HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use lamivudine and tenofovir disoproxil fumarate safely and effectively. See full prescribing information for lamivudine and tenofovir disoproxil fumarate tablets.

Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 300 mg/300 mg

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATONS OF HEPATITIS B

See full prescribing information for complete boxed warning.

- **Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues including lamivudine and tenofovir disoproxil fumarate. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.1)**
- **Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine and tenofovir disoproxil fumarate. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)**

----------INDICATIONS AND USAGE----------
Lamivudine and Tenofovir Disoproxil Fumarate Tablets, a combination of lamivudine and tenofovir disoproxil fumarate, both nucleo(t)side analog HIV-1 reverse transcriptase inhibitors, are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older and weighing at least 35 kg. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dose: One tablet (containing 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally on an empty stomach. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Lactic acidosis and severe hepatomegaly with steatosis: Reported with the use of nucleoside analogues. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.1)
- Severe acute exacerbations of hepatitis B: Reported in patients who are co-infected with hepatitis B virus and HIV-1 and have discontinued lamivudine or tenofovir disoproxil fumarate. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)
- Coadministration with Other Products: Do not use with other lamivudine- or tenofovir-containing products or emtricitabine-containing products. Do not administer in combination with adefovir dipivoxil. (5.3)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon and ribavirin-based regimens. Monitor for treatment-associated toxicities. Discontinue lamivudine and tenofovir disoproxil fumarate tablets, as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue lamivudine and tenofovir disoproxil fumarate tablets as clinically appropriate. (5.5)
- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess creatinine clearance (CrCl) before initiating treatment with tenofovir disoproxil fumarate, a component of lamivudine and tenofovir disoproxil fumarate tablets. Monitor CrCl and serum phosphorus in patients at risk. Avoid administering lamivudine and tenofovir disoproxil fumarate with concurrent or recent use of nephrotoxic drugs. (5.6)
- Decreases in bone mineral density (BMD): Observed in HIV-infected patients. Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss. (5.7)
- Immune reconstitution syndrome: Observed in HIV-infected patients. May necessitate further evaluation and treatment. (5.8)
- Redistribution/accumulation of body fat: Observed in HIV-infected patients receiving antiretroviral combination therapy. (5.9)
- Triple nucleoside-only regimens: Early virologic failure has been reported in HIV-infected patients. Monitor carefully and consider treatment modification. (5.10)

----------ADVERSE REACTIONS----------
- Most common adverse reactions are headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, rash, pain, depression, asthenia, and cough. (6)

To report SUSPECTED ADVERSE REACTIONS, contact AB Pharmaceuticals LLC on behalf of Macleods Pharmaceuticals Limited at 1-888-825-5249 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) when coadministered. Consider dose reductions or discontinuations of didanosine if warranted. (7. 4)
- Atazanavir: Coadministration decreases atazanavir

concentrations and increases tenofovir concentrations. Use atazanavir with lamivudine and tenofovir disoproxil fumarate only with ritonavir; monitor for evidence of tenofovir toxicity. (7. 5)

- Lopinavir/ritonavir: Coadministration increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity. (7. 6)

----------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: March 2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATIONS OF HEPATITIS B

Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues including lamivudine and tenofovir disoproxil fumarate. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur *[See Warnings and Precautions (5.1)]*.

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine and tenofovir disoproxil fumarate. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment *[See Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

Lamivudine and tenofovir disoproxil fumarate tablets, a combination of lamivudine and tenofovir disoproxil fumarate, are indicated in combination with other antiretrovirals for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older and weighing at least 35 kg.

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

- Lamivudine and tenofovir disoproxil fumarate tablets should not be used in combination with ATRIPLA® (efavirenz, emtricitabine, and tenofovir disoproxil fumarate), EMTRIVA® (emtricitabine), TRUVADA® (emtricitabine and tenofovir disoproxil fumarate), VIREAD® (tenofovir disoproxil fumarate), HEPSERA® (adefovir dipivoxil) or lamivudine-containing products including EPIVIR® (lamivudine), EPIVIR-HBV® (lamivudine), COMBIVIR® (lamivudine/zidovudine), EPZICOM® (abacavir sulfate and lamivudine), TRIZIVIR® (abacavir sulfate, lamivudine, and zidovudine), and COMPLERA® (rilpivirine/emtricitabine/tenofovir) *[See Warnings and Precautions (5.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose in Adults and Pediatric Patients (12 Years of Age and Older and Greater than or Equal to 35 kg)

The dose of lamivudine and tenofovir disoproxil fumarate tablets containing 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil) is one tablet per day taken orally on an empty stomach.

2.2 Dose Adjustment for Renal Impairment

Because lamivudine and tenofovir disoproxil fumarate tablets are a fixed-dose combination tablet, it is not recommended for patients with impaired renal function (creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis.

3 DOSAGE FORMS AND STRENGTHS

Lamivudine and Tenofovir disoproxil fumarate film-coated Tablets contain 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate which is equivalent to 245 mg of tenofovir disoproxil. White to off-white colored, capsule shaped, biconvex, film coated tablets debossed “CL 71” on one side of the tablet and plain on the other side.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis/Severe Hepatomegaly With Steatosis
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including lamivudine and tenofovir disoproxil fumarate, components of lamivudine and tenofovir disoproxil fumarate tablets, in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with lamivudine and 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).

5.2 Patients Coinfected with HIV-1 and HBV
It is recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. Discontinuation of anti-HBV therapy, including lamivudine and tenofovir disoproxil fumarate, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue lamivudine and 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.

Important Differences Among Lamivudine-Containing Products: Lamivudine Tablets contain a higher dose of the same active ingredient (lamivudine) than EPIVIR-HBV Tablets. EPIVIR-HBV was developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine in EPIVIR-HBV are not appropriate for patients co-infected with HIV-1 and HBV. Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV.

If treatment with EPIVIR-HBV or tenofovir disoproxil fumarate-containing product such as VIREAD is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV-1 infection, rapid emergence of HIV-1 resistance is likely to result because of the subtherapeutic dose and the inappropriateness of monotherapy HIV-1 treatment.

Emergence of Lamivudine-Resistant HBV: In non-HIV-l-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see full prescribing information for EPIVIR-HBV for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus

5.3 Coadministration with Other Products
Lamivudine and tenofovir disoproxil fumarate tablets are a fixed dose combination product of lamivudine and tenofovir disoproxil fumarate. Lamivudine and tenofovir disoproxil fumarate

tablets should not be coadministered comcomitantly with other lamivudine-containing, tenofovir-containing, or emtricitabine-containing drugs, including COMBIVIR® (lamivudine/zidovudine), EPIVIR® or EPIVIR-HBV® (lamivudine), EPZICOM® (abacavir sulfate/lamivudine), TRIZIVIR® (abacavir sulfate/lamivudine/zidovudine), EMTRIVA® (emtricitabine), TRUVADA® (emtricitabine/tenofovir disoproxil fumarate), VIREAD (tenofovir disoproxil fumarate), ATRIPLA® (emtricitabine/efavirenz/tenofovir disoproxil fumarate) or COMPLERA® (rilpivirine/emtricitabine/tenofovir).

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

5.4 Use With Interferon- and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine, a component of lamivudine and tenofovir disoproxil fumarate tablets. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients *[see Clinical Pharmacology (12.3)]*, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of lamivudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh >6). See the complete prescribing information for interferon and ribavirin.

5.5 Pancreatitis

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine, a component of lamivudine and tenofovir disoproxil fumarate tablets, should be used with caution. Treatment with lamivudine and tenofovir disoproxil fumarate tablets should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur *[see Adverse Reactions (6.1)]*.

