℞ **LAMIVUDINE + TENOFOVIR DISOPROXIL FUMARATE**

300 mg/300 mg Film-coated tablet

Nucleoside and Nucleotide Reverse Transcriptase Inhibitor Combination

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.

Lamivudine and Tenofovir Disoproxil Fumarate Tablets

Lamivudine

WARNING: LACTIC ACIDOSIS, POSTTREATMENT EXACERBATIONS OF HEPATITS B IN CO-INFECTED PATIENTS, DIFFERENT FORMULATIONS OF LAMIVUDINE

See full prescribing information for complete boxed warning

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been 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 have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine.**

  Monitor hepatic function closely in these patients and, if appropriate, initiate anti- hepatitis B treatment. (5.2)
- **Patients with HIV-1 infection should receive only dosage forms of lamivudine appropriate for treatment of HIV-1. (5.2)**

Tenofovir Disoproxil Fumarate

WARNINGS:LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS

See full prescribing information for complete boxed warning.

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs including tenofovir disoproxil fumarate. (5.1)**
- **Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including tenofovir disoproxil fumarate. Hepatic function should be monitored closely in these patients. If appropriate, resumption of anti-hepatitis B therapy may be warranted. (5.2)**

RECENT MAJOR CHANGES

Lamivudine

Warnings and Precautions, Immune Reconstitution Syndrome (5.6)	(11/2012)
Tenofovir Disoproxil Fumarate	
Indications and Usage (1.1)	07/2013
Dosage and Administration (2.1, 2.2, 2.3)	07/2013
Warnings and Precautions	
Coadministration with Other Products (5.4)	09/2011
Immune Reconstitution Syndrome (5.8)	11/2011
Decrease in Bone Mineral Density (5.6)	01/2012

INDICATIONS AND USAGE

Lamivudine and Tenofovir Disoproxil Fumarate tablet is a nucleoside analogue reverse transcriptase inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

DOSAGE AND ADMINISTRATION

The dose of Lamivudine and Tenofovir disoproxil fumarate Tablets is one tablet (containing 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food. Lamivudine and Tenofovir Disoproxil Fumarate Tablets are not recommended for patients with impaired renal function

DOSAGE FORMS AND STRENGTHS

- Tablets: 300 mg/300 mg (3)

CONTRAINDICATIONS

Lamivudine and Tenofovir Disoproxil Fumarate Tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., anaphylaxis) to any of the components of the products. (4)

WARNINGS AND PRECAUTIONS

Lamivudine

- 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 hepatoxicity occur. (5.1)
- Severe acute exacerbations of hepatitis: Reported in patients who are co-infected with hepatitis B virus and HIV-1 and discontinued lamivudine. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)
- Patients with HIV-1 infection should receive only dosage forms of lamivudine appropriate for treatment of HIV-1. (5.2)
- Co-infected HIV-1/HBV Patients: Emergence of lamivudine- resistant HBV variants associated with lamivudine-containing antiretroviral regimens has been reported. (5.2)
- Emtricitabine should not be administered concomitantly with lamivudine-containing products. (5.3)
- Hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving interferon and ribavirin-based regimens. Monitor for treatment- associated toxicities. Discontinue lamivudine 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 treatment as clinically appropriate. (5.5)
- Immune reconstitution syndrome (5.6) and redistribution/accumulation of body fat (5.7) have been reported in patients treated with combination antiretroviral therapy.

Tenofovir Disoproxil Fumarate

- 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. Monitor CrCl and serum phosphorus in patients at risk. Avoid administering tenofovir disoproxil fumarate with concurrent or recent use of nephrotoxic drugs. (5.3)
- Coadministration with Other Products: Do not use with other tenofovir-containing products (e.g., Efavirenz, emitricitabine and tenofovir disoproxil fumarate, Rilpivirine/Emtricitabine/Tenofovir, and Emitricitabine and tenofovir disoproxil fumarate). Do not administer in combination with Adefovir dipivoxil. (5.4)
- HIV testing: HIV antibody testing should be offered to all HBV-infected patients before initiating therapy with tenofovir disoproxil fumarate. Tenofovir disoproxil fumarate should only be used as part of an appropriate antiretroviral combination regimen in HIV-infected patients with or without HBV coinfection. (5.5)
- Decreases in bone mineral density (BMD): 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. (5.6)
- Redistribution/accumulation of body fat: Observed in HIV-infected patients receiving antiretroviral combination therapy. (5.7)
- Immune reconstitution syndrome: Observed in HIV-infected patients. May necessitate further evaluation and treatment. (5.8)
- Triple nucleoside-only regimens: Early virologic failure has been reported in HIV- infected patients. Monitor carefully and consider treatment modification. (5.9)

