PRODUCT MONOGRAPH

Pr MYLAN-TENOFOVIR DISOPROXIL

(Tenofovir Disoproxil Fumarate) Tablets

300 mg

Mylan Std.

Antiretroviral Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet, 300 mg	Croscarmellose Sodium, Lactose Monohydrate, Magnesium Stearate and Microcrystalline Cellulose. The film coating contains: FD&C Blue #2, hypromellose, lactose monohydrate, titanium dioxide and triacetin.

INDICATIONS AND CLINICAL USE

HIV-1 Infection

Mylan-Tenofovir Disoproxil (tenofovir disoproxil fumarate (TDF)) 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

Mylan-Tenofovir Disoproxil 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 DF 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 DF in adolescent patients aged 12 to <18 years is supported by data from one randomized study in which tenofovir DF was administered to HIV-1 infected treatment experienced subjects. In this study, the pharmacokinetic profile of tenofovir DF 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

Mylan-Tenofovir Disoproxil (tenofovir DF) 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 tenofovir DF, 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 DF. 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 tenofovir DF. 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 DF during

clinical practice **(see WARNINGS AND PRECAUTIONS, Renal)**.

General

For the effect of coadministered 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.

Mylan-Tenofovir Disoproxil should not be used in combination with the following:

- Products containing TDF (ATRIPLA®, COMPLERA®, STRIBILD® or TRUVADA®).
- Products containing tenofovir alafenamide (DESCOVY® or GENVOYA®, ODEFSEY™ , or VEMLIDY™).
- adefovir dipivoxil (HEPSERA®)

Bone Effects

In HIV-infected patients treated with tenofovir DF 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 DF and stavudine treatment arms of the study and significantly greater decreases were seen in the lumbar spine measurement in the tenofovir DF 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 DF -treated group compared to the placebo group. Six tenofovir DF 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 DF, 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 DF -treated adolescents increased bone turnover, consistent with the effects observed in adults. The effects of tenofovir DF -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 DF (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

TDF 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.

TDF was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, TDF was negative 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 TDF 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 Tenofovir DF is coadministered with HARVONI® (ledipasvir/sofosbuvir) EPCLUSA® (sofosbuvir/velpatasvir), or VOSEVI™ (sofosbuvir/velpatasvir/voxilaprevir). Patients receiving a regimen containing TDF concomitantly with HARVONI,EPCLUSA or VOSEVI, particularly those at increased risk for renal dysfunction, should be monitored for TDF-associated adverse reactions (see **DRUG INTERACTIONS**).

Use with Didanosine

Pharmacokinetic studies have shown that coadministration of didanosine and TDF results in 40-60% increase in Cmax 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 TDF 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 TDF, 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 Mylan-Tenofovir Disoproxil 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 DF. Caution should be used when administering nucleoside analogues (including Mylan-Tenofovir Disoproxil) 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 TDF 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 Mylan-Tenofovir Disoproxil, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue tenofovir DF 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 Inflamatory 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 TDF (**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 DF 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 Mylan-Tenofovir Disoproxil. 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 HEPSERA.

Particular caution should be exercised when administering Mylan-Tenofovir Disoproxil 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. Mylan-Tenofovir Disoproxil 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 Mylan-Tenofovir Disoproxil 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, Mylan-Tenofovir Disoproxil should only be used in HIV and HBV coinfected patients as part of an appropriate antiretroviral combination therapy.
HIV antibody testing should be offered to all HBV-infected patients before initiating therapy with Mylan-Tenofovir Disoproxil. It is also recommended that all patients with HIV be tested for the presence of chronic hepatitis B before initiating treatment with Mylan-Tenofovir Disoproxil.

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, TDF 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 Mylan-Tenofovir Disoproxil, 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 TDF are unknown. **Mothers should be instructed not to breast-feed if they are receiving Mylan-Tenofovir Disoproxil 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 DF in HIV adolescent patients aged 12 to <18 years is supported by data from one randomized study in which tenofovir DF was administered to HIV-1 infected treatment experienced subjects. In this study, the pharmacokinetic profile of tenofovir DF 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 DF 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 DF 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 DF 300 mg once daily in Phase 1-3 clinical trials; over 11,000 patients have received tenofovir DF 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 DF 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 DF (N = 368) (Week 0–24)	Placebo (N = 182) (Week 0–24)	Tenofovir DF (N = 368) (Week 0–48)	Placebo Crossover to Tenofovir DF (N = 170) (Week 24–48)
Body as a Whole				
Asthenia	7%	6%	11%	1%
Pain	7%	7%	12%	4%
Headache	5%	5%	8%	2%
Abdominal pain	4%	3%	7%	6%
Back pain	3%	3%	4%	2%
Chest pain	3%	1%	3%	2%
Fever	2%	2%	4%	2%
Digestive System				
Diarrhea	11%	10%	16%	11%
Nausea	8%	5%	11%	7%
Vomiting	4%	1%	7%	5%
Anorexia	3%	2%	4%	1%
Dyspepsia	3%	2%	4%	2%
Flatulence	3%	1%	4%	1%
Respiratory				
Pneumonia	2%	0%	3%	2%
Nervous System				
Depression	4%	3%	8%	4%
Insomnia	3%	2%	4%	4%
Peripheral neuropathy[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 DF 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 DF Patients in Study 907 (0–48 weeks)