5.6 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, a component of lamivudine and tenofovir disoproxil fumarate tablets *[See Adverse Reactions (6.2)]*.

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with tenofovir disoproxil fumarate, a component of lamivudine and tenofovir disoproxil fumarate tablets. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment, including patients who have previously experienced renal events while receiving HEPSERA® (adefovir dipivoxil).

Tenofovir disoproxil fumarate, a component of lamivudine and tenofovir disoproxil fumarate tablets should be avoided with concurrent or recent use of a nephrotoxic agent.

5.7 Decreases in Bone Mineral Density

Assessment of bone mineral density (BMD) should be considered for adults and pediatric patients 12 years of age and older 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.

In HIV-1 infected adult subjects treated with tenofovir disoproxil fumarate, a component of lamivudine and tenofovir disoproxil fumarate tablets, in Study 903 through 144 weeks, decreases from baseline in BMD were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving tenofovir disoproxil fumarate + lamivudine + efavirenz (-2.2% ± 3.9) compared with subjects receiving stavudine + lamivudine + efavirenz (-1.0% ± 4.6). Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the 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 to 48 weeks of the study 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) in the tenofovir disoproxil fumarate group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1, 25 Vitamin D levels were also higher in the tenofovir disoproxil fumarate group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range.

In a clinical study of HIV-1 infected pediatric subjects 12 years of age and older (Study 321), bone effects were similar to adult subjects. Under normal circumstances BMD increases rapidly in this age group. In this study, the mean rate of bone gain was less in the tenofovir disoproxil fumarate-treated group compared to the placebo group. Six tenofovir disoproxil fumarate treated subjects and one placebo treated subject had significant (greater than 4%) lumbar spine BMD loss at 48 weeks. Among 28 subjects receiving 96 weeks of tenofovir disoproxil fumarate, Z-scores declined by -0.341 for lumbar spine and -0.458 for total body. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in tenofovir disoproxil fumarate-treated pediatric subjects 12 years of age and older suggest increased bone turnover, consistent with the effects observed in adults.

The effects of tenofovir disoproxil fumarate-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

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

The bone effects of tenofovir disoproxil fumarate have not been studied in patients with chronic HBV infection.

5.8 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including lamivudine and 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-Barre 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.

5.9 Fat Redistribution

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

5.10 Early Virologic Failure

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

6 ADVERSE REACTIONS

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

- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[See Boxed Warning, Warnings and Precautions (5.1)]*.
- Severe Acute Exacerbations of Hepatitis B *[See Boxed Warning, Warnings and Precautions (5.2)]*.
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C *[See Warnings and Precautions (5.4)]*.
- Pancreatitis *[See Warnings and Precautions (5.5)]*.
- New Onset or Worsening Renal Impairment *[See Warnings and Precautions (5.6)]*.
- Decreases in Bone Mineral Density *[See Warnings and Precautions (5.6)]*.
- Immune Reconstitution Syndrome *[See Warnings and Precautions (5.7)]*.

6.1 Clinical Trials Experience

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

Lamivudine

Clinical Trials in Adult Patients with HIV-1 infection: The safety profile of lamivudine in

adults is primarily based on 3,568 HIV-1-infected patients in 7 clinical trials.

The most common adverse reactions are headache, nausea, malaise, fatigue, nasal signs and symptoms, diarrhea and cough.

Pancreatitis: Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who received EPIVIR in the controlled clinical trials EPV20001, NUCA3001, NUCB3001, NUCA3002, NUCB3002, and NUCB3007 *[see Warnings and Precautions (5.5)]*.

Lamivudine 300 mg Once Daily: The types and frequencies of clinical adverse reactions reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) for 48 weeks were similar.

The frequencies of selected laboratory abnormalities reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) were similar.

Pediatric Patients – Clinical Trials in HIV-1: Lamivudine Oral Solution has been studied in 638 pediatric patients 3 months to 18 years of age in 3 clinical trials.

Selected clinical adverse reactions and physical findings with a ≥5% frequency during therapy with lamivudine 4 mg/kg twice daily plus zidovudine 160 mg/m^2 3 times daily in therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 1.

Table 1. Selected Clinical Adverse Reactions and Physical Findings (≥5% Frequency) in Pediatric Patients in Study ACTG300

Adverse Reaction	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
Body as a Whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
Respiratory		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
Ear, Nose, and Throat		
Signs or symptoms of ears[a]	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

[a] Includes pain, discharge, erythema, or swelling of an ear.

Pancreatitis: Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric patients receiving lamivudine alone or in combination with other antiretroviral agents. In an open-label dose-escalation study (A2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with lamivudine. Three of these patients died of complications of pancreatitis. In a second open-label study

(A2005), 12 patients (18%) developed pancreatitis. In Study ACTG300, pancreatitis was not observed in 236 patients randomized to lamivudine plus zidovudine. Pancreatitis was observed in 1 patient in this study who received open-label lamivudine in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy *[see Warnings and Precautions (5.5)]*.

Paresthesias and Peripheral Neuropathies: Paresthesias and peripheral neuropathies were reported in 15 patients (15%) in Study A2002, 6 patients (9%) in Study A2005, and 2 patients (<1%) in Study ACTG300.

Selected laboratory abnormalities experienced by therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 2.

Table 2. Frequencies of Selected Grade 3-4 Laboratory Abnormalities in Pediatric Patients in Study ACTG300

Test (Threshold Level)	Lamivudine plus Zidovudine	Didanosine
Absolute neutrophil count (<400/mm^3)	8%	3%
Hemoglobin (<7.0 g/dL)	4%	2%
Platelets (<50,000/mm^3)	1%	3%
ALT (>10 x ULN)	1%	3%
AST (>10 x ULN)	2%	4%
Lipase (>2.5 x ULN)	3%	3%
Total Amylase (>2.5 x ULN)	3%	3%

ULN = Upper limit of normal.

Tenofovir Disoproxil Fumarate

Clinical Trials in Adult Patients with HIV-1 Infection

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 studies. 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 studies.

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

Treatment-Naïve Patients
Study 903 - Treatment-Emergent Adverse Reactions: The most common adverse reactions seen in a double-blind comparative controlled study in which 600 treatment-naïve subjects received 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 3.

Table 3 Selected Treatment-Emergent Adverse Reactions[a] (Grades 2 to 4) Reported in ≥5% in Any Treatment Group in Study 903 (0 to 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 study occurred with similar frequency in the tenofovir disoproxil fumarate and stavudine treatment arms. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 4.

Table 4 Grade 3/4 Laboratory Abnormalities Reported in ≥1% of Tenofovir Disoproxil Fumarate-Treated 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/mm^3)	3%	1%
Fasting Triglycerides (>750 mg/dL)	1%	9%

Study 934 - Treatment Emergent Adverse Reactions: In Study 934, 511 antiretroviral-naïve subjects received either tenofovir disoproxil fumarate + emtricitabine administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254). Adverse reactions observed in this study were generally consistent with those seen in previous studies in treatment-experienced or treatment-naïve subjects (Table 5).

Table 5 Selected Treatment-Emergent Adverse Reactions[a] (Grades 2 to 4) Reported in ≥5% in Any Treatment Group in Study 934 (0 to 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 study, subjects received TRUVADA (emtricitabine/tenofovir disoproxil fumarate) with efavirenz in place of tenofovir disoproxil fumarate + emtricitabine with efavirenz.

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

Laboratory Abnormalities: Laboratory abnormalities observed in this study were generally consistent with those seen in previous studies (Table 6).

Table 6 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/mm^3)	3%	5%
Fasting Triglycerides (>750 mg/dL)	4%	2%

[a.] From Weeks 96 to 144 of the study, subjects received TRUVADA (emtricitabine/tenofovir disoproxil fumarate) with efavirenz in place of tenofovir disoproxil fumarate + emtricitabine with efavirenz.

