Do not print pink colour line.

Space for 15 Digit - Sequential 2D Data matrix Barcode shall be printed by the vendor.

1035924
300 mg
Fumarate Tablets
Tenofovir Disoproxil

Tenofovir Disoproxil Fumarate Tablets 300 mg
1035924

Pharmacode Position shall be changed depending upon the Printer's Machine suitability.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TENOFOVIR DISOPROXIL FUMARATE TABLETS safely and effectively. See full prescribing information for TENOFOVIR DISOPROXIL FUMARATE TABLETS

TENOFOVIR DISOPROXIL FUMARATE tablets, for oral use

Initial U.S. Approval Date: 2001

WARNINGS: POST TREATMENT EXACERBATION OF HEPATITIS
See full prescribing information for complete boxed warning.
- **Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including tenofovir disoproxil fumarate. Hepatic function should be monitored closely in these patients. If appropriate, resumption of anti-hepatitis B therapy may be warranted. (5.1)**

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

Tenofovir disoproxil fumarate is a nucleotide analog HIV-1 reverse transcriptase inhibitor and an HBV reverse transcriptase inhibitor.

Tenofovir disoproxil fumarate is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 2 years of age and older. (1)

Tenofovir disoproxil fumarate is indicated for the treatment of chronic hepatitis B in adults and pediatric patients 12 years of age and older. (1)

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

- Recommended dose for the treatment of HIV-1 or chronic hepatitis B in adults and pediatric patients 12 years of age and older (35 kg or more): 300 mg once daily taken orally without regard to food. (2.1)
- Recommended dose for the treatment of HIV-1 in pediatric patients (2 to less than 12 years of age): Tablets: for pediatric patients weighing greater than or equal to 17 kg who can swallow an intact tablet, one Tenofovir disoproxil fumarate tablet (300 mg based on body weight) once daily taken orally without regard to food. (2.2)
- Dose recommended in renal impairment in adults: Creatinine clearance 30-49 mL/min: 300 mg every 48 hours (2.3)
  Creatinine clearance 10-29 mL/min: 300 mg every 72 to 96 hours. (2.3)
  Hemodialysis: 300 mg every 7 days or after approximately 12 hours of dialysis. (2.3)

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

Tablets: 300 mg (3)

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

None. (4)

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

- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess estimated creatinine clearance before initiating treatment with Tenofovir disoproxil fumarate. In patients at risk for renal dysfunction, assess estimated creatinine clearance, serum phosphorus, urine glucose and urine protein before initiating treatment with tenofovir disoproxil fumarate and periodically during treatment. Avoid administering tenofovir disoproxil fumarate with concurrent or recent use of nephrotoxic drugs. (5.2)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronouncedhepatotoxicity. (5.3)
- Coadministration with Other Products: Do not use with other tenofovir-containing products (e.g., ATRIPLA, COMPLERA, DESCOVY, GENVOYA, ODEFSEY, STRIBILD, TRUVAD or VEMLIDY). Do not administer in combination with HEPSERA. (5.4)
- HIV testing: HIV antibody testing should be offered to all HBV- infected patients before initiating therapy with tenofovir disoproxil fumarate. Tenofovir disoproxil fumarate should only be used as part of an appropriate antiretroviral combination regimen in HIV-infected patients with or without HBV coinfection. (5.5)
- Decreases in bone mineral density (BMD): Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss. (5.6)
- Immune reconstitution syndrome: Observed in HIV-infected patients. May necessitate further evaluation and treatment. (5.7)
- Triple nucleoside-only regimens: Early virologic failure has been reported in HIV-infected patients. Monitor carefully and consider treatment modification. (5.8)

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

In HIV-infected adult subjects: Most common adverse reactions (incidence greater than or equal to 10%, Grades 2 - 4) are rash, diarrhea, headache, pain, depression, asthenia, and nausea. (6.1)

In HBV-infected subjects with compensated liver disease: most common adverse reaction (all grades) was nausea (9%). (6.1)

In pediatric subjects: Adverse reactions in pediatric subjects were consistent with those observed in adults. (6.1)

In HBV–infected subjects with decompensated liver disease: most common adverse reactions (incidence greater than or equal to 10%, all grades) were abdominal pain, nausea, insomnia, pruritus, vomiting, dizziness, and pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Strides Pharma Inc. at 1877-244-9825 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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

- Didanosine: Coadministration increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy). Consider dose reductions or discontinuations of didanosine if warranted. (7.1)
- HIV-1 protease inhibitors: Coadministration decreases atazanavir concentrations and increases tenofovir concentrations. When coadministered with tenofovir disoproxil fumarate, use atazanavir given with ritonavir. Coadministration of tenofovir disoproxil fumarate with atazanavir and ritonavir, darunavir and ritonavir, or lopinavir/ritonavir increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity. (7.2)

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

- Nursing mothers: Women infected with HIV should be instructed not to breast feed. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.