ADVERSE REACTIONS

In HIV-infected subjects: Most common adverse reactions (incidence greater than or equal to 10%, Grades 2 to 4) are rash, diarrhea, headache, pain, depression, asthenia, and nausea. (6)

In HIV-infected pediatric subjects: Adverse reactions in pediatric subjects were consistent with those observed in adults. (6)

To report SUSPECTED ADVERSE REACTIONS, contact www.fda.gov.ph

DRUG INTERACTIONS

Lamivudine

Zalcitabine is not recommended for use in combination with lamivudine. (7.2)

Tenofovir Disoproxil Fumarate

- Didanosine: Coadministration increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy). Consider dose reductions or discontinuations of didanosine if warranted. (7.1)
- Atazanavir: Coadministration decreases atazanavir concentrations and increases tenofovir concentrations. Use atazanavir with tenofovir disoproxil fumarate only with additional ritonavir; monitor for evidence of tenofovir toxicity. (7.2)
- Lopinavir/ritonavir: Coadministration increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity. (7.3)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Women infected with HIV should be instructed not to breast feed. (8.3)
- Safety and efficacy not established in patients less than 2 years of age. (8.4)

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

Revised: July 2013

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 EXACERBATION OF HEPATITIS

Lactic Acidosis and Severe Hepatomegaly: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including tenofovir disoproxil fumarate alone or in combination with other antiretrovirals. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur *[see Warnings and Precautions (5.1)]*.

Exacerbation of Hepatitis B: Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued Lamivudine and Tenofovir disoproxil fumarate Tablets. Hepatic function should be monitored closely in patients. If appropriate, resumption of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

Lamivudine and Tenofovir Disoproxil Fumarate Tablet is a nucleoside analogue indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-I) infection.

Additional important information regarding the use of Lamivudine and Tenofovir disoproxil fumarate Tablets for the treatment of HIV-1 infection:

- It is not recommended that Lamivudine and Tenofovir disoproxil fumarate Tablets be used a component of a triple nucleoside regimen.
- Lamivudine and Tenofovir disoproxil fumarate Tablets should not be coadministered with ATRIPLA (efavirenz, emtricitabine, and tenofovir), EMTRIVA (emtricitabine), TRUVADA (emtricitabine and tenofovir), 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), COMPLERA[TM] and TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine) *[See Warnings]*.

2 DOSAGE AND ADMINISTRATION

Adults

The dose of Lamivudine and Tenofovir disoproxil fumarate Tablets is one tablet (containing 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food.

Renal Impairment

Lamivudine and Tenofovir Disoproxil Fumarate Tablets are 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 Tablets are available as tablets. Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil and 300 mg of lamivudine. The tablets are light blue colored capsule shaped biconvex tablets debossed with '129' on one side and 'H' on other side.

4 CONTRAINDICATIONS

Lamivudine and Tenofovir Disoproxil Fumarate tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., anaphylaxis) to any of the components of the products

5 WARNINGS AND PRECAUTIONS

Lamivudine and Tenofovir disoproxil fumarate

Lamivudine and Tenofovir disoproxil fumarate Tablets should not be administered concomitantly with formulations containing any of the two drugs. The complete prescribing information for all agents being considered for use with Lamivudine and Tenofovir disoproxil fumarate Tablets should be consulted before combination therapy with Lamivudine and Tenofovir disoproxil fumarate Tablets is initiated.

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 analogues alone or in combination, including lamivudine, tenofovir disoproxil fumarate, and 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 lamivudine 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 tablets 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).

Lamivudine

5.2 Patients With HIV-1 and Hepatitis B Virus Co-infection

Posttreatment Exacerbations of Hepatitis: In clinical trials in non-HIV-1-infected patients treated with lamivudine for chronic hepatitis B, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from postmarketing experience after changes from lamivudine-containing HIV-1 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of posttreatment exacerbations of hepatitis.

Important Differences Among Lamivudine-Containing Products: Lamivudine Tablets contain a higher dose of the same active ingredient lamivudine Tablets. lamivudine was developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine 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 lamivudine 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. If a decision is made to administer lamivudine to patients co-infected with HIV-1 and HBV, lamivudine tablets, lamivudine/zidovudine Tablets, abacavir sulfate and lamivudine Tablets, or abacavir sulfate, lamivudine, and zidovudine Tablets should be used as part of an appropriate combination regimen.