	Tenofovir DF (N = 368) (Week 0–24) (%)	Placebo (N = 182) (Week 0–24) (%)	Tenofovir DF (N = 368) (Week 0–48) (%)	Placebo Crossover to Tenofovir DF (N = 170) (Week 24–48) (%)
Any ≥ Grade 3 Laboratory Abnormality	25%	38%	35%	34%
Triglycerides (> 750 mg/dL)	8%	13%	11%	9%
Creatine Kinase (M: > 990U/L) (F: > 845 U/L)	7%	14%	12%	12%
Serum Amylase (> 175 U/L)	6%	7%	7%	6%
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 DF (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 DF + 3TC + EFV N = 299	d4T + 3TC + EFV 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 DF (3%), laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir DF 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 DF-Treated Patients in Study 903 (0–144 Weeks)

	Tenofovir DF + 3TC + EFV N = 299	d4T + 3TC + 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 DF 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 DF -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 DF 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 DF 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 DF group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of tenofovir DF -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 Study 903

	Mean Percent Change (± SD) to Week 144 in BMD	
	Tenofovir DF + 3TC+ EFV	d4T + 3TC +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 DF + EMTRIVA (emtricitabine) administered in combination with efavirenz (N = 257) or Combivir®

(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 DF +FTC+ EFV N = 257	**AZT/3TC+EFV N = 254**
Blood and Lymphatic System Disorders		5%
Anemia	< 1%	
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 EMTRIVA + Tenofovir DF 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)

Week 48[1]	**Tenofovir DF + FTC + EFV**	**AZT/3TC +EFV**
	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)

	EMTRIVA+ Tenofovir DF +EFV N = 257	**AZT/3TC+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 (> 175U/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%

	EMTRIVA+ Tenofovir DF +EFV N = 257	AZT/3TC+EFV N = 254
Neutrophil (> 750/mm^3)	3%	4%
Fasting Triglycerides (> 750mg/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 DF (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 DF 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 DF (N = 426) or HEPSERA (N = 215) for 48 weeks in studies 0102 (HBeAg-) and 0103 (HBeAg+).

The most common adverse events in TDF-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 TDF-treated patients) in Pooled Studies GS-US-174-0102 and GS-US-174-0103 (0-48 weeks)

	Tenofovir DF (N = 426)	HEPSERA (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 DF.

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

No new adverse events causally associated with TDF were identified from a double-blind active controlled study (Study 0108) in which patients with decompensated liver disease received treatment containing TDF (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 TDF-containing regimen, including 4 of 45 patients (9%) receiving tenofovir DF, 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 DF).**

No new adverse reactions to TDF were identified from a randomized, double-blind study (Study 0121) in which lamivudine-resistant patients received treatment containing TDF (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 DF 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 DF N = 426	**HEPSERA 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 DF 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 DF. 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 DF.

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 DF 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 the individual agents of tenofovir DF and/or in combination, or are potential drug interactions that may occur with tenofovir DF.

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 coadministration of didanosine and TDF 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 TDF with didanosine at a dose of 400 mg daily. A reduced dose of Videx EC® (ddI-EC) is recommended when coadministered with Mylan-Tenofovir Disoproxil. When coadministered with Mylan-Tenofovir Disoproxil, the Videx EC® Product Monograph recommends a reduced dose of 250 mg ddI-EC for HIV infected adults with body weight ≥60 kg and creatinine clearance ≥60 mL/min. For patients with body weight <60 kg, and creatinine clearance ≥60 mL/min, the recommended dose of ddI-EC 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 (Videx®). Caution should be used when coadministering 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 TDF 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 TDF-associated adverse events, including renal disorders. Patients should be monitored for TDF-associated adverse events when receiving atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir in combination with TDF..
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 TDF. The recommended regimen is atazanavir 300 mg given with ritonavir 100 mg when used in combination with TDF 300 mg (all as a single daily dose with food).
Hepatitis C Virus Antiviral Agents:		
Ledipasvir/sofosbuvir Sofosbuvir/velpatasvir Sofosbuvir/velpatasvir/voxilaprevir	↑ tenofovir	Coadministration of TDF and HARVONI, EPCLUSA (sofosbuvir/velpatasvir) or VOSEVI (sofosbuvir/velpatasvir/voxilaprevir) has been shown to increase tenofovir exposure (see Table 13). Patients receiving a regimen containing TDF concomitantly with HARVONI, EPCLUSA or VOSEVI should be monitored for adverse reactions associated with TDF.

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. Coadministration of tenofovir DF with drugs that are eliminated by active tubular secretion may increase serum concentrations of either tenofovir or the coadministered 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.

Mylan-Tenofovir disoproxil should not be administered in combination with HEPSERA (adefovir dipivoxil) (see **WARNINGS AND PRECAUTIONS, General**).

Drugs without Clinically Significant Interactions with tenofovir DF

There were no clinically significant drug interactions observed when TDF was coadministered

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 DF as an individual agent and/or in combination with emtricitabine.

The effects of didanosine in the presence of tenofovir DF are shown in Table 12.

The effects of coadministered drugs on the exposure of tenofovir DF are shown in Table 13.
The effects of tenofovir DF on the exposure of coadministered drugs are shown in Table 14.