Revised: 12/2017

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: POST TREATMENT EXACERBATION OF HEPATITIS

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

FULL PRESCRIBING INFORMATION

WARNING: POST TREATMENT EXACERBATION OF HEPATITIS

Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including tenofovir disoproxil fumarate. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including tenofovir disoproxil fumarate. If appropriate, resumption of anti-hepatitis B therapy may be warranted *[See Warnings and Precautions (51)]*.

1 INDICATIONS AND USAGE

1.1 HIV-1 Infection

Tenofovir disoproxil fumarate is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 2 years of age and older.

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

- Tenofovir disoproxil fumarate should not be used in combination with ATRIPLA®, COMPLERA®, DESCOVY®, GENVOYA®, ODEFSEY®, STRIBILD®, TRUVAD® or VEMLIDY® *[See Warnings and Precautions (5.4)]*.

1.2 Chronic Hepatitis B

Tenofovir disoproxil fumarate is indicated for the treatment of chronic hepatitis B in adults and pediatric patients 12 years of age and older.

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

- The indication in adults is based on safety and efficacy data from treatment of subjects who were nucleoside-treatment-naive and subjects who were treatment-experienced with documented resistance to lamivudine. Subjects were adults with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease *[See Clinical Studies (14.2)]*.
- Tenofovir disoproxil fumarate was evaluated in a limited number of subjects with chronic hepatitis B and decompensated liver disease. *[See Adverse Reactions (6.1), Clinical Studies (14.2)]*.
- The numbers of subjects in clinical trials who had adefovir resistance-associated substitutions at baseline were too small to reach conclusions of efficacy *[See Microbiology (12.4), Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose in Adults and Pediatric Patients 12 Years of Age and Older (35 kg or more)

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

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

2.2 Recommended Dose in Pediatric Patients 2 Years to Less than 12 Years of Age

HIV-1 Infection

For the treatment of HIV-1 in pediatric patients 2 years of age and older, the recommended oral dose of tenofovir disoproxil fumarate tablet is 8 mg of tenofovir disoproxil fumarate per kilogram of body weight (up to a maximum of 300 mg) once daily administered as oral tablets.

Tenofovir disoproxil fumarate is available as tablets in 300 mg strengths for pediatric patients who weigh greater than or equal to 17 kg and who are able to reliably swallow intact tablets. The dose is one tablet once daily taken orally, without regard to food.

Tables 2 contain dosing recommendations for tenofovir disoproxil fumarate tablets based on body weight. Weight should be monitored periodically and the tenofovir disoproxil fumarate dose adjusted accordingly.

Table 2 Dosing Recommendations for Pediatric Patients ≥2 Years of Age and Weighing ≥17 kg Using Tenofovir disoproxil fumarate tablets.

Body Weight Kilogram (kg)	Tablets Once Daily
≥35	300 mg

Chronic Hepatitis B

Safety and efficacy of tenofovir disoproxil fumarate in patients younger than 12 years of age have not been established.

2.3 Dose Adjustment for Renal Impairment in Adults

Significantly increased drug exposures occurred when tenofovir disoproxil fumarate was administered to subjects with moderate to severe renal impairment *[see Clinical Pharmacology (12.3)]*. Therefore, the dosing interval of tenofovir disoproxil fumarate tablets 300 mg should be adjusted in patients with baseline creatinine clearance below 50 mL/min using the recommendations in Table 3. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate or severe renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients *[See Warnings and Precautions (5.2)]*. There are no data to recommend use of Tenofovir disoproxil fumarate tablets 300 mg in patients with renal impairment.

No dose adjustment of tenofovir disoproxil fumarate tablets 300 mg is necessary for patients with mild renal impairment (creatinine clearance 50-80 mL/min). Routine monitoring of estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein should be performed in patients with mild renal impairment *[See Warnings and Precautions (5.2)]*.