Emergence of Lamivudine-Resistant HBV: In non-HIV-I-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 lamivudine 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 Use With Other Lamivudine- and Emtricitabine-Containing Products

Lamivudine should not be administered concomitantly with other lamivudine-containing products including lamivudine Tablets, lamivudine/zidovudine Tablets, abacavir sulfate and lamivudine Tablets, or abacavir sulfate, lamivudine, and zidovudine or emtricitabine-containing products, includingefavirenz, emtricitabine, and tenofovir, emtricitabine, emtricitabine and tenofovir, or Rilpivirine/Emtricitabine/Tenofovir.

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. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-I/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-I/HCV co-infected patients *[see Clinical Pharmacology (12.3)]*, hepatic decompensation (some fatal) has occurred in HIV-I/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., Childs 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 should be used with caution. Treatment with lamivudine should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur *[see Adverse Reactions (6.1)]*.

5.6 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including lamivudine. 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.

5.7 Fat Redistribution

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 antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Tenofovir Disoproxil Fumarate

5.2 Exacerbation of Hepatitis after Discontinuation of Treatment

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

5.3 New Onset or Worsening Renal Impairment

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

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with tenofovir disoproxil fumarate. 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 Adefovir dipivoxil.

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

Tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent.

℞ **LAMIVUDINE + TENOFOVIR DISOPROXIL FUMARATE**
300 mg/300 mg Film-coated tablet
Nucleoside and Nucleotide Reverse Transcriptase Inhibitor Combination

5.4 Coadministration with Other Products

Tenofovir disoproxil fumarate should not be used in combination with the fixed-dose combination products Efavirenz, emitricitabine and tenofovir disoproxil fumarate, Rilpivirine/Emtricitabine/Tenofovir, or Emitricitabine and Tenofovir disoproxil fumarate since tenofovir disoproxil fumarate is a component of these products.

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

5.5 Patients Coinfected with HIV-1 and HBV

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

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

5.6 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 in trial 903 through 144 weeks, decreases from baseline in BMD were seen at the lumbar spine and hip in both arms of the trail. 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 trial and this reduction was sustained through Week 144. Twenty-eight percent of tenofovir disoproxil fumarate-treated subjects vs. 21% of the stavudine-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the tenofovir disoproxil fumarate group and 6 subjects in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) 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 clinical trials evaluating tenofovir disoproxil fumarate in HIV-1 infected pediatric subjects 2 to less than 18 years of age, bone effects were similar to those observed in adult subjects. Under normal circumstances BMD increases rapidly in pediatric patients. In Study 352 (2 to less than 12 years), the mean rate of BMD gain in lumbar spine at Week 48 was similar between the tenofovir disoproxil fumarate and the d4T or AZT treatment groups. Total body BMD gain was less in the tenofovir disoproxil fumarate compared to the d4T or AZT treatment group. One tenofovir disoproxil fumarate-treated subject and none of the d4T or AZT-treated subjects experienced significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline in BMD Z-scores were -0.012 for lumbar spine and -0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. In Study 321 (12 to less than 18 years), the mean rate of BMD gain at Week 48 was less in the tenofovir disoproxil fumarate compared to the placebo treatment group. Six tenofovir disoproxil fumarate treated subjects and one placebo treated subject had significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline BMD Z-scores were -0.341 for lumbar spine and -0.458 for total body in the 28 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. In both trials, skeletal growth (height) appeared to be unaffected. Markers of bone turnover in tenofovir disoproxil fumarate -treated pediatric subjects 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.

5.7 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.

5.8 Immune Reconstitution Syndrome

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

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

5.9 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

Adverse reactions with lamivudine and tenofovir disoproxil fumarate may be expected with the use of Lamivudine and Tenofovir disoproxil fumarate Tablets. The adverse reactions reported with lamivudine and tenofovir disoproxil fumarate are presented below.

Lamivudine

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, 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.

Body as a Whole: Redistribution/accumulation of body fat *[see Warnings and Precautions (5.7)]*.

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

6.1 Adverse Reactions from Clinical Trials Experience

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 programs. A total of 1,544 subjects have received tenofovir disoproxil fumarate 300 mg once daily in clinical trials; over 11,000 subjects have received tenofovir disoproxil fumarate in expanded access programs.

The most common adverse reactions (incidence greater than or equal to 10%, Grades 2 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 1.

Table 1 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 trial 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 2.