Table 12. Drug Interactions: Pharmacokinetic Parameters for Didanosine in the Presence of Tenofovir DF.

Didanosine[1] Dose (mg)/Method of Administration[2]	Tenofovir DF Method of Administration[2]	N	% Difference (90% CI) vs. Didanosine 400 mg Alone, Fasted[3]	
			Cmax	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 didanosine	28	↓ 29 (↓ 39 to ↓ 18)	↓ 11 (↓ 23 to ↑ 2)

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

Table 13. Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[1] in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters[2] (90% CI)		
			Cmax	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 (entericcoated)	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 ↑ 10)	↑ 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 x10 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 (↑ 8 to ↑ 45)	↓ 2 (↓ 9 to ↑ 5)	↓ 1 (↓ 9 to ↑ 7)
Sofosbuvir/			↑55	↑30	↑39

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters[2] (90% CI)		
			Cmax	AUC	C_{min}
Velpatasvir[13]	400/100 once daily	24	(↑43 to ↑68)	(↑24 to ↑36)	(↑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 DF 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 ddI 250 mg.
5. Weight <60kg: 250 mg, ≥60 kg more: 400 mg
6. Data generated from simultaneous dosing with HARVONI. Staggered administration (12 hours apart) provides similar results.
7. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/TDF coadministered with HARVONI (ledipasvir/sofosbuvir).
8. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/TDF coadministered with HARVONI.
9. Study conducted with ATRIPLA (efavirenz/emtricitabine/TDF) coadministered with HARVONI.
10. Study conducted with COMPLERA (emtricitabine/rilpivirine/TDF) coadministered with HARVONI.
11. Study conducted with emtricitabine and TDF + dolutegravir coadministered with HARVONI.
12. Study conducted with ATRIPLA coadministered with SOVALDI® (sofosbuvir).
13. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/TDF coadministered with EPCLUSA.
14. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/TDF tablets coadministered with EPCLUSA.
15. Study conducted with ATRIPLA (efavirenz/emtricitabine/TDF) coadministered with EPCLUSA.
16. Study conducted with COMPLERA (emtricitabine/rilpivirine/TDF) coadministered with EPCLUSA.
17. Study conducted with STRIBILD (elvitegravir/cobicistat/emtricitabine/TDF) coadministered with EPCLUSA.
18. Administered as raltegravir + emtricitabine and tenofovir DF tablets coadministered with EPCLUSA.
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 Coadministered Drug in the Presence of Tenofovir DF

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered 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 το ↓ 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 ↑1)	↓ 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 ↑ 24)	↑ 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)	↑ 10 (↑ 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)

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[1] (90% CI)		
			C_{max}	AUC	C_{min}
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
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]	14	↑ 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]	24	↑ 9 (↓ 5 to ↑ 25)	↑ 16 (↑ 9 to ↑ 24)	NC
GS-331007[8]			↓ 4 (↓ 10 to ↑ 1)	↑ 4 (0 to ↑ 7)	↑ 12 (↑ 7 to ↑ 17)
Velpatasvir			↓ 4 (↓ 15 to ↑ 10)	↓ 1 (↓ 12 to ↑ 11)	↑ 2 (↓ 9 to ↑ 15)
Sofosbuvir	400/100 once daily[18]	24	↑ 1 (↓ 15 to ↑ 19)	↑ 24 (↑ 13 to ↑ 37)	NC
GS-331007[8]			↑ 13 (↑ 7 to ↑ 18)	↑ 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]	30	↑ 9 (↓ 3 to ↑ 23)	↑ 16 (↑ 7 to ↑ 25)	NC
GS-331007[8]			↓ 5 (↓ 9 to ↓ 2)	↑ 3 (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)

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[1] (90% CI)		
			C_{max}	AUC	C_{min}
M8 metabolite			↓ 8 (↓ 16 to 0)	↓ 7 (↓ 17 to ↑ 5)	↓ 2 (↓ 16 to ↑ 15)
Norgestimate[6]	Ethinyl Estradiol/ Norgestimate (Ortho-Tricyclen®) 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
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 TDF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3 and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.
4. R-(active), S-and total methadone exposures were equivalent when dosed alone or with tenofovir DF.
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 DF.
7. Increase in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when TDF and ritonavir-boosted saquinavir are coadministered.
8. The predominant circulating nucleoside metabolite of sofosbuvir.
9. Data generated from simultaneous dosing with HARVONI. Staggered administration (12 hours apart) provides similar results.
10. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/TDF coadministered with HARVONI (ledipasvir/sofosbuvir).
11. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/TDF coadministerd with HARVONI.
12. Study conducted with ATRIPLA (efavirenz/emtricitabine/TDF) coadministered with HARVONI.
13. Study conducted with COMPLERA (emtricitabine/rilpivirine/TDF) coadministered with HARVONI.
14. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine and TDF tablets coadministered with EPCLUSA (sofosbuvir/velpatasvir).
15. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine and TDF tablets coadministered with EPCLUSA.
16. Study conducted with ATRIPLA (efavirenz/emtricitabine/TDF) coadministered with EPCLUSA.
17. Study conducted with COMPLERA (emtricitabine/rilpivirine/TDF) coadministered with EPCLUSA.
18. Study conducted with STRIBILD (elvitegravir/cobicistat/emtricitabine/TDF) coadministered with EPCLUSA.
19. Comparison based on exposures when administered as raltegravir + emtricitabine and tenofovir DF tablets coadministered with EPCLUSA.
20. Study conducted with ATRIPLA coadministered with SOVALDI (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/TDF.**

Drug-Food Interactions

Mylan-Tenofovir Disoproxil can be taken with or without food. Administration of Mylan-Tenofovir Disoproxil 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 tenofovir DF with herbs have not been established.

