

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022344Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LAMIVUDINE and TENOFOVIR DISOPROXIL FUMARATE tablets, for oral use

Initial U.S. Approval: 2018

WARNING: POST TREATMENT ACUTE EXACERBATIONS OF HEPATITIS B

See full prescribing information for complete boxed warning.

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

INDICATIONS AND USAGE

Lamivudine and tenofovir disoproxil fumarate tablets is a two-drug combination of lamivudine (3TC) and tenofovir disoproxil fumarate (TDF), both nucleoside reverse transcriptase inhibitors and is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult and pediatric patients weighing at least 35 kg. (1)

DOSAGE AND ADMINISTRATION

- Testing: Prior to initiation and during treatment with lamivudine and tenofovir disoproxil fumarate tablets, patients should be tested for hepatitis B virus infection, and estimated creatinine clearance, urine glucose, and urine protein should be obtained. (2.1)
- Recommended dose: One tablet taken orally once daily with or without food. (2.2)
- Renal Impairment: Not recommended in patients with CrCL less than 50 mL/min or patients with end-stage renal disease requiring hemodialysis. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil). (3)

CONTRAINDICATIONS

- Lamivudine and tenofovir disoproxil fumarate tablets is contraindicated in patients with previous hypersensitivity to any of the components of this product. (4)

WARNINGS AND PRECAUTIONS

- Lactic acidosis and severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.1)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon and ribavirin-based regimens. Monitor for treatment-

associated toxicities. Discontinue lamivudine and tenofovir disoproxil fumarate tablets, as medically appropriate, and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.3)

- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue lamivudine and tenofovir disoproxil fumarate tablets as clinically appropriate. (5.4)
- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess estimated creatinine clearance (CrCl) before initiating treatment with tenofovir disoproxil fumarate, a component of lamivudine and tenofovir disoproxil fumarate tablets. In patients at risk for renal dysfunction, assess estimated creatinine clearance, serum phosphorus, urine glucose and urine protein before initiating treatment with tenofovir and periodically during treatment. Avoid administering lamivudine and tenofovir disoproxil fumarate tablets with concurrent or recent use of nephrotoxic drugs. (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)
- Immune reconstitution syndrome: Observed in HIV-infected patients. May necessitate further evaluation and treatment. (5.7)
- Triple nucleoside-only regimens: Early virologic failure has been reported in HIV-infected patients. Monitor carefully and consider treatment modification. (5.8)

ADVERSE REACTIONS

- Most common adverse reactions (> 10% with lamivudine and tenofovir disoproxil fumarate tablets) are headache, pain, depression, diarrhea, and rash. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Aurobindo Pharma USA, Inc. at 1-866-850-2876 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Atazanavir: Atazanavir should be co-administered with ritonavir when coadministered with lamivudine and tenofovir disoproxil fumarate tablets. (7.2)
- HIV-1 Protease Inhibitors: Monitor for evidence of tenofovir toxicity when lamivudine and tenofovir disoproxil fumarate tablets is co-administered with atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir. (7.2)
- Sorbitol: Avoid chronic administration of sorbitol with lamivudine and tenofovir disoproxil fumarate tablets. (7.5)

USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding not recommended due to potential for HIV transmission. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/2018

FULL PRESCRIBING INFORMATION: CONTENTS***WARNING: POST TREATMENT ACUTE EXACERBATIONS OF HEPATITIS B**

- 7.1 Drugs Affecting Renal Function
- 7.2 HIV-1 Protease Inhibitors
- 7.3 Hepatitis C Antiviral Agents
- 7.4 Drugs Inhibiting Organic Cation Transporters
- 7.5 Sorbitol

1 INDICATIONS AND USAGE**2 DOSAGE AND ADMINISTRATION**

- 2.1 Testing Prior to Initiation and During Treatment with Lamivudine and Tenofovir Disoproxil Fumarate Tablets
- 2.2 Recommended Dosage for Adult and Pediatric Patients Weighing at Least 35 kg
- 2.3 Not Recommended in Renal Impairment

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- 5.1 Lactic Acidosis and Severe Hepatomegaly with Steatosis
- 5.2 Severe Acute Exacerbations of Hepatitis B in Patients Coinfected with HIV-1 and HBV
- 5.3 Risk of Hepatic Decompensation When Used with Interferon- and Ribavirin-Based Regimens
- 5.4 Pancreatitis
- 5.5 New Onset or Worsening Renal Impairment
- 5.6 Bone Effects
- 5.7 Immune Reconstitution Syndrome
- 5.8 Early Virologic Failure