Treatment-Experienced Patients

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

A summary of moderate to severe, treatment-emergent adverse reactions that occurred during the first 48 weeks of Study 907 is provided in Table 7.

Table 7 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 study occurred with similar frequency in the tenofovir disoproxil fumarate and placebo-treated groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 8.

Table 8 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/mm^3)	1%	1%	2%	1%

Clinical Trials in Pediatric Subjects 12 Years of Age and Older with HIV-1 Infection

Assessment of adverse reactions is based on one randomized trial (Study 321) in 87 HIV-1 infected pediatric subjects (12 to less than 18 years of age) who received treatment with VIREAD (N=45) or placebo (N=42) 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.

6.2 Postmarketing Experience

Lamivudine

The following adverse reactions have been reported during postmarketing use of lamivudine. Because these reactions are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine and tenofovir DF.

Body as a Whole: Redistribution/accumulation of body fat *[see Warnings and Precautions (5.9)]*.
Endocrine and Metabolic: Hyperglycemia.

General: Weakness.

Hemic and Lymphatic: Anemia (including pure red cell aplasia and severe anemias progressing on therapy).

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, posttreatment exacerbation of hepatitis B *[see Boxed Warning, Warnings and Precautions (5.1, 5.2)]*.

Hypersensitivity: Anaphylaxis, urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Skin: Alopecia, pruritus.

Tenofovir Disoproxil Fumarate

Immune System Disorders: Allergic reaction, including angioedema

Metabolism and Nutrition Disorders: Lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, and Mediastinal Disorders: Dyspnea

Gastrointestinal Disorders: Pancreatitis, increased amylase, abdominal pain

Renal and Urinary Disorders: Renal insufficiency, 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 *[see Warnings and Precautions (5.6)]*.

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

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

No drug interaction studies have been conducted using lamivudine and tenofovir disoproxil fumarate tablets. Drug interaction studies have been conducted with lamivudine and tenofovir disoproxil fumarate, the components of lamivudine and tenofovir disoproxil fumarate tablets *[see Clinical Pharmacology (12.3)]*.

Lamivudine

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim).

No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

7.1 Interferon- and Ribavirin-Based Regimens

Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3)]*.

7.2 Trimethoprim/Sulfamethoxazole (TMP/SMX)

No change in dose of either drug is recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat PCP.

7.3 Drugs with No Observed Interactions with Lamivudine

A drug interaction study showed no clinically significant interaction between lamivudine and zidovudine.

Tenofovir Disoproxil Fumarate

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

In patients weighing greater than 60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with tenofovir DF. Data are not available to recommend a dose adjustment of didanosine for adults or pediatric patients weighing less than 60 kg. When coadministered, tenofovir disoproxil fumarate and didanosine enteric coated capsule may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with tenofovir disoproxil fumarate should be under fasted conditions.

7.5 Atazanavir

Atazanavir has been shown to increase tenofovir concentrations *[See Clinical Pharmacology (12.3)]*. The mechanism of this interaction is unknown. Patients receiving atazanavir and tenofovir disoproxil fumarate 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.

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. Atazanavir without ritonavir should not be coadministered with tenofovir disoproxil fumarate.

7.6 Lopinavir/Ritonavir

Lopinavir/ritonavir has been shown to increase tenofovir concentrations *[See Clinical Pharmacology (12.3)]*. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir and tenofovir disoproxil fumarate 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.

7.7 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, and valganciclovir. Drugs that decrease renal function may also increase serum concentrations of tenofovir.

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

8 USE IN SPECIFIC POPULATION

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to lamivudine and tenofovir tablets during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Lamivudine and Tenofovir Disoproxil Fumarate

Lamivudine is classified under category C. Tenofovir disoproxil fumarate is classified under category B. There are no adequate and well-controlled studies of the combination of lamivudine and tenofovir disoproxil fumarate in pregnant women. Lamivudine and tenofovir disoproxil fumarate tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lamivudine: Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical studies conducted in South Africa. The study assessed pharmacokinetics in 16

women at 36 weeks gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation using lamivudine 300 mg twice daily without other antiretrovirals. These studies were not designed or powered to provide efficacy information.

Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, lamivudine amniotic fluid specimens were collected following natural rupture of membranes. Amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg/mL (150 mg twice daily) and 2.1 to 5.2 mcg/mL (300 mg twice daily). It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared with other HIV-1-infected patients.

Animal reproduction studies performed at oral doses up to 130 and 60 times the adult dose in rats and rabbits, respectively, revealed no evidence of teratogenicity due to lamivudine. Increased early embryolethality occurred in rabbits at exposure levels similar to those in humans. However, there was no indication of this effect in rats at exposure levels up to 35 times those in humans. Based on animal studies, lamivudine crosses the placenta and is transferred to the fetus *[see Nonclinical Toxicology (13.2)]*.

Tenofovir Disoproxil Fumarate: 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.

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
The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Because of both the potential for HIV-1 transmission and serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving lamivudine and tenofovir disoproxil fumarate.

Lamivudine: Lamivudine is excreted into human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Tenofovir Disoproxil Fumarate: Samples of breast milk obtained from five HIV-1 infected mothers in the first post-partum week show that tenofovir is excreted in human milk at low levels. The impact of this exposure in breastfed infants is unknown.

8.4 Pediatric Use
Lamivudine and tenofovir disoproxil fumarate tablets are not recommended in patients less

than 12 years of age weighing less than 35 kg (77 lb) because it is a fixed dose combination formulation containing a component, tenofovir disoproxil fumarate, for which safety and efficacy have not been established in this age group.

8.5 Geriatric Use

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

8.6 Patients with impaired renal function

Lamivudine and tenofovir disoproxil fumarate tablets are not recommended for patients with impaired renal function (i.e., creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis because it is a fixed-dose combination formulation that cannot be adjusted.

10 OVERDOSAGE

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

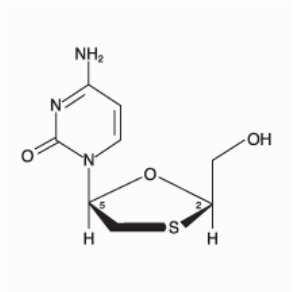
Lamivudine: There is no known antidote for lamivudine. One case of an adult ingesting 6 grams of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

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

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

11 DESCRIPTION

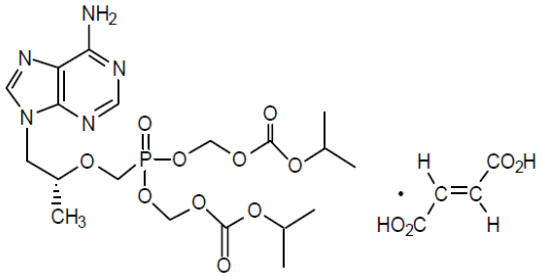
Lamivudine: The chemical name of lamivudine is (□-)-1-[(2R, 5S)-2-(Hydroxymethyl)-1, 3-oxathiolan-5-yl] _cytosine. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2′,3′-dideoxy, 3′-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3. Lamivudine has the following structural formula:



Tenofovir: Tenofovir disoproxil fumarate (a prodrug of tenofovir) is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. Tenofovir disoproxil fumarate is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate.

The chemical name is Bis (hydroxymethyl) [[(R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy] methyl] phosphonate, bis (isopropyl carbonate) (ester), fumarate (1:1); fumarate (1:1).

Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in distilled water at 25°C. It has an octanol/phosphate buffer (pH 6.5) partition coefficient (log p) of 1.25 at 25 °C. The molecular formula is $C_{19}H_{30}N_5O_{10}P.C_4H_4O_4$ and molecular weight is 635.51. Tenofovir has the following structural formula:



Each tablet contains 300 mg Lamivudine and 300 mg of Tenofovir Disoproxil Fumarate, which is equivalent to 245 mg of tenofovir disoproxil, and the following inactive ingredients: croscarmellose sodium, magnesium stearate and microcrystalline cellulose.. The tablets are coated with Opadry II White 30K580000, which contains hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide, and triacetin. In this insert, all dosages are expressed in terms of Tenofovir Disoproxil Fumarate except where otherwise noted.

12 CLINICAL PHARMACOLOGY

For additional information on Mechanism of Action, Antiviral Activity, Resistance and Cross Resistance, please consult the lamivudine and tenofovir disoproxil fumarate prescribing information.

12.1 Mechanism of Action

Lamivudine and Tenofovir Disoproxil Fumarate Tablets are a fixed dose combination of antiviral drugs lamivudine and tenofovir disoproxil fumarate *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

Pharmacokinetics in Adults

Lamivudine and tenofovir disoproxil fumarate from the combination tablets (300 mg/300 mg) were bioequivalent to that from EPIVIR Tablets and VIREAD Tablets respectively, when administered to healthy volunteers under fasting conditions.

Lamivudine:
The steady-state pharmacokinetics properties of the lamivudine 300-mg tablet once daily for 7 days compared with the lamivudine 150-mg tablet twice daily for 7 days were assessed in a crossover study in 60 healthy volunteers. Lamivudine 300 mg once daily resulted in lamivudine exposures that were similar to lamivudine 150 mg twice daily with respect to plasma $AUC_{24,.ss}$; however, $C_{max,ss}$ was 66% higher and the trough value was 53% lower compared with the 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to $AUC_{24,ss}$ and $C_{max24,ss}$; however, trough values were lower compared with the 150-mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations. The clinical significance of observed differences for both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations is not known.

Absorption and Bioavailability: Lamivudine was rapidly absorbed after oral administration in HIV-1-infected patients. Absolute bioavailability in 12 adult patients was 86% ± 16% (mean ± SD) for the 150-mg tablet and 87% ± 13% for the oral solution. After oral administration of 2 mg/kg twice a day to 9 adults with HIV-1, the peak serum lamivudine concentration (C_{max}) was 1.5 ± 0.5 mcg/mL (mean ± SD). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to oral dose over the range from 0.25 to 10 mg/kg.

The accumulation ratio of lamivudine in HIV-1-positive asymptomatic adults with normal renal function was 1.50 following 15 days of oral administration of 2 mg/kg twice daily.

Distribution: The apparent volume of distribution after IV administration of lamivudine to 20 patients was 1.3 ± 0.4 L/kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight.

Binding of lamivudine to human plasma proteins is low (<36%). *In vitro* studies showed that over the concentration range of 0.1 to 100 mcg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

Metabolism: Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose of lamivudine in 6 HIV-l-infected adults, 5.2% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite have not been determined.

Elimination: The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300-mg oral dose of lamivudine, renal clearance was 199.7 ± 56.9 mL/min (mean ± SD). In 20 HIV-l-infected patients given a single IV dose, renal clearance was 280.4 ± 75.2 mL/min (mean ± SD), representing 71% ± 16% (mean ± SD) of total clearance of lamivudine.

In most single-dose studies in HIV-1-infected patients, HBV-infected patients, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to 7 hours. In HIV-1-infected patients, total clearance was 398.5 ± 69.1 mL/min (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range from 0.25 to 10 mg/kg.

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

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

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

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

Metabolism and Elimination: In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP enzymes.

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

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

Effect of Food on Absorption of Lamivudine and Tenofovir Disoproxil Fumarate Tablets: The effect of food on lamivudine and tenofovir disoproxil fumarate tablets was not determined; therefore, this product must be administered on an empty stomach.

Special Populations

Race

Lamivudine: There are no significant racial differences in lamivudine pharmacokinetics.

Tenofovir Disoproxil Fumarate: There were insufficient numbers from racial and ethnic

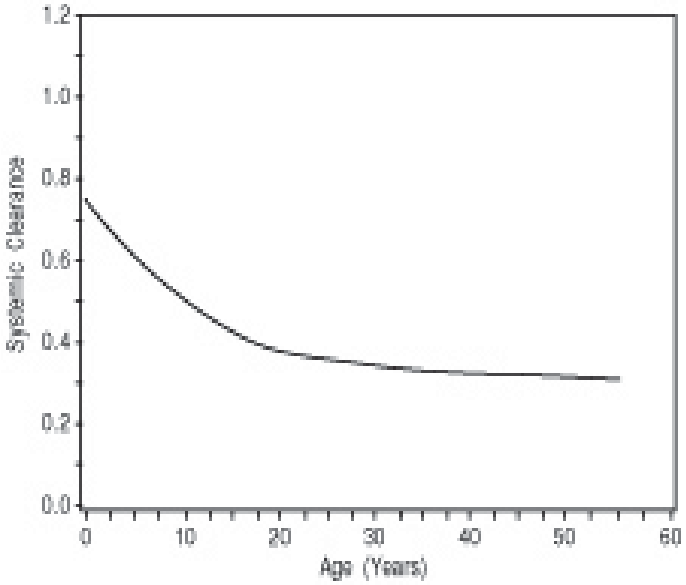
groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations.

Pediatric Patients:

Lamivudine: In Study NUCA2002, pharmacokinetic properties of lamivudine were assessed in a subset of 57 HIV-1-infected pediatric patients (age range: 4.8 months to 16 years, weight range: 5 to 66 kg) after oral and IV administration of 1, 2, 4, 8, 12, and 20 mg/kg/day. In the 9 infants and children (range: 5 months to 12 years of age) receiving oral solution 4 mg/kg twice daily (the usual recommended pediatric dose), absolute bioavailability was 66% ± 26% (mean ± SD), which was less than the 86% ± 16% (mean ± SD) observed in adults. The mechanism for the diminished absolute bioavailability of lamivudine in infants and children is unknown.

Systemic clearance decreased with increasing age in pediatric patients, as shown in Figure 1.

Figure 1. Systemic Clearance (L/hr•kg) of Lamivudine in Relation to Age



After oral administration of lamivudine 4 mg/kg twice daily to 11 pediatric patients ranging from 4 months to 14 years of age, C_{max} was 1.1 ± 0.6 mcg/mL and half-life was 2.0 ± 0.6 hours. (In adults with similar blood sampling, the half-life was 3.7 ± 1 hours.) Total exposure to lamivudine, as reflected by mean AUC values, was comparable between pediatric patients receiving an 8-mg/kg/day dose and adults receiving a 4-mg/kg/day dose.

Distribution of lamivudine into cerebrospinal fluid (CSF) was assessed in 38 pediatric patients after multiple oral dosing with lamivudine. CSF samples were collected between 2 and 4 hours postdose. At the dose of 8 mg/kg/day, CSF lamivudine concentrations in 8 patients ranged from 5.6% to 30.9% (mean ± SD of 14.2% ± 7.9%) of the concentration in a simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to 0.3 mcg/mL.

Tenofovir Disoproxil Fumarate:
Steady-state pharmacokinetics of tenofovir were evaluated in 31 HIV-1 infected pediatric

subjects 2 to less than 18 years (Table 9). Tenofovir exposure achieved in these pediatric subjects receiving oral once daily doses of tenofovir disoproxil fumarate 300 mg (tablet) or 8 mg/kg of body weight (powder) up to a maximum dose of 300 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil fumarate 300 mg.