Drug-Laboratory Interactions

Interactions of tenofovir DF with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Adults

For the treatment of HIV or chronic hepatitis B: The dose of Mylan-Tenofovir Disoproxil (TDF) 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. Mylan-Tenofovir Disoproxil 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 Mylan-Tenofovir Disoproxil tablet once daily orally, without regard to food.

Dose Adjustment for Renal Impairment

Significantly increased drug exposures occurred when tenofovir DF was administered to patients with moderate to severe renal impairment (**see ACTIONS AND CLINICAL PHARMACOLOGY, Renal Insufficiency**). Therefore, the dosing interval of Mylan-Tenofovir Disoproxil 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 tenofovir DF tablets (300 mg) is necessary with mild renal impairment (creatine clearance 50-80 mL/min). Routine monitoring of 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. Mylan-Tenofovir Disoproxil 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 Mylan-Tenofovir Disoproxil at once to make up for missing a dose.

OVERDOSAGE

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

Limited clinical experience at doses higher than the therapeutic dose of tenofovir DF 300 mg is available. In Study 901 TDF 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 DF, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

ACTION AND CLINICAL PHARMACOLOGY

Mylan-Tenofovir Disoproxil (tenofovir DF) is an acyclic nucleotide diester analog of adenosine monophosphate. TDF 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.

Mylan-Tenofovir Disoproxil is a water soluble diester prodrug of the active ingredient tenofovir. Following oral administration of a single dose of tenofovir DF 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 DF in fasted patients is approximately 25%. Administration of Mylan-Tenofovir Disoproxil 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 (elvitagravir or raltegravir), nucleoside reverse transcriptase inhibitors (abacavir, didanosine, emtricitabine, lamivudine, stavudine, zalcitabine or zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, and nevirapine or rilpivirine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, and 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 TDF 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 TDF 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 TDF 300 mg QD (Study GS-97-901) the median decrease in plasma log_{10} HIV-1 RNA level was 1.22 log10 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 TDF 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 DF is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from tenofovir DF in fasted patients is approximately 25%. Following oral administration of a single dose of tenofovir DF 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 DF 300 mg once daily (under fed conditions), 32±10% 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 DF 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 DF 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 DF 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 DF 300 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir DF 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 DF 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 tenofovir DF 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, Cmax, and AUC0-∞ of tenofovir were increased (Table 16). It is recommended that the dosing interval for Mylan-Tenofovir Disoproxil 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 DF

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

STORAGE AND STABILITY

Store at controlled room temperature (15ºC to 30ºC) in tight closed container. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability

Mylan-Tenofovir Disoproxil 300 mg tablets are supplied in HDPE bottles of 30's.

Composition

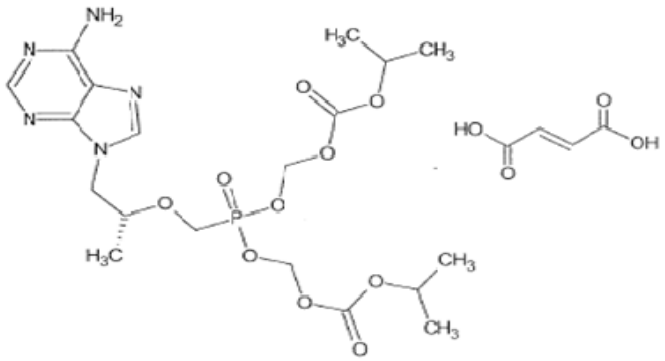
Mylan-Tenofovir Disoproxil 300 mg Tablets
Mylan-Tenofovir Disoproxil 300 mg tablets are light blue film-coated, almond shaped, biconvex tablets debossed with "M" on one side of the tablet and 'TN300' on the other side.

Each tablet contains 300 mg of tenofovir DF, which is equivalent to 245 mg of tenofovir disoproxil and the following non-medicinal ingredients: Croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The film coating contains: FD&C Blue #2, hypromellose, lactose monohydrate, titanium dioxide and triacetin.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Tenofovir Disoproxil Fumarate
Chemical name:	9-{(R)-2-[(Bis{[(isopropoxycarbonyl)oxy] methoxy}phosphinyl)methoxy]propyl} adenine fumarate. (R)-9-(2-phosphonomethoxypropyl) adenine disoproxil fumarate. [[(1R)-2-(6-Amino-9H-purin-9-yl)-1-methyl ethoxy] methyl] phosphoric acid disoproxil fumarate. 5-[[(1R-2-(6-Amino-9H-purin-9-yl)-1-methyl ethoxy] methyl]-2,4,6,8-tetraoxa-5-phosphanononanedioic acid bis (1-methlethyl) ester-5-oxide Fumarate salt.
Molecular formula and molecular mass:	$C_{19}H_{30}N_5O_{10}P.C_4H_4O_4$ Tenofovir Disoproxil Fumarate: 635.51 g/mol Tenofovir Disoproxil: 519.45 g/mol
Structural formula:	 TENOFOVIR DISOPROXIL FUMARATE
Physicochemical properties: Description:	White to off-white powder

