (25x human exposure). Monkeys treated chronically with tenofovir 10 mg/kg/day, sc, (AUC = 4x humans), had no clinical or radiographic evidence of bone toxicity.

Bone changes in rats and dogs did not appear to consistently reverse during the recovery period; osteomalacia in juvenile monkeys was reversible.

Studies designed to evaluate the mechanism underlying effects on bone suggest that tenofovir may not have direct toxicity to bone. The mechanism is as yet unclear, however data suggest bone effects may be secondary to negative phosphate balance resulting from tenofovir-related reductions in intestinal phosphate absorption and/or renal reabsorption of phosphate.

Mutagenicity

Tenofovir disoproxil fumarate was equivocal in the in vitro bacterial mutation (Ames) assay (Salmonella-Eschericia coli/ Mammalian-Microsome Reverse Mutation Assay) but positive in the in vitro mouse lymphoma assay (L5178Y TK +/- Forward Mutation Assay), with and without metabolic activation. Tenofovir disoproxil fumarate was negative in the in vivo mouse micronucleus assay at plasma exposure levels of more than 10x the human exposure.

Reproductive Toxicity

Reproductive toxicity was evaluated in rats and rabbits. Tenofovir disoproxil fumarate had no adverse effects on fertility or general reproductive performance in rats at doses up to 600 mg/kg/day. Tenofovir disoproxil fumarate had no adverse effects on embryo-fetal development in rats at doses 450 mg/kg/day and in rabbits at doses up to 300 mg/kg/day. In a study of effects on peri- and postnatal development in rats, effects considered due to maternal toxicity (450–600 mg/kg/day) were reduced survival and a slight delay in sexual maturation in the F1 generation. There were no adverse effects on growth, development, behavior, or reproductive parameters at non-maternally toxic doses (150 mg/kg/day).

Carcinogenicity

Long-term oral carcinogenicity studies were conducted in mice and rats receiving tenofovir disoproxil fumarate. In the mouse study, (60/sex/group), one male and two female mice in the 600 mg/kg/day group (15 times the human systemic exposure at the recommended human dose of 300 mg/day) had duodenal tumors. The mechanism underlying this effect is uncertain but may relate to high local drug concentrations in the gastrointestinal tract. No treatment-related tumors were seen in mice in the 100 or 300 mg/kg/day groups. In the rat study (60/sex/group) at doses of 30, 100 and 300 mg/kg/day (approximately 5 times human exposure), no treatment-related increase in tumor incidence was observed.

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PART III: CONSUMER INFORMATION

PrTEVA-TENOFOVIR
Tenofovir Disoproxil Fumarate Tablets 300 mg

This leaflet is Part III of a three-part "Product Monograph" published when TEVA-TENOFOVIR was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about TEVA-TENOFOVIR. Contact your healthcare professional if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- TEVA-TENOFOVIR is a type of medicine called a nucleotide analog reverse transcriptase inhibitor (NRTI).

- Use in the Treatment of HIV-Infection:
  TEVA-TENOFOVIR is a treatment for Human Immunodeficiency Virus (HIV) infection in adults and adolescents age 12 years and older and weighing at least 35 kg (77 lb). TEVA-TENOFOVIR is always used in combination with other anti-HIV medicines to treat people with HIV infection.

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

- Use in the Treatment of Chronic Hepatitis B:
  TEVA-TENOFOVIR is also used to treat chronic hepatitis B (an infection with hepatic B virus [HBV]) in adults age 18 years and older.

- If you have both HIV and HBV infection and are taking TEVA-TENOFOVIR, your healthcare professional should be prescribing TEVA-TENOFOVIR in combination with other anti-HIV medicines **(See: Proper Use of This Medication)**.

What it does:

Treatment of HIV infection:
- In patients with HIV infection, TEVA-TENOFOVIR helps to block HIV reverse transcriptase (enzyme) that is needed for HIV to multiply. TEVA-TENOFOVIR lowers the amount of HIV in the blood (called viral load).
- TEVA-TENOFOVIR does not cure HIV infection or AIDS. The long-term effects of TEVA-TENOFOVIR are not known at this time. People taking TEVA-TENOFOVIR may still get opportunistic infections or other conditions that happen with HIV infection. Opportunistic infections are infections that develop because the immune system is weak.