Table 9 Mean (± SD) Tenofovir Pharmacokinetic Parameters by Age Groups for Pediatric Patients

Dose and Formulation	**300 mg Tablet**	**8 mg/kg Oral Powder**
	12 to less than 18 Years (N=8)	**2 to less than 12 Years (N=23)**
C_{max} (μg/mL)	0.38 ± 0.13	0.24 ± 0.13
AUC_{tau} (μg•hr/mL)	3.39 ± 1.22	2.59 ± 1.06

Geriatric Patients: The pharmacokinetics of lamivudine and tenofovir disoproxil fumarate have not been studied in patients over 65 years of age.

Gender: Lamivudine: There are no significant gender differences in lamivudine's pharmacokinetics.

Tenofovir Disoproxil Fumarate: Tenofovir pharmacokinetics are similar in male and female subjects.

Patients with Impaired Renal Function: *See Use in Specific Populations (8.6)*.

Lamivudine and Tenofovir Disoproxil Fumarate Tablets are not recommended for patients with impaired renal function (i.e., creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis because it is a fixed-dose combination formulation that cannot be adjusted

Patients with Hepatic Impairment

Lamivudine: The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function; therefore, no dose adjustment for lamivudine is required for patients with impaired hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensate liver disease.

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

Assessment of Drug Interactions: *See Drug Interactions (7).*

No drug interaction studies have been conducted using lamivudine and tenofovir disoproxil fumarate tablets.

Lamivudine: There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a study of 19 healthy male subjects *[see Warnings and Precautions (5.4)]*.

In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected patients *[see Warnings and Precautions (5.4)]*.

Lamivudine and TMP/SMX were coadministered to 14 HIV-1-positive patients in a single-center, open-label, randomized, crossover study. Each patient received treatment with a single 300 mg dose of lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose in a crossover design.

Coadministration of TMP/SMX with lamivudine resulted in an increase of 43% ± 23% (mean ± SD) in lamivudine AUC_{∞}, a decrease of 29% ± 13% in lamivudine oral clearance, and a decrease of 30% ± 36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine *[see Drug Interactions (7.2)]*.

No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-l-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr) *[see Drug Interactions (7.3)]*.

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

Tenofovir Disoproxil Fumarate has been evaluated in healthy volunteers in combination with other antiretroviral and potential concomitant drugs. Tables 10 and 11 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of tenofovir disoproxil fumarate on the pharmacokinetics of coadministered drug. No clinically significant drug interactions have been observed between tenofovir and efavirenz, methadone, nelfinavir, oral contraceptives, or ribavirin.

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

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters[b] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	⇔	⇔	NC

Atazanavir[c]	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine[d]	250 or 400 once daily × 7 days	14	⇔	⇔	⇔
Emtricitabine	200 once daily × 7 days	17	⇔	⇔	⇔
Entecavir	1 mg once daily x 10 days	28	⇔	⇔	⇔
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Lamivudine	150 twice daily × 7 days	15	⇔	⇔	⇔
Lopinavir/Ritonavir	400/100 twice daily × 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Saquinavir/Ritonavir	1000/100 twice daily × 14 days	35	⇔	⇔	↑ 23 (↑ 16 to ↑ 30)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↑ 13 (↑ 1 to ↑ 27)	⇔	⇔

[a] Subjects received tenofovir disoproxil fumarate 300 mg once daily.
[b] Increase = ↑; Decrease = ↓; No Effect = ⇔; NC = Not Calculated
[c] Reyataz (atazanavir) Prescribing Information
[d] Subjects received didanosine buffered tablets.

Following multiple dosing to HIV-1 and HBV-negative subjects receiving either chronic methadone maintenance therapy or oral contraceptives, or single doses of ribavirin, steady-state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating lack of clinically significant drug interactions between these agents and tenofovir disoproxil fumarate.

Table 11 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir Disoproxil Fumarate

Coadministered Drug	**Dose of Coadministered Drug (mg)**	**N**	**% Change of Coadministered Drug Pharmacokinetic Parameters[a] (90% CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	⇔	NA
Atazanavir[b]	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir[b]	Atazanavir/Ritonavir 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25[c] (↓ 42 to ↓ 3)	↓ 23[c] (↓ 46 to ↑ 10)
Didanosine[d]	250 once, simultaneously with	33	↓ 20[f] (↓ 32 to ↓ 7)	⇔[f]	NA

	tenofovir and a light meal[e]				
Emtricitabine	200 once daily × 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Entecavir	1 mg once daily x 10 days	28	⇔	↑ 13 (↑ 11 to ↑ 15)	⇔
Indinavir	800 three times daily × 7 days	12	↓ 11 (↓ 30 to ↑ 12)	⇔	⇔
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	⇔ ⇔	⇔ ⇔	⇔ ⇔
Saquinavir Ritonavir	Saquinavir/Ritonavir 1000/100 twice daily × 14 days	32	↑ 22 (↑ 6 to ↑ 41) ⇔	↑ 29[g] (↑ 12 to ↑ 48) ⇔	↑ 47[g] (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	⇔	⇔	⇔

[a] Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable
[b] Reyataz (atazanavir) Prescribing Information
[c] In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.
[d] Videx EC Prescribing Information. Subjects received didanosine enteric-coated capsules.
[e] 373 kcal, 8.2 g fat
[f] Compared with didanosie (enteric-coated) 400 mg administered alone under fasting conditions.
[g] Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are coadministered.

Coadministration of tenofovir disoproxil fumarate and didanosine should be undertaken with caution *[See Drug Interactions (7.4)]*. When administered with multiple doses of tenofovir disoproxil fumarate, the C_{max} and AUC of didanosine 400 mg increased significantly. The mechanism of this interaction is unknown. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures to didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.

12.4 Microbiology

Mechanism of Action

Lamivudine: Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue. 3TC-TP is a weak inhibitor of cellular DNA polymerases α, β, and γ.

Tenofovir Disoproxil Fumarate: Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase and HBV polymerase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a

weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral Activity

Lamivudine: The antiviral activity of lamivudine tenofovir against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC_{50} values (50% effective concentrations) were in the range of 0.003 to 15 μM (1 μM = 0.23 mcg/mL). HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance gave median EC_{50} values of 0.429 μM (range: 0.200 to 2.007 μM) from Virco (n = 92 baseline samples from COLA40263) and 2.35 μM (1.37 to 3.68 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM, and against HIV-2 isolates from 0.003 to 0.120 μM in peripheral blood mononuclear cells. Ribavirin (50 μM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells. In HIV–1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity. Please see the full prescribing information for EPIVIR-HBV (lamivudine) for information regarding the inhibitory activity of lamivudine against HBV.

Tenofovir Disoproxil Fumarate: The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} (50% effective concentration) values for tenofovir were in the range of 0.04 μM to 8.5 μM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5 μM to 2.2 μM) and strain specific activity against HIV-2 (EC_{50} values ranged from 1.6 μM to 5.5 μM).

Resistance

Lamivudine: Lamivudine-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine (M184V/I).

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Lamivudine-resistant HBV isolates develop substitutions (rtM204V/I) in the YMDD motif of the catalytic domain of the viral reverse transcriptase. rtM204V/I substitutions are frequently accompanied by other substitutions (rtV173L, rtL180M) which enhance the level of lamivudine resistance or act as compensatory mutations improving replication efficiency.

Other substitutions detected in lamivudine-resistant HBV isolates include: rtL80I and rtA181T. Similar HBV mutants have been reported in HIV-1-infected patients who received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus *[see Warnings and Precautions (5.2)]*.

Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in reverse transcriptase and showed a 2 to 4 fold reduction in susceptibility to tenofovir.