Solubility:	Freely soluble in dimethylformamide and soluble in methanol.
pH:	About 3.25
pKa:	3.75
Melting point:	Between 114ºC and 118ºC
Hygroscopicity:	Non hygroscopic
Partition Coefficient (log P):	1.25

CLINICAL TRIALS

Comparative Bioavailability Studies

A double blind, randomized, two-treatment, two-period, cross-over, single-dose, oral bioequivalence study of Mylan-Tenofovir Disoproxil (tenofovir disoproxil fumarate) 300 mg Tablets (Test) of Mylan Pharmaceuticals ULC, and Viread® (tenofovir disoproxil fumarate) 300 mg Tablets (Reference) of Gilead Sciences Canada, Inc. was performed in 35 healthy male subjects under fasting condition.

A summary of the results is presented in the following table.

Tenofovir
(1 x 300 mg)
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Pharmacokinetic Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T‡ (hr*ng/mL)	1890.5 1973.1 (28.2)	1878.5 1953.3 (26.8)	100.6	94.4-107.3
AUC_I (hr*ng/mL)	2126.6 2198.9 (24.9)	2114.9 2182.4 (24.0)	100.6	94.9-106.5
C_{MAX} (ng/mL)	263.9 275.3 (29.2)	260.2 270.7 (26.9)	101.4	94.4-109.0
T_{MAX}§ (h)	0.8 (0.5-2.5)	0.7 (0.3-2.0)		
$T_{½}$€ (h)	19.4 (19.7)	19.9 (15.5)		

* Mylan- Tenofovir Disoproxil Fumarate Tablets 300 mg (Mylan Pharmaceuticals ULC).
† [Pr]Viread® (tenofovir disoproxil fumarate) 300 mg tablets were purchased from Canada.
§ Expressed as the median (range) only.
€ Arithmetic mean (%CV)

Clinical Efficacy in Patients with HIV

Study Demographics and Trial Design

Treatment-Experienced Adult Patients

Study 907 - Tenofovir DF + Standard Background Therapy (SBT) Compared to Placebo + SBT: Study 907 was a 24-week, double-blind placebo-controlled multicenter study of tenofovir DF 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 DF 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 DF + Standard Background Therapy (SBD) Compared to Placebo + SBD

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subject (N = 550)	Mean Age	Gender
GS-99-907	Randomized (2:1), Double-Blind, Placebo-Controlled	**Arm 1**: TDF 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 DF + 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 DF (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 DF + Lamivudine + Efavirenz Compared with Stavudine + Lamivudine + Efavirenz

Study No.	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:** TDF + lamivudine + efavirenz **Arm 2:** stavudine + lamivudine + efavirenz	**Arm 1:** TDF 300 mg tablets QD, stavudine placebo capsules BID, lamivudine 150 mg tablets BID, efavirenz 600 mg QD **Arm 2:** TDF placebo tablets QD, stavudine[1] capsules 40/30 mg BID, lamivudine 150 mg tablets BID, efavirenz 600 mg QD All for oral (PO) 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.)	Treatment-naive (HIV-1 RNA > 5,000 copies/mL) (N = 600)	36 years (18–64)	Male: 74% Female: 26%

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

Study 934 - Tenofovir DF + 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 DF (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 DF + emtricitabine received TRUVADA with efavirenz in place of emtricitabine + tenofovir DF. 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 log10 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: EMTRIVA+ Tenofovir DF + 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:	Arm 1[1]: Efavirenz 600 mg once daily for oral administration, emtricitabine 200 mg once and TDF 300 mg once daily Arm 2: Efavirenz 600 mg once daily for oral administration and	Antiretroviral naive patients (HIV-1 RNA > 10,000 copies/mL) (N = 511)	Mean 38 years Range 18–80	Male: 86% Female:14%

Study Number	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N = 511)	Mean Age	Gender
	emtricitabine+ TDF+ efavirenz Arm 2: lamivudine/ zidovudine + efavirenz	Combivir (lamivudine/ zidovudine 150/300 mg twice daily). 144 weeks			

[1] From weeks 96 to 144 of the study, patients received TRUVADA with efavirenz in place of emtricitabine + tenofovir DF

Study Results

Study 907 - Tenofovir DF + 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 (log10 copies/mL): Study 907 (48 weeks)

	HIV-1 RNA log10 copies/mL	
Study Week	**Tenofovir DF (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 DF (N = 368)	**Placebo Crossover to Tenofovir DF [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 DF, 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)

		0–24 weeks	0–48 weeks	24–48 weeks
Outcomes	**Tenofovir DF (N = 368) %**	**Placebo (N = 182) %**	**Tenofovir DF (N = 368) %**	**Placebo Crossover to Tenofovir DF (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%

		0–24 weeks	0–48 weeks	24–48 weeks
Outcomes	**Tenofovir DF (N = 368) %**	**Placebo (N = 182) %**	**Tenofovir DF (N = 368) %**	**Placebo Crossover to Tenofovir DF (N = 170) %**
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 DF 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 DF 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 DF group.