Table 2 Grade 3/4 Laboratory Abnormalities Reported in ≥1% of Tenofovir disoproxil fumarate-Treated Subjects in Study 903 (0 to 144 Weeks)

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

6.2 Postmarketing Experience

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

Immune System Disorders

allergic reaction, including angioedema

Metabolism and Nutrition Disorders

lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, and Mediastinal Disorders

dyspnea

Gastrointestinal Disorders

pancreatitis, increased amylase, abdominal pain

Hepatobiliary Disorders

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

Skin and Subcutaneous Tissue Disorders

rash

Musculoskeletal and Connective Tissue Disorders

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

Renal and Urinary Disorders

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

General Disorders and Administration Site Conditions

asthenia

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

7 DRUG INTERACTIONS

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-I/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV–I/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 Zalcitabine

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of lamivudine in combination with zalcitabine is not recommended.

7.3 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.

7.4 Drugs with No Observed Interactions With lamivudine

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

Tenofovir Disoproxil Fumarate

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

7.1 Didanosine

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

When administered with tenofovir disoproxil fumarate, C_{max} and AUC of didanosine (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 disoproxil fumarate. Data are not available to recommend a dose adjustment of didanosine for adult or pediatric patients weighing less than 60 kg. When coadministered, tenofovir disoproxil fumarate and didanosine EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with tenofovir disoproxil fumarate should be under fasted conditions.

7.2 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.

7.3 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.

7.4 Drugs Affecting Renal Function

Since tenofovir is primarily eliminated by the kidneys *[See Clinical Pharmacology (12.3)]*, coadministration of tenofovir disoproxil fumarate with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, 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 Adefovir dipivoxil.

8 USE IN SPECIFIC POPULATIONS

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.

8.1 Pregnancy

Lamivudine

Pregnancy Category C. There are no adequate and well-controlled studies of lamivudine in pregnant women. Animal reproduction studies in rats and rabbits revealed no evidence of teratogenicity. Increased early embryolethality occurred in rabbits at exposure levels similar to those in humans. Lamivudine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data: 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 the 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 Data: 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 Non clinical Toxicology (13.2)]*.

8.1 Pregnancy: Teratogenic Effects: *Pregnancy Category B*

Tenofovir Disoproxil Fumarate

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. There are, however, 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.

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-l infection. Because of the potential for serious adverse reactions in nursing infants and HIV-l transmission, 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: Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk.In humans, 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

Pediatric Patients 12 years of Age and Older

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

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

In Study 321, 87 treatment-experienced subjects 12 to less than 18 years of age were treated with lamivudine and tenofovir disoproxil fumarate (N=45) or placebo (N=42) in combination with an optimized background regimen (OBR) for 48 weeks. The mean baseline CD4 cell count was 374 cells/mm³ and the mean baseline plasma HIV-1 RNA was 4.6 log_{10} copies/mL. At baseline, 90% of subjects harbored NRTI resistance-associated substitutions in their HIV-1 isolates. Overall, the trial failed to show a difference in virologic response between the lamivudine and tenofovir disoproxil fumarate and placebo treatment groups. Subgroup analyses suggest the lack of difference in virologic response may be attributable to imbalances between treatment arms in baseline viral susceptibility to lamivudine and tenofovir disoproxil fumarate and OBR.

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

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

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

℞ **LAMIVUDINE + TENOFOVIR DISOPROXIL FUMARATE**

300 mg/300 mg Film-coated tablet

Nucleoside and Nucleotide Reverse Transcriptase Inhibitor Combination

PATIENT INFORMATION

Lamivudine and Tenofovir Disoproxil Fumarate Tablets

Generic Name: lamivudine and tenofovir disoproxil fumarate

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

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

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

4. Talk to your doctor about taking an HIV test before starting treatment with lamivudine and tenofovir disoproxil fumarate tablets for chronic hepatitis B. You should also get a test for HBV if you are taking tenofovir disoproxil fumarate 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 children 2 years of age and older. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).
  - When used with other HIV medicines, lamivudine and tenofovir disoproxil fumarate tablets may reduce the amount of HIV in your blood (called "viral load"). Lamivudine and tenofovir disoproxil fumarate tablets may also help to increase the number of CD4 (T) cells in your blood which help fight off other infections. Reducing the amount of HIV and increasing the CD4 (T) cell count may improve your immune system. This may reduce your risk of death or infections that can happen when your immune system is weak (opportunistic infections).
  - Lamivudine and tenofovir disoproxil fumarate does not cure HIV infection or AIDS. People taking lamivudine and tenofovir disoproxil fumarate tablets may still develop infections or other conditions associated with HIV infection.
  - Patients must stay on continuous HIV therapy to control infection and decrease HIV- related illnesses.
  - It is very important that you stay under the care of your healthcare provider.
- to treat chronic hepatitis B virus (HBV) in adults. Lamivudine and Tenofovir disoproxil fumarate tablets will not cure HBV.
  - Lamivudine and Tenofovir disoproxil fumarate tablets may lower the amount of HBV in your body.
  - Lamivudine and Tenofovir disoproxil fumarate may improve the condition of your liver.