In Study 903 of treatment-naïve subjects (tenofovir disoproxil fumarate + lamivudine + efavirenz versus stavudine + lamivudine + efavirenz) *[See Clinical Studies (14.1)]*, genotypic analyses of isolates from subjects with virologic failure through Week 144 showed development of efavirenz and lamivudine resistance-associated substitutions to occur most frequently and with no difference between the treatment arms. The K65R substitution occurred in 8/47 (17%) analyzed patient isolates on the tenofovir disoproxil fumarate arm and in 2/49 (4%) analyzed patient isolates on the stavudine arm. Of the 8 subjects whose virus developed K65R in the tenofovir disoproxil fumarate arm through 144 weeks, 7 of these occurred in the first 48 weeks of treatment and one at Week 96. Other substitutions resulting in resistance to tenofovir disoproxil fumarate were not identified in this study.

In Study 934 of treatment-naïve subjects (tenofovir disoproxil fumarate + emtricitabine + efavirenz versus zidovudine (AZT)/lamivudine (3TC) + efavirenz) *[See Clinical Studies (14.1)]*, genotypic analysis performed on HIV-1 isolates from all confirmed virologic failure subjects with greater than 400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation showed development of efavirenz resistance-associated substitutions occurred most frequently and was similar between the two treatment arms. The M184V substitution, associated with resistance to emtricitabine and lamivudine, was observed in 2/19 analyzed subject isolates in the tenofovir disoproxil fumarate + emtricitabine group and in 10/29 analyzed subject isolates in the zidovudine/lamivudine group. Through 144 weeks of Study 934, no subjects have developed a detectable K65R substitution in their HIV-1 as analyzed through standard.

Cross-Resistance

Lamivudine: Lamivudine-resistant HIV-1 mutants were cross-resistant to didanosine (ddI). In some patients treated with zidovudine plus didanosine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Genotypic and Phenotypic Analysis of On-Therapy HIV-1 Isolates From Patients With Virologic Failure: *Study EPV20001:* Fifty-three of 554 (10%) subjects enrolled in EPV20001 were identified as virological failures (plasma HIV-l RNA level ≥400 copies/mL) by Week 48. Of the 53 failures, 28 subjects were randomized to the lamivudine once-daily treatment group and 25 to the lamivudine twice-daily treatment group. The median baseline plasma HIV-l RNA levels of subjects in the lamivudine once-daily group and lamivudine twice-daily group were 4.9 $\log_{10}$ copies/mL and 4.6 $\log_{10}$ copies/mL, respectively. Genotypic analysis of on-therapy isolates from 22 subjects identified as virologic failures in the lamivudine once-daily group showed:

- isolates from 0/22 subjects contained treatment-emergent zidovudine resistance-associated amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E)
- isolates from 10/22 subjects contained treatment-emergent efavirenz resistance-associated amino acid substitutions (L100I, K101E, K103N, V108I, or Y181C)
- isolates from 8/22 subjects contained a treatment-emergent lamivudine resistance-associated amino acid substitution (M184I or M184V)

Phenotypic analysis of baseline-matched on-therapy HIV-l isolates from subjects (n =13) receiving lamivudine once daily showed:

- isolates from 12/13 subjects were susceptible to zidovudine
- isolates from 8/13 subjects exhibited a 25- to 295-fold decrease in susceptibility to efavirenz isolates from 7/13 subjects showed an 85- to 299-fold decrease in susceptibility to lamivudine

Study EPV40001: Fifty subjects received zidovudine 300 mg twice daily plus abacavir 300 mg twice daily plus lamivudine 300 mg once daily and 50 subjects received zidovudine 300 mg plus abacavir 300 mg plus lamivudine 150 mg all twice daily. The median baseline plasma HIV-1 RNA levels for subjects in the 2 groups were 4.79 $\log_{10}$ copies/mL and 4.83 $\log_{10}$ copies/mL, respectively. Fourteen of 50 subjects in the lamivudine once-daily treatment group and 9 of 50 subjects in the lamivudine twice-daily group were identified as virologic failures.

Genotypic analysis of on-therapy HIV-1 isolates from subjects (n = 9) in the lamivudine once-daily treatment group showed that isolates from 6 subjects had an abacavir and/or lamivudine resistance-associated substitution M184V alone. On-therapy isolates from subjects (n = 6) receiving lamivudine twice daily showed that isolates from 2 subjects had M184V alone, and isolates from 2 subjects harbored the M184V substitution in combination with zidovudine resistance-associated amino acid substitutions.

Phenotypic analysis of on-therapy isolates from subjects (n = 6) receiving lamivudine once daily showed that HIV-l isolates from 4 subjects exhibited a 32- to 53-fold decrease in susceptibility to lamivudine. HIV-1 isolates from these 6 subjects were susceptible to zidovudine.

Tenofovir Disoproxil Fumarate: Cross-resistance among certain reverse transcriptase inhibitors has been recognized. The K65R substitution selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir, didanosine, or zalcitabine. HIV-1 isolates with this mutation also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors the K65R substitution. HIV-1 isolates from patients (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated reverse transcriptase substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir.

In Studies 902 and 907 conducted in treatment-experienced subjects (tenofovir disoproxil fumarate + Standard Background Therapy (SBT) compared to Placebo + SBT) *[See Clinical Studies (14.1)]*, 14/304 (5%) of the tenofovir disoproxil fumarate-treated subjects with virologic failure through Week 96 had greater than 1.4-fold (median 2.7-fold) reduced

susceptibility to tenofovir. Genotypic analysis of the baseline and failure isolates showed the development of the K65R substitution in the HIV-1 reverse transcriptase gene.

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

Several exploratory analyses were conducted to evaluate the effect of specific substitutions and substitutional patterns on virologic outcome. Because of the large number of potential comparisons, statistical testing was not conducted. Varying degrees of cross-resistance of tenofovir disoproxil fumarate to pre-existing zidovudine resistance-associated substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) were observed and appeared to depend on the type and number of specific substitutions. Tenofovir disoproxil fumarate-treated subjects whose HIV-1 expressed 3 or more zidovudine resistance-associated substitutions that included either the M41L or L210W reverse transcriptase substitution showed reduced responses to tenofovir disoproxil fumarate therapy; however, these responses were still improved compared with placebo. The presence of the D67N, K70R, T215Y/F, or K219Q/E/N substitution did not appear to affect responses to tenofovir disoproxil fumarate therapy. Subjects whose virus expressed an L74V substitution without zidovudine resistance associated substitutions (N=8) had reduced response to tenofovir disoproxil fumarate. Limited data are available for subjects whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4), all of whom had a reduced response.

In the protocol defined analyses, virologic response to tenofovir disoproxil fumarate was not reduced in subjects with HIV-1 that expressed the abacavir/emtricitabine/lamivudine resistance-associated M184V substitution. HIV-1 RNA responses among these subjects were durable through Week 48.

Studies 902 and 907 Phenotypic Analyses

Phenotypic analysis of baseline HIV-1 from treatment-experienced subjects (N=100) demonstrated a correlation between baseline susceptibility to tenofovir disoproxil fumarate and response to tenofovir disoproxil fumarate therapy. Table 12 summarizes the HIV-1 RNA response by baseline tenofovir disoproxil fumarate susceptibility.