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

Study 903 - Tenofovir DF + 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)

Outcomes	**At Week 48**		**At Week 144**	
	Tenofovir DF + 3TC + EFV (N = 299) %	**Stavudine + 3TC + EFV (N = 301) %**	**Tenofovir DF + 3TC + EFV (N = 299) %**	**Stavudine + 3TC + 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 DF 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 DF arm and 283 cells/mm^3 for the stavudine arm.

Through 144 weeks, twelve patients in the tenofovir DF group and nine 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*†

	Proportion of Patients with HIV-1 RNA < 400 copies/mL (%)	
Study Week	**Tenofovir DF + 3TC + EFV (N = 299)**	**Stavudine + 3TC + EFV (N = 301)**
Week 24	86	86
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 DF + 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)

	At Week 48		**At Week 144[1]**	
Outcome	**Tenofovir DF + FTC + EFV (N = 244)**	**3TC/AZT + EFV (N = 243)**	**Tenofovir DF + FTC + EFV (N = 227)**	**3TC/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 DF + 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 DF + 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 DF + 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 DF + 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 DF + emtricitabine + efavirenz arm, and 158 cells/mm^3 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 DF + 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 DF (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 log10 copies/mL for the tenofovir DF group compared to −1.55 and −1.35 log10 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 DF group.

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

The virologic response to tenofovir DF 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 DF were observed in patients with pre-existing zidovudine-associated mutations and appeared to depend on the number of specific mutations. tenofovir DF 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 DF 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 DF therapy.

In the protocol defined analyses, virologic response to tenofovir DF 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 DF showed a -0.84 log10 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 DF 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 DF.

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 DF. Cross-resistance between tenofovir DF 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 DF 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 DF in Patients with Previous Antiretroviral Therapy (Studies 902 and 907)

The virologic response to tenofovir DF 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 DF and response to tenofovir DF therapy. Table 25 summarizes the HIV-1 RNA response by baseline tenofovir DF susceptibility.

Table 25. HIV-1 RNA Response at Week 24 by Baseline Tenofovir DF Susceptibility (Intent-To-Treat)

Baseline Tenofovir DF 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 $\log_{10}$ copies/mL.

Genotypic Analyses of Tenofovir DF 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 DF arm and in 2 patients on the stavudine arm. Of the 8 patients who developed K65R in the tenofovir DF arm through 144 weeks, 7 of these occurred in the first 48 weeks of treatment and the last one at Week 96. One patient in the tenofovir DF arm developed 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 DF.

In Study 934 (tenofovir DF + 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 DF + eEMTRIVA group and in 21 of 29 (72%) analyzed patients in the lamivudine/zidovudine group. The M184V substitution, associated with resistance to EMTRIVA and lamivudine, was observed in 2- of 19 (11%) analyzed patients in the tenofovir DF + emtricitabine group and in 10 of 29 (34%) analyzed patients in the lamivudine/zidovudine group.

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

In Study 321 (adolescent patients 12 - <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.

Clinical Efficacy in Patient with HBV

Study Demographics and Trial Design

HBeAg-Negative Chronic Hepatitis B: Study 0102 was a Phase 3, randomized, double-blind, active-controlled study of tenofovir DF 300 mg compared to HEPSERA 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 DF 300 mg compared to HEPSERA 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 DF Compared to HEPSERA

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subject	Mean Age (Range)	Gender
GS-US-174-0102	Randomized (2:1), Double-Blind, Parallel group	**Arm 1**: TDF 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 TDF 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**: TDF 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 TDF up to Week 384 (8 years)	N = 176 N = 90 HBeAg+; nucleoside-naïve HBV DNA > 10_6 copies/mL	34 years (18–64)	Male: 69% Female:31%

Study Results

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

In Study 0103, a significantly greater proportion of patients in the tenofovir DF group had normalized ALT and achieved HBsAg loss, when compared to HEPSERA.

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

	0102 (HBeAg-)		0103 (HBeAg+)	
	Tenofovir DF (N = 250)	**HEPSERA (N = 125)**	**Tenofovir DF (N = 176)**	**HEPSERA (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 DF 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 HEPSERA (Study 0102; 91%, 56%, p < 0.001 and study 0103; 69%, 9%, p < 0.001), respectively.

Response to treatment with tenofovir DF 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 DF 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 DF arm was 9.45 $\log_{10}$ copies/mL (N = 27). Treatment with tenofovir DF 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 $\log_{10}$ 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 HEPSERA were randomized to tenofovir DF 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 DF (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 DF 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 DF or HEPSERA rolled over with no interruption in treatment to open-label tenofovir DF. 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 DF and HEPSERA, respectively, completed 96 weeks of treatment and in Study 0103, 82% and 92% of patients who were randomized to tenofovir DF and HEPSERA, 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 DF treatment. In patients rolling over from HEPSERA to tenofovir DF at Week 48, HBV DNA rapidly declined in HEPSERA non-responders (HBV DNA ≥ 400 copies/ml at Week 48) and was maintained below 400 copies/ml in HEPSERA 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)