Table 3 Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)[a]			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[b]

[a] Calculated using ideal (lean) body weight.

[b] Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. Tenofovir disoproxil fumarate should be administered following completion of dialysis.

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

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

3 DOSAGE FORMS AND STRENGTHS

Tenofovir disoproxil fumarate is available as tablets.

Tenofovir disoproxil fumarate tablets 300 mg contain 300 mg of tenofovir disoproxil fumarate which is equivalent to 245 mg of tenofovir disoproxil. The tablets are white circular film coated, convex tablets engraved "TDF" on one side and plain on other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Exacerbation of Hepatitis after Discontinuation of Treatment

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

5.2 New Onset or Worsening Renal Impairment

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

It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with tenofovir disoproxil fumarate. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving HEPSERA®, it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of tenofovir disoproxil fumarate, and periodically during tenofovir disoproxil fumarate therapy.

Dosing interval adjustment of tenofovir disoproxil fumarate and close monitoring of renal function are recommended in all patients with creatinine clearance below 50 ml/min *[See Dosage and Administration (2.3)]*. No safety or efficacy data are available in patients with renal impairment who received tenofovir disoproxil fumarate using these dosing guidelines, so the potential benefit of tenofovir disoproxil fumarate therapy should be assessed against the potential risk of renal toxicity.

Tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)) *[See Drug Interactions (7.4)]*. Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir DF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

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

5.3 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs,including tenofovir tenofovir DF, alone or in combination with other antiretrovirals.Treatment with tenofovir disoproxil fumarate should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

5.4 Coadministration with Other Products

Tenofovir disoproxil fumarate should not be used in combination with other drugs containing tenofovir disoproxil fumurate or tenofovir alafenamide, including ATRIPLA, COMPLERA, DESCOVY, GENVOYA, ODEFSEY, STRIBILD, TRUVAD or VEMLIDY.

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

5.5 Patients Coinfected with HIV-1 and HBV

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

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

5.6 Bone Effects

Bone Mineral Density:

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

Clinical trials evaluating tenofovir disoproxil fumarate in pediatric and adolescent subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the tenofovir disoproxil fumarate-treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in chronic hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be unaffected *[See Adverse Reactions (6.1)]*.

The effects of tenofovir disoproxil fumarate-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adults and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. 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.

Mineralization Defects:

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of tenofovir disoproxil fumarate *[See Adverse Reactions (6.2)]*. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF *[See Warnings and Precautions (5.2)]*.

5.7 Immune Reconstitution Syndrome

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

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

5.8 Early Virologic Failure

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

6 ADVERSE REACTIONS

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

- Severe Acute Exacerbation of Hepatitis *[See Boxed Warning, Warnings and Precautions (5.1)]*.
- New Onset or Worsening Renal Impairment *[See Warnings and Precautions (5.2)]*.
- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[See Boxed Warning, Warnings and Precautions (5.3)]*.
- Bone Effects *[See Warnings and Precautions (5.6)]*.
- Immune Reconstitution Syndrome *[See Warnings and Precautions (5.7)]*.

6.1 Adverse Reactions from Clinical Trials Experience

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

<u>*Clinical Trials in Adult Patients with HIV-1 Infection*</u>

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

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

Treatment-Naïve Patients

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

Mild adverse reactions (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhea, and nausea. Selected treatment-emergent moderate to severe adverse reactions are summarized in Table 4.

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

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

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

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

[c] Peripheral neuropathy includes peripheral neuritis and neuropathy.

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

Laboratory Abnormalities: With the exception of fasting cholesterol and fasting triglyceride elevations that were more common in the stavudine group (40% and 9%) compared with tenofovir disoproxil fumarate (19% and 1%) respectively, laboratory abnormalities observed in this trial occurred with similar frequency in the tenofovir disoproxil fumarate and stavudine treatment arms. A summary of Grade 3-4 laboratory abnormalities is provided in Table 5.