Table 12 HIV-1 RNA Response at Week 24 by Baseline Tenofovir Disoproxil Fumarate Susceptibility (Intent-To-Treat)[a]

Baseline tenofovir disoproxil fumarate Susceptibility[b]	Change in HIV-1 RNA[c] (N)
<1	-0.74 (35)
>1 and ≤3	-0.56 (49)
>3 and ≤4	-0.3 (7)
>4	-0.12 (9)

a. Tenofovir susceptibility was determined by recombinant phenotypic Antivirogram assay (Virco).
b. Fold change in susceptibility from wild-type.
c. Average HIV-1 RNA change from baseline through Week 24 ($DAVG_{24}$) in log_{10} copies/mL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV-1 infection. Lamivudine was not active in a microbial mutagenicity screen or an in vitro cell transformation assay, but showed weak in vitro mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of in vivo genotoxic activity in the rat at oral doses of up to 2,000 mg/kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection. In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

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

Tenofovir Disoproxil Fumarate was mutagenic in the *in vitro* mouse lymphoma assay and negative in an *in vitro* bacterial mutagenicity test (Ames test). In an *in vivo* mouse micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

13.2 Animal Toxicology and/or Pharmacology

Lamivudine

Reproduction studies have been performed in rats and rabbits at orally administered doses up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

Tenofovir Disoproxil Fumarate

Tenofovir and Tenofovir Disoproxil Fumarate administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6 fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose

reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2 to 20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.-

14 CLINICAL STUDIES

14.1 Clinical Efficacy in Patients with HIV-1 Infection

Treatment-Naïve Adult Patients

Study 903

Data through 144 weeks are reported for Study 903, a double-blind, active-controlled multicenter study comparing tenofovir disoproxil fumarate (300 mg once daily) administered in combination with lamivudine and efavirenz versus stavudine (d4T), lamivudine, and efavirenz in 600 antiretroviral-naïve subjects. Subjects had a mean age of 36 years (range 18 to 64), 74% were male, 64% were Caucasian and 20% were Black. The mean baseline $CD4^+$ cell count was 279 cells/mm^3 (range 3 to 956) and median baseline plasma HIV-1 RNA was 77,600 copies/mL (range 417 to 5,130,000). Subjects were stratified by baseline HIV-1 RNA and $CD4^+$ cell count. Forty-three percent of subjects had baseline viral loads >100,000 copies/mL and 39% had $CD4^+$ cell counts <200 cells/mm^3. Treatment outcomes through 48 and 144 weeks are presented in Table 13.

Table 13 Outcomes of Randomized Treatment at Week 48 and 144 (Study 903)

Outcomes	At Week 48		At Week 144	
	Tenofovir disoproxil fumarate+3TC +EFV (N=299)	d4T+3TC +EFV (N=301)	Tenofovir disoproxil fumarate+3TC+EFV (N=299)	d4T+3TC+ EFV (N=301)
Responder[a]	79%	82%	68%	62%
Virologic failure[b]	6%	4%	10%	8%
Rebound	5%	3%	8%	7%
Never suppressed	0%	1%	0%	0%
Added an antiretroviral agent	1%	1%	2%	1%
Death	<1%	1%	<1%	2%
Discontinued due to adverse event	6%	6%	8%	13%
Discontinued for other reasons[c]	8%	7%	14%	15%

a. Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48 and 144.
b. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48 and 144.
c. Includes lost to follow-up, subject's withdrawal, noncompliance, protocol violation and other reasons.

Achievement of plasma HIV-1 RNA concentrations of less than 400 copies/mL at Week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (> or ≤100,000 copies/mL) and $CD4^+$ cell count (< or ≥200 cells/mm^3). Through 144 weeks of therapy, 62% and 58% of subjects in the tenofovir

disoproxil fumarate and stavudine arms, respectively achieved and maintained confirmed HIV-1 RNA <50 copies/mL. The mean increase from baseline in $CD4^+$ cell count was 263 cells/mm^3 for the tenofovir disoproxil fumarate arm and 283 cells/mm^3 for the stavudine arm. Through 144 weeks, 11 subjects in the tenofovir disoproxil fumarate group and 9 subjects in the stavudine group experienced a new CDC Class C event.

16 HOW SUPPLIED/STORAGE AND HANDLING

Lamivudine and Tenofovir disoproxil fumarate tablets 300mg/300mg
White to off-white colored, capsule shaped, biconvex, film-coated tablets debossed 'CL 71' on one side of the tablet and having plain surface on the other side.
Bottle of 30 tablets with silica gel desiccant and induction seal - NDC 33342-095-07
Blister pack of 100 tablets (10 x 10s) – NDC 33342-095-12

Store below 30°C (86°F).

Disclaimer:
Other brands (TRUVADA, ATRIPLA, TRIZIVIR®, COMBIVIR, EPZICOM, HEPSERA, VIREAD) listed are the registered trademarks of their respective owners and are not of Macleods Pharmaceuticals Limited.

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Patients should be advised that:

- Lamivudine and Tenofovir Disoproxil Fumarate Tablets are not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using lamivudine and tenofovir disoproxil fumarate tablets.
- Patients shoud avoid doing things that can spread HIV-1 infection to others.
  - **Do not share 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.
  - **Do not breastfeed.** Lamivudine and tenofovir are excreted in breast milk. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.
- The long term effects of lamivudine and tenofovir disoproxil fumarate tablets are unknown.
- Lamivudine and tenofovir disoproxil fumarate tablets are for oral ingestion only.
- Lamivudine and Tenofovir Disoproxil Fumarate Tablets should not be discontinued without first informing their physician.
- If you have HIV-1 infection, with or without HBV coinfection, it is important to take lamivudine and tenofovir disoproxil fumarate tablets with combination therapy.
- It is important to take lamivudine and tenofovir disoproxil fumarate tablets on a regular dosing schedule and to avoid missing doses.
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been

reported. Treatment with lamivudine and tenofovir disoproxil fumarate tablets should be suspended in any patient who develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) *[See Warnings and Precautions (5.1)]*.

- Patients with HIV-1 should be tested for Hepatitis B virus (HBV) before initiating antiretroviral therapy.
- Severe acute exacerbations of hepatitis have been reported in patients who are infected with HBV or coinfected with HBV and HIV-1 and have discontinued lamivudine and tenofovir disoproxil fumarate tablets *[See Warnings and Precautions (5.2)]*.
- Patients with HIV-1/HCV co-infection should be informed that hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin *[see Warnings and Precautions (5.4)]*.
- In patients with chronic hepatitis B, it is important to obtain HIV antibody testing prior to initiating lamivudine and tenofovir disoproxil fumarate tablets.
- Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported. Lamivudine and Tenofovir Disoproxil Fumarate Tablets should be avoided with concurrent or recent use of a nephrotoxic agent. Lamivudine and tenofovir disoproxil fumarate tablets are not recommended for patients with impaired renal function (i.e., creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis *[See Dosage and Administration (2.2)]*.
- Lamivudine and tenofovir disoproxil fumarate tablets should not be administered in combination with HEPSERA (adefovir dipivoxil) *[See Warnings and Precautions (5.3)]*.
- Lamivudine and tenofovir disoproxil fumarate tablets should not be coadministered with other lamivudine-containing or emtricitabine-containing drugs, including COMBIVIR (lamivudine/zidovudine), EPIVIR or EPIVIR-HBV (lamivudine), EPZICOM (abacavir sulfate/lamivudine), or TRIZIVIR (abacavir sulfate/lamivudine/zidovudine), EMTRIVA® (emtricitabine), and TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) *[See Warnings and Precautions (5.3)]*
- Lamivudine and Tenofovir Disoproxil Fumarate should not be coadministered with other tenofovir disoproxil fumarate-containing drugs, including VIREAD (tenofovir disoproxil fumarate), TRUVADA (emtricitabine/tenofovir disoproxil fumarate) or ATRIPLA (emtricitabine/efavirenz/tenofovir disoproxil fumarate) *[See Warnings and Precautions (5.3)]*.
- Decreases in bone mineral density have been observed with the use of lamivudine and tenofovir disoproxil fumarate tablets in patients with HIV. Bone mineral density monitoring should be considered in patients who have a history of pathologic bone fracture or at risk for osteopenia *[See Warnings and Precautions (5.7)]*.
- Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including lamivudine and tenofovir disoproxil fumarate, and that the cause and long-term health effects of these conditions are not known at this time *[See Warnings and Precautions (5.9)]*.
- Pregnancy Registry
  Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to lamivudine and tenofovir disoproxil fumarate tablets. [*see Use in Specific Populations (8.1)*].