	0102 (HBeAg-)				0102 (HBeAg-)			
	Tenofovir DF[f] (N = 250)		HEPSERA Rollover to Tenofovir DF[f] (N = 125)		Tenofovir DF[f] (N = 176)		HEPSERA Rollover to Tenofovir DF[f] (N = 90)	
Outcomes[a]	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 HEPSERA Responder[g]	-	-	100%	100%	-	-	100%	100%
Week 48 HEPSERA 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 DF regimen at or beyond Week 72.

b 48 weeks double-blind tenofovir DF followed by up to 48 weeks open-label tenofovir DF.

c 48 weeks double-blind HEPSERA followed by up to 48 weeks open-label tenofovir DF.

d 48 weeks double-blind tenofovir DF followed by up to 240 weeks open-label tenofovir DF.

e 48 weeks double-blind HEPSERA followed by up to 240 weeks open-label tenofovir DF.

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 TDF + 200 mg emtricitabine (administered as fixed dose combination TRUVADA).

g Patients treated with HEPSERA 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 HEPSERA 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 DF N = 250[c]	**HEPSERA Rollover to Tenofovir DF N = 125[d]**	**Tenofovir DF N = 176[c]**	**HEPSERA Rollover to Tenofovir DF 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 TDF followed by up to 192 weeks open-label TDF.
d 48 weeks double-blind adefovir dipivoxil followed by up to 192 weeks open-label TDF.

Patients with Lamivudine-Resistant Chronic Hepatitis B: Study GS-US-174-0121 explored the safety and efficacy of tenofovir DF (TDF 300mg) compared to an unapproved antiviral regimen [TRUVADA (FTC 200 mg/TDF 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 DF and to the comparator, respectively, had HBV DNA < 400 copies/mL, and 49 of 79 subjects (62%) randomized to tenofovir DF had ALT normalization. Among the HBeAg-positive subjects randomized to tenofovir DF, 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 DF 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 DF monotherapy and remained viremic (HBV DNA ≥ 400 copies/mL) at the last evaluable study visit on tenofovir DF monotherapy was performed. Of the 612 subjects who received at least 24 weeks of tenofovir DF monotherapy, 57 (9.3%) were viremic with up to 288 weeks of cumulative treatment with tenofovir DF

monotherapy. Overall, no amino acid substitutions in the HBV polymerase were associated with resistance to tenofovir DF (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 4/57 (7%) had conserved site changes.

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

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

In Study 0121, 141 patients with lamivudine resistance substitutions at screening received treatment with tenofovir DF 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 DF. No amino acid substitutions associated with resistance to tenofovir DF 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 non-clinical safety profile of TDF has been studied in mice, rats, guinea pigs, rabbits, dogs, and monkeys. In all species, TDF 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 TDF 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 TDF 500 mg/kg; no effect was observed at 50 mg/kg. When rats were administered TDF (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 TDF (≥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 TDF 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 TDF 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 TDF 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

TDF 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. TDF 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. TDF had no adverse effects on fertility or general reproductive performance in rats at doses up to 600 mg/kg/day. TDF 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 TDF. 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

[Pr]Mylan-Tenofovir Disoproxil
Tenofovir Disoproxil Fumarate Tablets, Mylan Std.
300 mg

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

ABOUT THIS MEDICATION

What the medication is used for:

- Mylan-Tenofovir Disoproxil is a type of medicine called a nucleotide analog reverse transcriptase inhibitor (NRTI).
- Use in the Treatment of HIV-Infection:
  Mylan-Tenofovir Disoproxil 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). Mylan-Tenofovir Disoproxil 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:

  Mylan-Tenofovir Disoproxil 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 Mylan-Tenofovir Disoproxil, your doctor should be prescribing Mylan-Tenofovir Disoproxil 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, Mylan-Tenofovir Disoproxil helps to block HIV reverse transcriptase (enzyme) that is needed for HIV to multiply. Mylan-Tenofovir Disoproxil lowers the amount of HIV in the blood (called viral load).
- Mylan-Tenofovir Disoproxil does not cure HIV infection or AIDS. The long-term effects of Mylan-Tenofovir Disoproxil are not known at this time. People taking Mylan-Tenofovir Disoproxil 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, Mylan-Tenofovir Disoproxil works by interfering with the normal working of enzymes (HBV DNA polymerase) that are essential for the HBV virus to reproduce itself. Mylan-Tenofovir Disoproxil 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 Mylan-Tenofovir Disoproxil may help your hepatitis. Sometimes viruses change in your body and medicines no longer work. This is called drug resistance.

Mylan-Tenofovir Disoproxil 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 Mylan-Tenofovir Disoproxil if you are allergic to Mylan-Tenofovir Disoproxil or any of its ingredients **(See: What the important nonmedicinal ingredients are)**.
- Do not take Mylan-Tenofovir Disoproxil if you are already taking TRUVADA®, ATRIPLA®, or COMPLERA®, or STRIBILD® because Mylan-Tenofovir Disoproxil is one of the active ingredients in these products.
- Do not take Mylan-Tenofovir Disoproxil if you have not already discontinued treatment with HEPSERA®.

What the medicinal ingredient is:
Tenofovir disoproxil fumarate (TDF)

What the nonmedicinal ingredients are:
Croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The film coating contains: FD&C Blue #2, hypromellose, lactose monohydrate, titanium dioxide and triacetin.