Table 5 Grades 3-4 Laboratory Abnormalities Reported in ≥1% of Tenofovir Disoproxil Fumarate-Treated Subjects in Study 903 (0–144 Weeks)

	Tenofovir disoproxil fumarate + 3TC + EFV	d4T + 3TC + EFV
	N=299	N=301
Any ≥ Grade 3 Laboratory Abnormality	36%	42%
Fasting Cholesterol (>240 mg/dL)	19%	40%
Creatine Kinase (M: >990 U/L; F: >845 U/L)	12%	12%
Serum Amylase (>175 U/L)	9%	8%
AST (M: >180 U/L; F: >170 U/L)	5%	7%
ALT (M: >215 U/L; F: >170 U/L)	4%	5%
Hematuria (>100 RBC/HPF)	7%	7%
Neutrophils (<750/mm³)	3%	1%
Fasting Triglycerides (>750 mg/dL)	1%	9%

Study 934 - Treatment Emergent Adverse Reactions: In Study 934, 511 antiretroviral-naïve subjects received either tenofovir disoproxil fumarate + EMTRIVA® administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254). Adverse reactions observed in this trial were generally consistent with those seen in previous studies in treatment-experienced or treatment-naïve subjects (Table 6).

Changes in Bone Mineral Density:

In HIV-1 infected adult subjects in Study 903, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving tenofovir disoproxil fumarate + lamivudine + efavirenz (-2.2% ± 3.9) compared with subjects receiving stavudine + lamivudine + efavirenz (-1.0% ± 4.6) through 144 weeks. Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the tenofovir disoproxil fumarate group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the trial and this reduction was sustained through Week 144. Twenty-eight percent of tenofovir disoproxil fumarate-treated subjects vs. 21% of the stavudine-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the tenofovir disoproxil fumarate group and 6 subjects in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide) and higher serum parathyroid hormone levels and 1,25 Vitamin D levels in the tenofovir disoproxil fumarate group relative to the stavudine group; however, except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range *[See Warnings and Precautions (5.6)]*.

Table 6 Selected Treatment-Emergent Adverse Reactions[a] (Grades 2–4) Reported in ≥5% in Any Treatment Group in Study 934 (0–144 Weeks)

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

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

[b] From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of tenofovir disoproxil fumarate + EMTRIVA with efavirenz.

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

Laboratory Abnormalities: Laboratory abnormalities observed in this trial were generally consistent with those seen in previous trials (Table 7).

Table 7 Significant Laboratory Abnormalities Reported in ≥1% of Subjects in Any Treatment Group in Study 934 (0–144 Weeks)

	Tenofovir disoproxil fumarate[a] + FTC + EFV	AZT/ 3TC + EFV
	N=257	N=254
Any ≥ Grade 3 Laboratory Abnormality	30%	26%
Fasting Cholesterol (>240 mg/dL)	22%	24%
Creatine Kinase (M: >990 U/L; F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L, F: >170 U/L)	3%	3%
ALT (M: >215 U/L; F: >170 U/L)	2%	3%
Hemoglobin (<8.0 mg/dL)	0%	4%
Hyperglycemia (>250 mg/dL)	2%	1%
Hematuria (>75 RBC/HPF)	3%	2%
Glycosuria (≥3+)	<1%	1%
Neutrophils (<750/mm³)	3%	5%
Fasting Triglycerides (>750 mg/dL)	4%	2%

a. From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of tenofovir disoproxil fumarate + EMTRIVA with efavirenz.

Treatment-Experienced Patients

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

A summary of moderate to severe, treatment-emergent adverse reactions that occurred during the first 48 weeks of Study 907 is provided in Table 8.

Table 8 Selected Treatment-Emergent Adverse Reactions[a] (Grades 2–4) Reported in ≥3% in Any Treatment Group in Study 907 (0–48 Weeks)

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

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

b. Peripheral neuropathy includes peripheral neuritis and neuropathy.

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

Laboratory Abnormalities: Laboratory abnormalities observed in this trial occurred with similar frequency in the tenofovir disoproxil fumarate and placebo-treated groups. A summary of Grade 3-4 laboratory abnormalities is provided in Table 9.