The long-term effects of taking lamivudine and tenofovir disoproxil fumarate tablets for treatment of chronic hepatitis B infection are not known.

It is not known if lamivudine and tenofovir disoproxil fumarate tablets are safe and effective for treatment of chronic hepatitis B in children under the age of 18 years.

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.

Talk to your healthcare provider about how you can take part in this registry.

Do not breastfeed if you are taking lamivudine and tenofovir disoproxil fumarate. Lamivudine and Tenofovir Disoproxil fumarate passes into your breast milk. You should not breastfeed because of the risk of passing HIV to your baby. Talk to your healthcare provider about the best way to feed your baby.

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

Size : 500 x 520 mm
Book Folding : 40 x 40 mm
Color : Black
Spec: Printed on 40 GSM Bible paper, front & back side printing.
Note: Position of the pharma code and product name will change as per folding machine feasibility.

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

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

- other medicines that contain tenofovir
- adefovir

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

- didanosine
- atazanavir
- lopinavir with ritonavir

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 it.
- Take lamivudine and tenofovir disoproxil fumarate tablets at the same time every day.
- For adults: the usual dose of lamivudine and tenofovir disoproxil fumarate tablets is one 300 mg tablet each day. If you have kidney problems, your healthcare provider may tell you to take lamivudine and tenofovir disoproxil fumarate tablets less often.
- Tell your healthcare provider if your child has problems with swallowing tablets.
- Take lamivudine and tenofovir disoproxil fumarate tablets by mouth, with or without food.
- 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 healthcare provider 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

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

- sleeping problems
- itching
- vomiting
- dizziness
- fever

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

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

Call your doctor for medical advice about side effects. You may report side effects to FDA at www.fda.gov.ph

How should I store lamivudine and tenofovir disoproxil fumarate tablets?

- Store below 30°C and protect from light and moisture.
- Keep lamivudine and tenofovir disoproxil fumarate tablets in the original container.
- Do not use lamivudine and tenofovir disoproxil fumarate tablets if the seal over the bottle opening is broken or missing.
- Keep the bottle tightly closed.

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

General information about lamivudine and tenofovir disoproxil fumarate tablets:

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information 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.

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

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

This leaflet summarizes the most important information about 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 Ingredient: lamivudine and tenofovir disoproxil fumarate

Inactive Ingredients: lactose monohydrate, corn starch, croscarmellose sodium, povidone, isopropyl alcohol, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, FD&C Blue #2/ indigo caramine AL and magnesium stearate.

July 2013

Manufactured by:
HETERO LABS LIMITED
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Hyderabad, Telangana State, INDIA

8.5 Geriatric Use

Lamivudine and Tenofovir Disoproxil Fumarate: Clinical trails of lamivudine 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 an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In particular, because lamivudine is substantially excreted by the kidney and elderly patients are more likely to have decreased renal function, renal function should be monitored and dosage adjustments should be made accordingly *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Lamivudine

There is no known antidote for lamivudine. One case of an adult ingesting 6 g of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Two cases of pediatric overdose were reported in ACTG300. One case involved a single dose of 7 mg/kg of lamivudine; the second case involved use of 5 mg/kg of lamivudine twice daily for 30 days. There were no clinical signs or symptoms noted in either case. 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.

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

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

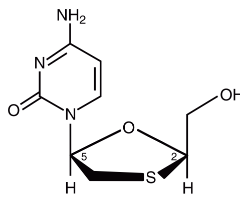
11 DESCRIPTION

Lamivudine and Tenofovir disoproxil fumarate Tablets are fixed dose combination tablets containing lamivudine and tenofovir disoproxil fumarate. Lamivudine (Epivir, also known as 3TC) belongs to the synthetic nucleoside analogue class of antiretroviral drugs. Tenofovir disoproxil fumarate (Viread, also known as tenofovir DF) is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Both lamivudine and tenofovir DF exhibit inhibitory activity against HIV-1 reverse transcriptase.

Lamivudine and Tenofovir disoproxil fumarate Tablets are for oral administration. Each tablet contains 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate, (which is equivalent to 245 mg of tenofovir disoproxil), as active ingredients. The tablets also have the following inactive ingredients lactose monohydrate, corn starch, croscarmellose sodium, povidone, isopropyl alcohol, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, FD&C Blue #2/ indigo caramine AL and magnesium stearate.