What dosage forms it comes in:
Mylan-Tenofovir Disoproxil is available as tablets.

Each tablet contains 300 mg of tenofovir DF, which is equivalent to 245 mg of tenofovir disoproxil. Mylan-Tenofovir Disoproxil 300 mg tablets are light blue film-coated, almond shaped, biconvex tablets debossed with “M” on one side of the tablet and ‘TN300’ on the other side.

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 Mylan-Tenofovir Disoproxil. Some patients treated with TDF (a component of Mylan-Tenofovir Disoproxil) have had kidney problems. Your doctor 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 Mylan-Tenofovir Disoproxil. Do not stop taking Mylan-Tenofovir Disoproxil without your healthcare professional's advice. If you stop taking Mylan-Tenofovir Disoproxil, tell your healthcare professional immediately about any new, unusual or worsening symptoms that you notice after stopping treatment. After you stop taking Mylan-Tenofovir Disoproxil, 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 Mylan-Tenofovir Disoproxil belong (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 heart beat. This rare but serious side effect has occasionally been fatal.

- Severe liver problems can happen in people who take Mylan-Tenofovir Disoproxil 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 Mylan-Tenofovir Disoproxil. If you notice these symptoms, stop taking Mylan-Tenofovir Disoproxil and consult a healthcare professional immediately.

- TDF caused harm to the bones of animals. TDF 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 Mylan-Tenofovir Disoproxil if you are already taking ATRIPLA®, COMPLERA®, DESCOVY®, GENVOYA®, ODEFSEY™, STRIBILD®, TRUVADA® or VEMLIDY™ because these medicines contain the same or similar active ingredients.
- Do not take Mylan-Tenofovir Disoproxil if you have not already discontinued treatment with HEPSERA®.

BEFORE you use Mylan-Tenofovir Disoproxil talk to your healthcare professional if:

- ***You are pregnant or planning to become pregnant:*** Pregnant mothers should not take Mylan-Tenofovir Disoproxil unless specifically directed by the healthcare professional. If you take Mylan-Tenofovir Disoproxil while you are pregnant, talk to your doctor 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 Mylan-Tenofovir Disoproxil. 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.

- Drugs that contain didanosine (Videx®, Videx EC®). TDF (Mylan-Tenofovir Disoproxil) may increase the amount of Videx in your blood. **You may need to be followed more carefully if you are taking Mylan-Tenofovir Disoproxil and Videx together.** Also, the dose of didanosine may need to be reduced.

- Reyataz® (atazanavir sulfate) Kaletra® (lopinavir/ritonavir). Prezista® (darunavir), HARVONI ® (ledipasvir /sofosbuvir) or EPCLUSA™ (sofosbuvir/velpatasvir), or VOSEVI™ (sofosbuvir/velpatasvir/voxilaprevir) may increase the amount of TDF (Mylan-Tenofovir Disoproxil) in your blood, which could result in more side effects. You may need to be followed more carefully if you are taking Mylan-Tenofovir Disoproxil together with Reyataz, Kaletra, Prezista, HARVONI, EPCLUSA or VOSEVI. Mylan-Tenofovir Disoproxil may decrease the amount of Reyataz in your blood. If you are taking Mylan-Tenofovir Disoproxil and Reyataz together, you should also be taking Norvir® (ritonavir).

PROPER USE OF THIS MEDICATION

Stay under a healthcare professional's care when taking Mylan-Tenofovir Disoproxil. 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 Mylan-Tenofovir Disoproxil 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 Mylan-Tenofovir Disoproxil and become harder to treat.

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

If you have HBV only (without HIV), Mylan-Tenofovir Disoproxil 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 Mylan-Tenofovir Disoproxil for chronic hepatitis B.

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

Usual Adult Dose:

- The usual dose of Mylan-Tenofovir Disoproxil is one 300 mg tablet orally (by mouth) once a day.
- Mylan-Tenofovir Disoproxil 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 Mylan-Tenofovir Disoproxil tablet once daily orally.

- Mylan-Tenofovir Disoproxil 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 Mylan-Tenofovir Disoproxil, 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 tenofovir DF 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-Barre 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 doctor 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 health care 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		√ √ √	
Rare	**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 problems) with hepatomegaly (liver enlargement) and steatosis (fat in the liver)** **Symptoms** • Jaundice (skin or the white part of eyes turn 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		√ √ √ √ √ √	
Very Rare	**Effect: Flare-ups of hepatitis B virus infection following drug discontinuation**			

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 health care professional
		Only if severe	In all cases	
	Symptoms • Jaundice (skin or the white part of eyes turn 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 Mylan-Tenofovir Disoproxil, 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 side effects while taking Mylan-Tenofovir Disoproxil, contact your healthcare professional.

HOW TO STORE IT

- Keep Mylan-Tenofovir Disoproxil and all other medications out of reach and sight of children.
- Mylan-Tenofovir Disoproxil should be stored at 15ºC – 30ºC (59-86ºF). 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 health 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 can be found at: www.mylan.ca.

The full Product Monograph prepared for health professionals can be obtained by contacting the sponsor, Mylan Pharmaceuticals ULC at: 1-844-596-9526

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