Table 9 Grade 3-4 Laboratory Abnormalities Reported in ≥1% of Tenofovir Disoproxil Fumarate-Treated Subjects in Study 907 (0–48 Weeks)

	Tenofovir disoproxil fumarate (N=368) (Week 0–24)	Placebo (N=182) (Week 0-24)	Tenofovir disoproxil fumarate (N=368) (Week 0–48)	Placebo Crossover to tenofovir disoproxil fumarate (N=170) (Week 24–48)
Any ≥ Grade 3 Laboratory Abnormality	25%	38%	35%	34%
Triglycerides (>750 mg/dL)	8%	13%	11%	9%
Creatine Kinase (M: >990 U/L; F: >845 U/L)	7%	14%	12%	12%
Serum Amylase (>175 U/L)	6%	7%	7%	6%
Glycosuria (≥3+)	3%	3%	3%	2%
AST (M: >180 U/L; F: >170 U/L)	3%	3%	4%	5%
ALT (M: >215 U/L; F: >170 U/L)	2%	2%	4%	5%
Serum Glucose (>250 U/L)	2%	4%	3%	3%
Neutrophils (<750/mm³)	1%	1%	2%	1%

<u>*Clinical Trials in Pediatric Subjects 2 Years of Age and Older with HIV-1 Infection*</u>

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

Eighty-nine pediatric subjects (2 to less than 12 years of age) received tenofovir disoproxil fumarate in Study 352 for a median exposure of 104 weeks. of these, 4 subjects discontinued from the trial due to adverse reactions consistent with proximal renal tubulopathy. Three of these 4 subjects presented with hypophosphatemia and also had decreases in total body or spine BMD Z score *[See Warnings and Precautions (5.6)]*.

Changes in Bone Mineral Density:

Clinical trials in HIV-1 infected children and adolescents evaluated BMD changes. In Study 321 (12 to less than 18 years), the mean rate of BMD gain at Week 48 was less in the tenofovir disoproxil fumarate compared to the placebo treatment group. Six tenofovir disoproxil fumarate treated subjects and one placebo treated subject had significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline BMD Z-scores were -0.341 for lumbar spine and -0.458 for total body in the 28 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. In Study 352 (2 to less than 12 years), the mean rate of BMD gain in lumbar spine at Week 48 was similar between the tenofovir disoproxil fumarate and the d4T or AZT treatment groups. Total body BMD gain was less in the tenofovir disoproxil fumarate compared to the d4T or AZT treatment groups. One tenofovir disoproxil fumarate -treated subject and none of the d4T or AZT-treated subjects experienced significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline in BMD Z scores were -0.012 for lumbar spine and -0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. In both trials, skeletal growth (height) appeared to be unaffected *[See Warnings and Precautions (5.6)]*.

<u>*Clinical Trials in Adult Subjects with Chronic Hepatitis B and Compensated Liver Disease*</u>

Treatment-Emergent Adverse Reactions: In controlled clinical trials in 641 subjects with chronic hepatitis B (0102 and 0103), more subjects treated with tenofovir disoproxil fumarate during the 48-week double-blind period experienced nausea: 9% with tenofovir disoproxil fumarate versus 2% with HEPSERA. Other treatment-emergent adverse reactions reported in more than 5% of subjects treated with tenofovir disoproxil fumarate included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain and skin rash.

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

Laboratory Abnormalities: A summary of Grade 3-4 laboratory abnormalities through Week 48 is provided in Table 10. Grade 3-4 laboratory abnormalities were similar in subjects continuing tenofovir disoproxil fumarate treatment for up to 384 weeks in these trials.

Table 10 Grades 3-4 Laboratory Abnormalities Reported in ≥1% of Tenofovir Disoproxil Fumarate–Treated Subjects in Studies 0102 and 0103 (0-48 Weeks)

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

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

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

<u>*Clinical Trials in Adult Subjects with Chronic Hepatitis B and Decompensated Liver Disease*</u>

In a small randomized, double-blind, active-controlled trial (0108), subjects with CHB and decompensated liver disease received treatment with tenofovir disoproxil fumarate or other antiviral drugs for up to 48 weeks *[See Clinical Studies (14.2)]*. Among the 45 subjects receiving tenofovir disoproxil fumarate, the most frequently reported treatment-emergent adverse reactions of any severity were abdominal pain (22%), nausea (20%), insomnia (18%), pruritus (16%), vomiting (13%), dizziness (13%), and pyrexia (11%). Two of 45 (4%) subjects died through Week 48 of the trial due to progression of liver disease. Three of 45 (7%) subjects discontinued treatment due to an adverse event. Four of 45 (9%) subjects experienced a confirmed increase in serum creatinine of 0.5 mg dL (1 subject also had a confirmed serum phosphorus less than 2mg/dL through Week 48). Three of these subjects (each of whom had a Child-Pugh score greater than or equal to 10 and MELD score greater than or equal to 14 at entry) developed renal failure. Because both tenofovir disoproxil fumarate and decompensated liver disease may have an impact on renal function, the contribution of tenofovir disoproxil fumarate to renal impairment in this population is difficult to ascertain.