Lamivudine

Lamivudine (also known as 3TC), a synthetic nucleoside analogue with activity against HIV-1 and HBV. The chemical name of lamivudine is (2R, cis)-4-amino-1-(2-hydroxymethyl-1, 3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. 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. It has the following structural formula:

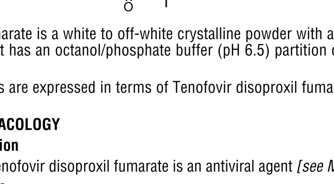


Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.

Tenofovir Disoproxil Fumarate

Tenofovir disoproxil fumarate which is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. *In vivo* tenofovir disoproxil fumarate is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir exhibits activity against HIV-1 reverse transcriptase.

The chemical name of tenofovir disoproxil fumarate is 9-[(*R*)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy] phosphinyl]methoxy]propyl] adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula:



Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in distilled water at 25°C. It has an octanol/phosphate buffer (pH 6.5) partition coefficient (log p) of 1.25 at 25 °C.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lamivudine and Tenofovir disoproxil fumarate is an antiviral agent *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

Lamivudine

Pharmacokinetics in Adults:

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 mononulear 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.

Effects of Food on Oral Absorption: An investigational 25-mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-1-infected patients on 2 occasions, once in the fasted state and once with food (1,099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate). Absorption of lamivudine was slower in the fed state (T_{max}: 3.2±1.3 hours) compared with the fasted state (T_{max}: 0.9±0.3 hours); C_{max} in the fed state was 40% 23% (mean±SD) lower than in the fasted state. There was no significant difference in systemic exposure (AUC∞) in the fed and fasted states; therefore, lamivudine tablets may be administered with or without food.

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-I-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-I-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 mcg/mL and 2.29 ± 0.69 mcg•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 mcg/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 to 80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of tenofovir disoproxil fumarate, 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.

Effects of Food on Oral Absorption

Administration of tenofovir disoproxil fumarate following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40% and an increase in C_{max} of approximately 14%. However, administration of tenofovir disoproxil fumarate with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the drug. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 0.33 ± 0.12 mcg/mL and 3.32 ± 1.37 mcg•hr/mL following multiple doses of tenofovir disoproxil fumarate 300 mg once daily in the fed state, when meal content was not controlled.

Special Population

Renal Impairment

Lamivudine and Tenofovir disoproxil fumarate Tablets: Because lamivudine and tenofovir require dose adjustment in the presence of renal impairment, Lamivudine and Tenofovir Disoproxil Fumarate Tablets are not recommended for patients with impaired renal function (Creatitine clearance below 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis (see **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS**)

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.

Pediatric Patients

Pediatric Patients 2 Years of Age and Older: Steady-state pharmacokinetics of tenofovir were evaluated in 31 HIV-1 infected pediatric subjects 2 to less than 18 years (Table 3). 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 3 Mean (± SD) Tenofovir Pharmacokinetic Parameters by Age Groups for Pediatric Patients

Dose and Formulation	300 mg Tablet
	12 to <18 Year (N=8)
C_{max} (mcg/mL)	0.38 ± 0.13
AUC_{tau} (mcg •hr/mL)	3.39 ± 1.22

Pharmacokinetic trials have not been performed in pediatric subjects under 12 years of age.

Geriatric Patients

The pharmacokinetics of lamivudine and tenofovir after administration of lamivudine and tenofovir to patients over 65 years of age have not been studied *[see Use in Specific Populations (8.5)]*.

Gender

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

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

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.

Drug Interactions

Lamivudine

Interferon Alfa: 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)]*.

Ribavirin: 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-I/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-I/HCV co-infected patients *[see Warnings and Precautions (5.4)]*.

Trimethoprim/Sulfamethoxazole: 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 (7.3)]*.

Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-I-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 (7.4)]*.

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 with other medicinal products is low *[See Clinical Pharmacology (12.3)]*.

Tenofovir disoproxil fumarate has been evaluated in healthy volunteers in combination with abacavir, atazanavir, didanosine, efavirenz, emtricitabine, entecavir, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin, saquinavir/ritonavir, and tacrolimus. Tables 3 and 4 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of tenofovir disoproxil fumarate on the pharmacokinetics of coadministered drug.