Treatment of Chronic Hepatitis B:
- In patients with HBV infection, TEVA-TENOFOVIR works by interfering with the normal working of enzymes (HBV DNA polymerase) that are essential for the HBV virus to reproduce itself. TEVA-TENOFOVIR may help lower the amount of hepatitis B virus in your body by lowering the ability of the virus to multiply and infect new liver cells.

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

TEVA-TENOFOVIR does not reduce the risk of passing HIV or HBV to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles.

When it should not be used:
- Do not take TEVA-TENOFOVIR if you are allergic to TEVA-TENOFOVIR or any of its ingredients **(See: What the nonmedicinal ingredients are)**.

What the medicinal ingredient is:
Tenofovir disoproxil fumarate

What the nonmedicinal ingredients are:
Colloidal anhydrous silica, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, FD&C Blue #2, carmine, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

What dosage forms it comes in:
TEVA-TENOFOVIR is available as tablets. Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil. The tablets are light blue to blue, modified capsule-shaped film-coated tablets debossed with "93" on one side and with "7104" on the other side. Each bottle contains 30 tablets and a child-resistant cap with desiccant silica gel (3 gm.) sorbit canister.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- The most serious possible side effect is harm to the kidneys, including damage to kidney cells, kidney tissue inflammation and kidney failure. Your healthcare professional may monitor your kidney function before beginning and while receiving TEVA-TENOFOVIR.

Some patients treated with tenofovir disoproxil fumarate (a component of TEVA-TENOFOVIR) have had kidney problems. Your healthcare professional may need to perform additional blood tests if you have had kidney problems in the past or need to take another drug that can cause kidney problems.

- **If you have Hepatitis B Virus infection or if you have HIV and HBV infection together, "flare-ups" of Hepatitis B Virus infection,** in which the disease suddenly returns in a worse way than before, can occur if you stop taking TEVA-TENOFOVIR. Do not stop taking TEVA-TENOFOVIR without your healthcare professional's advice. If you stop taking TEVA-TENOFOVIR, tell your healthcare professional immediately about any new, unusual or worsening symptoms that you notice after stopping treatment. After you stop taking TEVA-TENOFOVIR, your healthcare professional will still need to check your health and take blood tests to check your liver for several months.

- The class of medicines to which TEVA-TENOFOVIR belongs (NRTIs) can cause a condition called lactic acidosis (build-up of acid in the blood). The symptoms that may be signs of lactic acidosis include: feeling very weak, tired or uncomfortable, unusual or unexpected stomach discomfort, feeling cold, feeling dizzy or lightheaded, suddenly developing a slow or irregular heartbeat. This rare but serious side effect has occasionally been fatal.

- Severe liver problems can happen in people who take TEVA-TENOFOVIR or similar medicines. You may develop an enlarged liver (hepatomegaly) or a fatty liver (steatosis). Non-specific symptoms such as yellowing of the skin and eyes, nausea, vomiting, and stomach pain might indicate the development of liver problems.

  Lactic acidosis or severe liver problems occur more often in women, particularly if they are very overweight. You should consult your healthcare professional immediately if such symptoms occur while you are receiving TEVA-TENOFOVIR. If you notice these symptoms, stop taking TEVA-TENOFOVIR and consult a healthcare professional immediately.

- Tenofovir disoproxil fumarate caused harm to the bones of animals. Tenofovir disoproxil fumarate reduced bone density in humans. If you notice bone pain, suffer a bone fracture, or other bone problem, consult your healthcare professional. If you have bone problems, you may wish to discuss calcium and/or vitamin D supplements with your healthcare professionals.

- Do not take TEVA-TENOFOVIR if you are already taking ATRIPLA® (efavirenz/emtricitabine/tenofovir disoproxil fumarate), COMPLERA® (emtricitabine/rilpivirine/tenofovir disoproxil fumarate), DESCOVY® (emtricitabine/tenofovir alafenamide), GENVOYA® (elvitegravir/tenofovir alafenamide (as the hemifumarate)/emtricitabine/cobicistat), ODEFSEY™ (emtricitabine/rilpivirine/tenofovir alafenamide), STRIBILD® (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate), TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) or VEMLIDY™ (tenofovir alafenamide).
- because these medicines contain the same or similar active ingredients.
- Do not take TEVA-TENOFOVIR if you have not already discontinued treatment with HEPSERA® (adefovir dipivoxil).