One of 45 subjects experienced as on-treatment hepatic flare during the 48 Week trial.

<u>*Clinical Trials in Pediatric Subjects 12 Years of Age and Older with Chronic Hepatitis B*</u>

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

In this study, both the tenofovir disoproxil fumarate and placebo treatment arms experienced an overall increase in mean lumbar spine BMD over 72 weeks, as expected for an adolescent population. The BMD gains from baseline to Week 72 in lumbar spine and total body BMD in tenofovir disoproxil fumarate-treated subjects (+5% and +3%, respectively) were less than the BMD gains observed in placebo-treated subjects (+8% and +5%, respectively). Three subjects in the tenofovir disoproxil fumarate group and two subjects in the placebo group had significant (greater than 4%) lumbar spine BMD loss at Week 72. At baseline, mean BMD Z-scores in subjects randomized to tenofovir disoproxil fumarate were −0.43 for lumbar spine and −0.20 for total body, and mean BMD Z-scores in subjects randomized to placebo were −0.28 for lumbar spine and −0.26 for total body. In subjects receiving tenofovir disoproxil fumarate for 72 weeks, the mean change in BMD Z-score was −0.05 for lumbar spine and −0.15 for total body compared to +0.07 and +0.06, respectively, in subjects receiving placebo. As observed in pediatric studies of HIV infected patients, skeletal growth (height) appeared to be unaffected [See Warnings and Precautions (5.6)].

6.2 Postmarketing Experience

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

Immune System Disorders
allergic reaction, including angiodema

Metabolism and Nutrition Disorders
lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, and Mediastinal Disorders
dyspnea

Gastrointestinal Disorders
pancreatitis, increased amylase, abdominal pain

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

Skin and Subcutaneous Tissue Disorders
rash

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

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

General Disorders and Administration Site Conditions
asthenia

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

7 DRUG INTERACTIONS

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

7.1 Didanosine

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

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

In patients weighing greater than 60 kg, the didanosine dose should be reduced to 250 mg once daily when it is coadministered with tenofovir disoproxil fumarate. In patients weighing less than 60 kg, the didanosine dose should be reduced to 200 mg once daily when it is coadministered with tenofovir disoproxil fumarate. When coadministered, tenofovir disoproxil fumarate and didanosine EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat). For additional information on coadministration of tenofovir disoproxil fumarate and didanosine, please refer to the full prescribing information for didanosine.

7.2 HIV-1 Protease Inhibitors

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

Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir coadministered with ritonavir have been shown to increase tenofovir concentrations *[See Clinical Pharmacology (12.3)]*. Tenofovir disoproxil fumarate is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters. When tenofovir disoproxil fumarate is co-administered with an inhibitor of these transporters, an increase in absorption may be observed. Patients receiving tenofovir disoproxil fumarate concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir should be monitored for tenofovir disoproxil fumarate -associated adverse reactions. Tenofovir disoproxil fumarate should be discontinued in patients who develop tenofovir disoproxil fumarate-associated adverse reactions.

7.3 Hepatitis C Antiviral Agents

Coadministration of tenofovir disoproxil fumarate and EPCLUSA® (sofosbuvir/velpatasvir) or HARVONI (ledipasvir/sofosbuvir) has been shown to increase tenofovir exposure *[See Clinical Pharmacology (12.3)]*.

In patients receiving Tenofovir disoproxil fumarate concomitantly with EPCLUSA, monitor for adverse reactions associated with tenofovir DF.

In patients receiving tenofovir disoproxil fumarate concomitantly with HARVONI without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, monitor for adverse reactions associated with tenofovir disoproxil fumarate.

In patients receiving tenofovir disoproxil fumarate concomitantly with HARVONI and an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, consider an alternative HCV or antiretroviral therapy, as the safety of increased tenofovir concentrations in this setting has not been established. If coadministration is necessary, monitor for adverse reactions associated with tenofovir disoproxil fumarate.

7.4 Drugs Affecting Renal Function

Since tenofovir is primarily eliminated by the kidneys *[See Clinical Pharmacology (12.3)]*, coadministration of tenofovir disoproxil fumarate with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[See Warnings and Precautions (5.2)]*.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, tenofovir disoproxil fumarate should be used during pregnancy only if clearly needed.