Table 4 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 x 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine (enteric-coated)	400 once	25	⇔	⇔	⇔
Didanosine (buffered)	250 or 400 once daily x 7 days	14	⇔	⇔	⇔
Efavirenz	600 once daily x 14 days	29	⇔	⇔	⇔
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	⇔
Entecavir	1 mg once daily x 10 days	28	⇔	⇔	⇔
Indinavir	800 three times daily x 7 days	13	↑14 (↓ 3 to ↑ 33)	⇔	⇔
Lamivudine	150 twice daily x 7 days	15	⇔	⇔	⇔
Lopinavir/Ritonavir	400/100 twice daily x 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Nelfinavir	1250 twice daily x 14 days	29	⇔	⇔	⇔
Saquinavir/ Ritonavir	1000/100 twice daily x 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 Prescribing Information

Following multiple dosing to HIV- 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 trials, indicating lack of clinically significant drug interactions between these agents and tenofovir disoproxil fumarate.

Table 5 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 x 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir[b]	Atazanavir/ Ritonavir 300/100 once daily x 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25[c] (↓ 42 to ↓ 3)	↓ 23[c] (↓ 46 to ↑ 10)
Efavirenz	600 once daily x 14 days	30	⇔	⇔	⇔
Emtricitabine	200 once daily x 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 x 7 days	12	↓11 (↓ 30 to ↑ 12)	⇔	⇔
Lamivudine	150 twice daily x 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24	⇔ ⇔	⇔ ⇔	⇔ ⇔
Methadone[d]	40 -110 once daily x 14 days[e]	13	⇔	⇔	⇔
Nelfinavir M8 metabolite	1250 twice daily x 14 days	29	⇔ ⇔	⇔ ⇔	⇔ ⇔
Oral Contraceptives[f]	Ethinyl Estradiol/ Norgestimate (Ortho-Tricyclen) once daily x 7 days	20	⇔	⇔	⇔
Ribavirin	600 once	22	⇔	⇔	NA
Saquinavir	Saquinavir/Ritonavir 1000/100 twice daily x 14 days	32	↑ 22 (↑ 6 to ↑ 41)	↑ 29[g] (↑ 12 to ↑ 48)	↑ 47[g] (↑ 23 to ↑ 76)
Ritonavir			⇔	⇔	↑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 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. R-(active), S- and total methadone exposures were equivalent when dosed alone or with tenofovir disoproxil fumarate.
e. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
f. Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir disoproxil fumarate.
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.

Table 6 summarizes the drug interaction between tenofovir disoproxil fumarate and didanosine. Coadministration of tenofovir disoproxil fumarate and didanosine should be undertaken with caution *[See Drug Interactions (7.1)]*. 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.

Table 6 Drug Interactions: Pharmacokinetic Parameters for Didanosine in the Presence of Tenofovir disoproxil fumarate

Didanosine Dose (mg)/ Method of Administration	Tenofovir disoproxil fumarate Method of Administration[a]	N	% Difference (90% CI) vs. Didanosine 400 mg Alone, Fasted[b]	
			C_{max}	AUC
Buffered tablets				
400 once daily[c] x 7 days	Fasted 1 hour after didanosine	14	↑28 (↑ 11 to ↑ 48)	↑ 44 (↑ 31 to ↑ 59)
Enteric coated capsules				
400 once, fasted	With food, 2 hours after didanosine	26	↑ 48 (↑ 25 to ↑ 76)	↑ 48 (↑ 31 to ↑ 67)
400 once, with food	Simultaneously with didanosine	26	↑ 64 (↑ 41 to ↑ 89)	↑ 60 (↑ 44 to ↑ 79)
250 once, fasted	With food, 2 hours after didanosine	28	↓ 10 (↓ 22 to ↑ 3)	⇔
250 once, fasted	Simultaneously with didanosine	28	⇔	↑ 14 (0 to ↑ 31)
250 once, with food	Simultaneously with didanosine	28	↓ 29 (↓ 39 to ↓ 18)	↓11 (↓ 23 to ↑ 2)

a. Administration with food was with a light meal (~373 kcal, 20% fat).
b. Increase = ↑; Decrease = ↓; No Effect = ⇔
c. Includes 4 subjects weighing less than 60 kg receiving ddI 250 mg.

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 the inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue into viral DNA. 3TC-TP is a weak inhibitor of mammalian 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 reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral Activity

Lamivudine

The antiviral activity of lamivudine against HIV-I 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 (1μM = 0.23 mcg/mL). HIV-I 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-I 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 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 trial.

In Study 934 of treatment-naïve subjects (tenofovir disoproxil fumarate + EMTRIVA + 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 EMTRIVA and lamivudine, was observed in 2/19 analyzed subject isolates in the tenofovir disoproxil fumarate + EMTRIVA 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 genotypic analysis.