PATIENT INFORMATION

Lamivudine and
Tenofovir Disoproxil Fumarate Tablets, 300 mg/300 mg

Read this leaflet carefully before you start taking lamivudine and tenofovir disoproxil fumarate tablets and each time you get a refill. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

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

Lamivudine and tenofovir disoproxil fumarate tablets can cause serious side effects, including:

1. **Build-up of an acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take lamivudine, tenofovir disoproxil fumarate or similar (nucleoside analog) medicines. **Lactic acidosis** is a serious medical emergency that can lead to death.

   Lactic acidosis can be hard to identify early, because the symptoms could seem like symptoms of other health problems. **Call your healthcare provider right away if you get the following symptoms which could be signs of lactic acidosis:**

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

2. **Severe liver problems.** Severe liver problems can happen in people who take lamivudine, tenofovir disoproxil fumarate or similar medicines. In some cases these liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis) when you take lamivudine and tenofovir disoproxil fumarate tablets.

   Call your healthcare provider right away if you have any of the following symptoms of liver problems:

   - Your skin or the white part of your eyes turns yellow (jaundice).
   - dark "tea-colored" urine
   - light-colored bowl movements (stools)
   - loss of appetite for several days or longer
   - nausea
   - stomach pain

   You may be more likely to get lactic acidosis or severe liver problems if you are female, very overweight (obese), or have been taking lamivudine, tenofovir disoproxil fumarate or a similar medicine for a long time.

3. **Worsening of your Hepatitis B infection.** If you are also infected with hepatitis B Virus (HBV) infection, you need close medical follow-up for several months after stopping treatment with lamivudine and tenofovir disoproxil fumarate tablets. Follow-up includes medical exams and blood test to check for HBV that could be getting worse. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.

4. **Talk to your doctor about taking an HBV test before starting treatment with lamivudine and tenofovir disoproxil fumarate tablets for treatment of HIV.**

What are lamivudine and tenofovir disoproxil fumarate tablets?

Lamivudine and tenofovir disoproxil fumarate tablets are a prescription medicine used:

- with other antiviral medicines to treat Human Immunodeficiency Virus (HIV) in adults and pediatric patients 12 years of age and older and weighing at least 35 kg (77 lb). HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). Lamivudine and tenofovir disoproxil fumarate tablets do not cure HIV or AIDS. People taking lamivudine and tenofovir disoproxil fumarate tablets may still get infections common in people with HIV (opportunistic infections). It is very important that you stay under the care of your healthcare provider.

What should I tell my healthcare provider before taking lamivudine and tenofovir disoproxil fumarate tablets?

Before you take lamivudine and tenofovir disoproxil fumarate tablets, 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 lamivudine and tenofovir disoproxil fumarate tablets will harm your unborn baby.
- are breast-feeding or plan to breast-feed. You should not breast-feed if you have HIV infection or AIDS. The virus that causes HIV can pass through your breast milk to your baby. Talk to your healthcare provider about the best way to feed your baby.

Pregnancy Registry. There is a pregnancy registry for women who take lamivudine and tenofovir disoproxil fumarate tablets during pregnancy. The purpose of this registry 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.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Lamivudine and tenofovir disoproxil fumarate tablets may affect the way other medicines work, and other medicines may affect how lamivudine and tenofovir disoproxil fumarate tablets work.

Do not take lamivudine and tenofovir disoproxil fumarate tablets if you also take:

- other medicines that contain tenofovir (TRUVADA, ATRIPLA, VIREAD)
- other medicines that contain lamivudine or emtricitabine (EPIVIR, EPIVIR-HBV, COMBIVIR, EPZICOM, TRIZIVIR, EMTRIVA)
- adefovir (HEPSERA)

Especially tell your healthcare provider if you take the following medications, as the dose of these other medications may need to be changed:

- didanosine (VIDEX, VIDEX EC)
- atazanavir (REYATAZ)
- lopinavir with ritonavir (KALETRA)

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 lamivudine and tenofovir disoproxil fumarate tablets?

- See "What is the most important information I should know about lamivudine and tenofovir disoproxil fumarate tablets?"
- Take lamivudine and tenofovir disoproxil fumarate tablets exactly as your healthcare provider tells you to take them.
- Take lamivudine and tenofovir disoproxil fumarate tablets at the same time every day.
- The usual dose of lamivudine and tenofovir disoproxil fumarate tablets is 1 tablet each day. If you are an adult and have kidney problems, your healthcare provider may tell you not to take lamivudine and tenofovir disoproxil fumarate tablets.
- Take lamivudine and tenofovir disoproxil fumarate tablets by mouth on an empty stomach.
- Do not miss a dose of lamivudine and tenofovir disoproxil fumarate tablets. If you miss a dose of lamivudine and tenofovir disoproxil fumarate tablets, take the missed dose as soon as you remember. If it is almost time for your next dose of lamivudine and tenofovir disoproxil fumarate tablets, do not take the missed dose. Take the next dose of lamivudine and tenofovir disoproxil fumarate tablets at your regular time.
- If you take too much lamivudine and tenofovir disoproxil fumarate tablets, call your local poison control center or go right away to the nearest hospital emergency room.

What are the possible side effects of lamivudine and tenofovir disoproxil fumarate tablets?

Lamivudine and tenofovir disoproxil fumarate tablets may cause serious side effects, including:

- **See "What is the most important information I should know about lamivudine and tenofovir disoproxil fumarate tablets"?**
- **New or worse kidney problems** can happen in some people who take lamivudine and 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 lamivudine and tenofovir disoproxil fumarate tablets.
- **Bone problems** can happen in some people who take lamivudine and tenofovir disoproxil fumarate tablets. 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 body fat** can happen in some people who take antiviral medicines. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.
- **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 doctor if you start having new symptoms after starting your HIV medicine.

The most common side effects of lamivudine and tenofovir disoproxil fumarate tablets are:

- nausea
- rash
- diarrhea
- headache
- pain
- depression
- weakness
- fatigue
- nasal signs and symptoms
- cough

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 lamivudine and tenofovir disoproxil fumarate tablets. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects.

How do I store lamivudine and tenofovir disoproxil fumarate tablets?

- Keep lamivudine and tenofovir disoproxil fumarate tablets and all medicines out of the reach of children.
- Store lamivudine and tenofovir disoproxil fumarate tablets at below 30°C (86°F). It should remain stable until the expiration date printed on the label.
- Do not keep your medicine in places that are too hot or cold.
- Do not keep medicine that is out of date or that you no longer need. If you throw any medicines away make sure that children will not find them.

General information about lamivudine and tenofovir disoproxil fumarate tablets:

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

Lamivudine and tenofovir disoproxil fumarate tablets do not reduce the risk of passing HIV-1 to others through sexual contact or blood contamination. Continue to practice safer sex and

do not use or share dirty needles. Do not share personal items that can have blood or body fluids on them, like toothbrushes or razor blades.

This leaflet summarizes the most important information about lamivudine and 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 lamivudine and tenofovir disoproxil fumarate that is written for health professionals.

What are the ingredients in lamivudine and tenofovir disoproxil fumarate tablets?

Active Ingredients: Lamivudine and Tenofovir Disoproxil Fumarate

Inactive Ingredients: croscarmellose sodium, magnesium stearate and microcrystalline cellulose. Tablet Coating: Opadry II White 30K580000, which contains hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide, and triacetin.

Rx Only
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Manufactured by:
Macleods Pharmaceutical Limited
Daman (U.T) INDIA
OR
Manufactured by:
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