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

Risk Summary
Animal Data
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.

8.3 Nursing Mothers

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1. Samples of breast milk obtained from five HIV-1 infected mothers in the first post-partum week show that tenofovir is secreted in human milk. The impact of this exposure in breastfed infants is unknown. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving tenofovir disoproxil fumarate.

8.4 Pediatric Use

Pediatric Patients 2 Years of Age and Older with HIV-1 infection

The safety of tenofovir disoproxil fumarate in pediatric patients aged 2 to less than 18 years is supported by data from two randomized trials in which tenofovir disoproxil fumarate was administered to HIV-1 infected treatment-experienced subjects. In addition, the pharmacokinetic profile of tenofovir in patients 2 to less than 18 years of age at the recommended doses was similar to that found to be safe and effective in adult clinical trials *[See Clinical Pharmacology (12.3)]*.

In Study 352, 92 treatment-experienced subjects 2 to less than 12 years of age with stable, virologic suppression on stavudine-or zidovudine-containing regimen were randomized to either replace stavudine or zidovudine with tenofovir disoproxil fumarate (N=44) or continue their original regimen (N=48) for 48 weeks. Five additional subjects over the age of 12 were enrolled and randomized (Tenofovir disoproxil fumarate N=4, original regimen N=1) but are not included in the efficacy analysis. After 48 weeks, all eligible subjects were allowed to continue in the study receiving open-label tenofovir disoproxil fumarate. At Week 48, 89% of subjects in the tenofovir disoproxil fumarate treatment group and 90% of subjects in the stavudine or zidovudine treatment group had HIV-1 RNA concentrations less than 400 copies/mL. During the 48 week randomized phase of the study, 1 subject in the tenofovir disoproxil fumarate group discontinued the study prematurely because of virologic failure/lack of efficacy and 3 subjects (2 subjects in the tenofovir disoproxil fumarate group and 1 subject in the stavudine or zidovudine group) discontinued for other reasons.

In Study 321, 87 treatment-experienced subjects 12 to less than 18 years of age were treated with tenofovir disoproxil fumarate (N=45) or placebo (N=42) in combination with an optimized background regimen (OBR) for 48 weeks. The mean baseline CD4 cell count was 374 cells/mm³ and the mean baseline plasma HIV-1 RNA was 4.6 log10 copies/mL. At baseline, 90% of subjects harbored NRTI resistance-associated substitutions in their HIV-1 isolates. Overall, the trial failed to show a difference in virologic response between the tenofovir disoproxil fumarate and placebo treatment groups. Subgroup analyses suggest the lack of difference in virologic response may be attributable to imbalances between treatment arms in baseline viral susceptibility to tenofovir disoproxil fumarate and OBR.

Although changes in HIV-1 RNA in these highly treatment-experienced subjects were less than anticipated, the comparability of the pharmacokinetic and safety data to that observed in adults supports the use of tenofovir disoproxil fumarate in pediatric patients 12 years of age and older who weigh greater than or equal to 35 kg and whose HIV-1 isolate is expected to be sensitive to tenofovir disoproxil fumarate. *[See Warnings and Precautions (5.6), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)]*.

Safety and effectiveness of tenofovir disoproxil fumarate in pediatric patients younger than 2 years of age with HIV-1 infection have not been established.

PATIENT INFORMATION

Tenofovir Disoproxil Fumarate Tablets

(ten of' oh vir)

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

What is the most important information I should know about tenofovir disoproxil fumarate tablets?

Tenofovir disoproxil fumarate tablets can cause serious side effects, including:

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

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

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

What is tenofovir disoproxil fumarate tablet?

Tenofovir disoproxil fumarate tablet is a prescription medicine used:

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

2. to treat chronic (long-lasting) hepatitis B virus (HBV) in people 12 years of age and older.
- Tenofovir disoproxil fumarate will not cure HBV.
- Tenofovir disoproxil fumarate may lower the amount of HBV in your body.
- Tenofovir disoproxil fumarate may improve the condition of your liver.
- The long-term effects of taking tenofovir disoproxil fumarate for treatment of chronic hepatitis B infection are not known.
- It is not known if tenofovir disoproxil fumarate is safe and effective for treatment of chronic hepatitis B in children under the age of 12 years.