Cross-Resistance

Lamivudine

Lamivudine-resistant HIV-1 mutants were cross-resistant to didanosine (ddI) and zalcitabine (ddC). In some patients treated with zidovudine plus didanosine or zalcitabine, 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%) patients enrolled in EPV20001 were identified as virological failures (plasma HIV-I RNA level ≥400 copies/mL) by Week 48. Twenty-eight patients were randomized to the lamivudine once-daily treatment group and 25 to the lamivudine twice-daily treatment group. The median baseline plasma HIV-I RNA levels of patients 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 patients identified as virologic failures in the lamivudine once-daily group showed that isolates from 0/22 patients contained treatment-emergent amino acid substitutions associated with zidovudine resistance (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E), isolates from 10/22 patients contained treatment-emergent amino acid substitutions associated with efavirenz resistance (L100I, K101E, K103N, V108I, or Y181C), and isolates from 8/22 patients contained a treatment-emergent lamivudine resistance-associated substitution (M184I or M184V).

Genotypic analysis of on-therapy isolates from patients (n = 22) in the lamivudine twice-daily treatment group showed that isolates from 1/22 patients contained treatment-emergent zidovudine resistance substitutions, isolates from 7/22 contained treatment-emergent efavirenz resistance substitutions, and isolates from 5/22 contained treatment-emergent lamivudine resistance substitutions.

Phenotypic analysis of baseline-matched on-therapy HIV-I isolates from patients (n =13) receiving lamivudine once daily showed that isolates from 12/13 patients were susceptible to zidovudine; isolates from 8/13 patients exhibited a 25- to 295-fold decrease in susceptibility to efavirenz, and isolates from 7/13 patients showed an 85- to 299-fold decrease in susceptibility to lamivudine.

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from patients (n=13) receiving lamivudine twice daily showed that isolates from all 13 patients were susceptible to zidovudine; isolates from 3/13 patients exhibited a 21- to 342-fold decrease in susceptibility to efavirenz, and isolates from 4/13 patients exhibited a 29- to 159-fold decrease in susceptibility to lamivudine.

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

Genotypic analysis of on-therapy HIV-1 isolates from patients (n = 9) in the lamivudine once-daily treatment group showed that isolates from 6 patients had an abacavir and/or lamivudine resistance-associated substitution M184V alone. On-therapy isolates from patients (n = 6) receiving lamivudine twice daily showed that isolates from 2 patients had M184V alone, and isolates from 2 patients harbored the M184Vsubstitution in combination with zidovudine resistance-associated amino acid substitutions.

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

Phenotypic analysis of on-therapy isolates from patients (n = 4) receiving lamivudine twice daily showed that HIV-I isolates from 1 patient exhibited a 45-fold decrease in susceptibility to lamivudine and a 4.5-fold decrease in susceptibility 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 subjects (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 trials, 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 trial results.

Several exploratory analyses were conducted to evaluate the effect of specific substitutions and substitutional patterns on virologic outcome. Because of the large number of potential comparisons, statistical testing was not conducted. Varying degrees of cross-resistance of 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 6 summarizes the HIV-1 RNA response by baseline tenofovir disoproxil fumarate susceptibility.

Table 7 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

Lamivudine

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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-I 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-I 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.

13.2 Reproductive Toxicology Studies

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

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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 trial 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/mm³ (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/mm³. Treatment outcomes through 48 and 144 weeks are presented in Table 8.

Table 8 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, subjects 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/mm³). 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/mm³ for the tenofovir disoproxil fumarate arm and 283 cells/mm³ 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 are available as tablets. Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil and 300 mg of lamivudine. The tablets are light blue colored capsule shaped biconvex tablets debossed with '129' on one side and 'H' on other side.

Bottles of 30 tablets

Store below 30ºC and protect from light and moisture.

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

Do not use if seal over bottle opening is broken or missing.

17 PATIENT COUNSELING INFORMATION

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 should be advised that the use of Lamivudine and Tenofovir disoproxil fumarate Tablets has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination. Patients should be advised to continue to practice safer sex and to use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Patients should be advised never to re-use or share needles or other equipment. Patients should be advised to never share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.

Patients co-infected with HIV-1 and HBV should be informed that deterioration of liver disease has occurred in some cases when treatment with Lamivudine and Tenofovir disoproxil fumarate Tablets was discontinued. Patients should be advised to discuss any changes in regimen with their physician. Patients should be advised that the long-term effects of lamivudine are unknown at this time.

Lamivudine and tenofovir disoproxil fumarate is excreted in human breast milk. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including Lamivudine and Tenofovir Disoproxil fumarate tablets, and that the cause and long-term health effects of these conditions are not known at this time.

Patients should be informed to take lamivudine and tenofovir disoproxil fumarate tablets exactly as prescribed.

Caution:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription

ADR REPORTING STATEMENT:
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

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