BEFORE you use TEVA-TENOFOVIR talk to your healthcare professional if:

- ***You are pregnant or planning to become pregnant:*** Pregnant mothers should not take TEVA-TENOFOVIR unless specifically directed by the healthcare professional. If you take TEVA-TENOFOVIR while you are pregnant, talk to your healthcare professional about how you can be included in the Antiviral Pregnancy Registry.

- ***You are breastfeeding or planning to breastfeed:*** Do not breastfeed if you are taking TEVA-TENOFOVIR. Tenofovir passes to your baby in your breast milk. You should not breastfeed because of the risk of passing HIV or HBV to your baby. Talk to your healthcare professional about the best way to feed your baby.

- ***You have other medical conditions:*** Let your healthcare professional know if you have other medical conditions, especially hepatitis (inflammation of the liver), pancreatitis (inflammation of the pancreas), and bone and kidney problems.

- ***You have HIV Infection.***

- ***You are taking other medicines:*** Some medicines can interact when taken together, including prescription and non-prescription medicines and dietary supplements.

Other Special Warnings:
Your blood sugar levels (glucose) or levels of fats (lipids) in your blood may increase with HIV treatment. Your doctor may order blood tests for you.

INTERACTIONS WITH THIS MEDICATION

- Drugs that contain didanosine (Videx®, Videx EC®). TEVA-TENOFOVIR may increase the amount of didanosine (Videx®) in your blood. **You may need to be followed more carefully if you are taking TEVA-TENOFOVIR and drugs containing didanosine** (Videx®) **together**. Also, the dose of didanosine may need to be reduced.
- Reyataz® (Atazanavir sulfate), Kaletra® (lopinavir/ritonavir), Prezista® (darunavir), HARVONI® (ledipsavir/sofosbuvir), EPCLUSA® (sofosbuvir/velpatasvir) or VOSEVI™ (sofosbuvir/velpatasvir/voxilaprevir) may increase the amount of tenofovir disoproxil fumarate in your blood, which could result in more side effects. You may need to be followed more carefully if you are taking TEVA-TENOFOVIR together with Reyataz® (atazanavir sulfate), Kaletra® (lopinavir/ritonavir), Prezista® (darunavir), HARVONI® (ledipsavir/sofosbuvir), EPCLUSA® (sofosbuvir/velpatasvir) or VOSEVI™ (sofosbuvir/velpatasvir/voxilaprevir). TEVA-TENOFOVIR may decrease the amount of atazanavir sulfate in your blood. If you are taking TEVA-TENOFOVIR and atazanavir sulfate together, you should also be taking ritonavir.

PROPER USE OF THIS MEDICATION

Stay under a healthcare professional's care when taking TEVA- TENOFOVIR. Do not change your treatment or stop treatment without first talking with your healthcare professional.

Carefully follow the directions and dosing schedule prescribed by your healthcare professional.

When your TEVA-TENOFOVIR supply starts to run low, see your healthcare professional for a refill. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to TEVA- TENOFOVIR and become harder to treat.

If you are taking TEVA-TENOFOVIR to treat your HIV or if you have HIV and HBV coinfection and are taking TEVA-TENOFOVIR, always take TEVA-TENOFOVIR in combination with other anti-HIV medicines. TEVA-TENOFOVIR and other products like TEVA-TENOFOVIR may be less likely to work in the future if you are not taking TEVA-TENOFOVIR with other anti-HIV medicines because you may develop resistance to those medicines.

If you have HBV only (without HIV), TEVA-TENOFOVIR can be prescribed as a single drug treatment for HBV.

Talk to your healthcare professional about taking an HIV test before you start treatment with TEVA-TENOFOVIR for chronic hepatitis B.

Only take medicine that has been prescribed specifically for you. Do not give TEVA-TENOFOVIR to others or take medicine prescribed for someone else.