What should I tell my healthcare provider before taking tenofovir disoproxil fumarate tablet?

Before you take tenofovir disoproxil fumarate tablet, tell your healthcare provider if you:

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

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

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

Tenofovir disoproxil fumarate tablet may affect the way other medicines work, and other medicines may affect how tenofovir disoproxil fumarate tablet works.

Do not take tenofovir disoproxil fumarate tablet if you also take:

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

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

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

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

How should I take tenofovir disoproxil fumarate tablet?

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

670 mm x 500 mm

ARTWORK DETAIL LABEL

7377

Product	Tenofovir Disoproxil Fumarate Tablets 300mg		
Buyer/Country	STRIDES PHARMA INC - US	Component	Out sert with medication guide
Dimension	670 x 500 mm with Perforation as indicated.	Pack	NA
New Item Code	1035924	Old Item Code	NA
Colour Shades	Black	No. of Colours	1

Change Control No.	NA	Artwork Version	1.0
Design/Style	Front & Back Printing. Booklet Form. (Folded size: 35 x 38 mm [±1 mm]). To be supplied in the folded Booklet form with pasting.		
Substrate	30 GSM Bible Paper		
Special Instructions	PRINTING CLARITY TO BE CLEAR AND SHARP.		
Autocartonator Requirements	NA		

Caution to the printer: Before processing, please ensure that the ARTWORK received for printing is exactly in line with APPROVED ARTWORK provided to you. In case of any FONTS/DESIGN are Mis-matching with the APPROVED ARTWORK, please inform PDC for further action. **DO NOT MAKE ANY CHANGE TO THE ARTWORK WITHOUT WRITTEN INSTRUCTIONS FROM PDC.**

RD/PD/003/F-08/R0

What are the possible side effects of tenofovir disoproxil fumarate tablet?

Tenofovir disoproxil fumarate tablet may cause serious side effects, including:

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

The most common side effects in all people who take tenofovir disoproxil fumarate are:

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

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

- sleeping problems
- itching
- vomiting
- dizziness
- fever

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

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

Call your doctor for medical advice about side effects. You may report side effects to Strides Pharma Inc at 1877-244-9825 or FDA at 1-800-FDA-1088.

How should I store tenofovir disoproxil fumarate tablet?

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

Keep tenofovir disoproxil fumarate tablet and all medicines out of the reach of children.

General information about tenofovir disoproxil fumarate tablet:

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

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

- **Do not share or re-use needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection**. Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

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

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

You may report side effects to Strides Pharma Inc. at 1-877-244-9825 or go to www. stridesshasun.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

What are the ingredients in tenofovir disoproxil fumarate tablet?

Active Ingredient: tenofovir disoproxil fumarate

Inactive Ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The tablets are coated with **Opadry White Y-1-7000**, which contains Hypromellose, Titanium dioxide USP & Polyethylene glycol 400 (Macrogol) USP.

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

Manufactured by:
Strides Shasun Limited
Bengaluru, India

Distributed by:
Strides Pharma Inc.
East Brunswick, NJ 08816

Revised: 12/2017

1035924

[illegible]

670 mm x 500 mm

ARTWORK DETAIL LABEL

7378

Product	**Tenofovir Disoproxil Fumarate Tablets 300mg**		
Buyer/Country	STRIDES PHARMA INC - US	Component	Out sert with medication guide
Dimension	**670 x 500 mm with Perforation as indicated.**	Pack	NA
New Item Code	**1035924**	Old Item Code	NA
Colour Shades	Black	No. of Colours	1

Change Control No.	NA	Artwork Version	1.0
Design/Style	Front & Back Printing. Booklet Form. (Folded size: 35 x 38 mm [±1 mm]). To be supplied in the folded Booklet form with pasting.		
Substrate	30 GSM Bible Paper		
Special Instructions	PRINTING CLARITY TO BE CLEAR AND SHARP.		
Autocartonator Requirements	**NA**		

Caution to the printer: Before processing, please ensure that the ARTWORK received for printing is exactly in line with APPROVED ARTWORK provided to you. In case of any FONTS/DESIGN are Mis-matching with the APPROVED ARTWORK, please inform PDC for further action. **DO NOT MAKE ANY CHANGE TO THE ARTWORK WITHOUT WRITTEN INSTRUCTIONS FROM PDC.**

RD/PD/003/F-08/R0