Usual Adult Dose:

- The usual dose of TEVA-TENOFOVIR is one 300 mg tablet orally (by mouth) once a day.
- TEVA-TENOFOVIR may be taken with or without a meal.

Usual Adolescent (12 Years of Age and Older) Dose for HIV infection:

- Body weight ≥35 kg (≥77 lb): Take one 300 mg TEVA-TENOFOVIR tablet once daily orally.
- TEVA-TENOFOVIR may be taken with or without a meal.

Overdosage:

In case of drug overdose, contact your healthcare professional, hospital emergency department or Regional Poison Control Centre, even if there are no symptoms.

Missed Dose:

- If you miss a dose of TEVA-TENOFOVIR, take it as soon as possible and then take your next scheduled dose at its regular time.
- Do not double the next dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects of TEVA-TENOFOVIR are:

- Diarrhea
- Nausea
- Vomiting
- Dizziness

Other side effects include:

- Flatulence (intestinal gas)
- Allergic reaction, including angioedema (swelling of the blood vessels) with symptoms such as skin rash, redness, swelling of the hands, legs, feet, face, lips, tongue or throat, with difficulty in breathing
- Stomach pain
- Weakness
- Inflammation of the pancreas
- Shortness of breath
- Headache

- Rash

Changes in your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time, or you could develop an autoimmune disease in which your immune system reacts against your own body [e.g. Grave's disease (which affects the thyroid gland), Guillain-Barré syndrome (which affects the nervous system) or polymyositis (which affects the muscles)] and it may develop at any time, sometimes months later after the start of HIV therapy. Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling or fatigue, or any new symptoms, contact your healthcare professional right away.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptoms / Effect	**Talk with your healthcare professional**		**Stop taking drug and call your healthcare professional**
	Only if severe	**In all cases**	
Rare			
Effect: Kidney problems **Symptoms** • Increased or decreased urination as well as increased thirst • Swelling of legs and feet • Feeling listless and tired		√ √ √	
Effect: Lactic acidosis Symptoms • Feeling very weak or tired • Unusual muscle pain • Stomach pain with nausea and vomiting • Feeling cold, especially in arms and legs • Feeling dizzy or lightheaded • Fast or irregular heartbeat		√ √ √ √ √ √	
Very Rare			
Effect: Hepatotoxicity (severe liver			

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptoms / Effect	**Talk with your healthcare professional**		**Stop taking drug and call your healthcare professional**
	Only if severe	**In all cases**	
problems) with hepatomegaly (liver enlargement) and steatosis (fat in the liver) **Symptoms** • Jaundice (skin or the white part of eyes turns yellow) • Urine turns dark • Bowel movements (stools) turn light in color • Loss of appetite for several days or longer • Feeling sick to your stomach (nausea) • Lower stomach pain		√ √ √ √ √	
Effect: Flare-ups of hepatitis B virus infection following drug discontinuation **Symptoms** • Jaundice (skin or the white part of eyes turns yellow) • Urine turns dark • Bowel movements (stools) turn light in color • Loss of appetite for several days or longer • Feeling sick to your stomach (nausea) • Lower stomach pain		√ √ √ √ √ √	

Lactic acidosis is a medical emergency and must be treated in the hospital. You may be more likely to get lactic acidosis or serious liver problems if you are very overweight (obese) or have been taking nucleoside analog medicines, like TEVA-TENOFOVIR, for a long time.

Muscle pain, muscle weakness, bone pain and softening of the bone (infrequently contributing to fractures) have also been reported.

This is not a complete list of side effects. For any unexpected effects while taking TEVA-TENOFOVIR, contact your healthcare professional.

HOW TO STORE IT

- Keep TEVA-TENOFOVIR and all other medications out of reach and sight of children.
- TEVA-TENOFOVIR should be stored between 15°C and 30°C. It should remain stable until the expiration date printed on the label.
- Do not keep medicine that is out of date or that you no longer need. If you throw any medicines away, make sure that children will not find them.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited by:
Phone: 1-800-268-4127 ext. 3;
Email: druginfo@tevacanada.com; or
Fax: 1-416-335-4472

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