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment

10 OVERDOSAGE**11 DESCRIPTION****12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 Clinical Efficacy in Patients with HIV-1 Infection

16 HOW SUPPLIED/STORAGE AND HANDLING**17 PATIENT COUNSELING INFORMATION**

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

FULL PRESCRIBING INFORMATION

WARNING: POST TREATMENT ACUTE EXACERBATIONS OF HEPATITIS B

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 or tenofovir disoproxil fumarate, components of lamivudine and tenofovir disoproxil fumarate tablets. Monitor hepatic function closely in these patients and if appropriate, initiate anti-hepatitis B treatment [see *Warnings and Precautions* (5.2)].

1 INDICATIONS AND USAGE

Lamivudine and tenofovir disoproxil fumarate tablets is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult and pediatric patients weighing at least 35 kg.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation and During Treatment with Lamivudine and Tenofovir Disoproxil Fumarate Tablets

Prior to initiation of lamivudine and tenofovir disoproxil fumarate tablets, test patients for hepatitis B virus infection [see *Warnings and Precautions* (5.2)].

It is recommended that serum creatinine, serum phosphorus, estimated creatinine clearance, urine glucose, and urine protein be assessed before initiating lamivudine and tenofovir disoproxil fumarate tablets and during therapy in all patients as clinically appropriate [see *Warnings and Precautions* (5.5)].

2.2 Recommended Dosage for Adult and Pediatric Patients Weighing at Least 35 kg

Lamivudine and tenofovir disoproxil fumarate tablets is a two-drug fixed-dose combination product containing 300 mg of lamivudine (3TC) and 300 mg of tenofovir disoproxil fumarate (TDF). The recommended dosage of lamivudine and tenofovir disoproxil fumarate tablets in HIV-1-infected adult and pediatric patients weighing at least 35 kg is one tablet taken orally once daily with or without food.

2.3 Not Recommended in Renal Impairment

Because lamivudine and tenofovir disoproxil fumarate tablets is a fixed-dose combination formulation and cannot be dose adjusted, it is not recommended for patients with impaired renal function (creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis [see *Use in Specific Populations* (8.6)].

3 DOSAGE FORMS AND STRENGTHS

Tablets: 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil).

The tablets are blue colored, oval shaped, beveled edge, biconvex, film-coated tablets, debossed with 'J' on one side and '27' on the other side.

4 CONTRAINDICATIONS

Lamivudine and tenofovir disoproxil fumarate tablets is contraindicated in patients with a previous hypersensitivity reaction to any of the components contained in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis and Severe Hepatomegaly with Steatosis

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

5.2 Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV

Posttreatment Exacerbations of Hepatitis: All patients with HIV-1 should be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. Discontinuation of anti-HBV therapy, including 3TC and TDF, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue lamivudine and tenofovir disoproxil fumarate tablets should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

Important Differences Among Lamivudine-Containing Products: Lamivudine and tenofovir disoproxil fumarate tablets contain a higher dose of the same active ingredient, 3TC, than EPIVIR-HBV[®] tablets. EPIVIR-HBV[®] was developed for patients with chronic hepatitis B. The formulation and dosage of 3TC in EPIVIR-HBV[®] are not appropriate for patients co-infected with HIV-1 and HBV. Safety and efficacy of 3TC have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV.

If treatment with EPIVIR-HBV, TDF or a tenofovir alafenamide (TAF)-containing product 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.

5.3 Risk of Hepatic Decompensation When Used with Interferon- and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as 3TC, a component of lamivudine and tenofovir disoproxil fumarate tablets. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with 3TC in HIV-1/HCV co-infected patients [see *Clinical Pharmacology* (12.3)], hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and 3TC should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of 3TC should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6). See the full prescribing information for interferon and ribavirin.

5.4 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, 3TC, a component of lamivudine and tenofovir disoproxil fumarate tablets, should be used with caution. Treatment with lamivudine and tenofovir disoproxil fumarate tablets should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur [see *Adverse Reactions* (6.1)].

5.5 New Onset or Worsening Renal Impairment

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

It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with TDF. In patients at risk of renal dysfunction, it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of tenofovir disoproxil fumarate, and periodically during TDF therapy.

Avoid lamivudine and tenofovir disoproxil fumarate tablets with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)) [see *Drug Interactions* (7.1)]. Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on TDF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

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

5.6 Bone Effects

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

The effects of TDF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adults who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected, then appropriate consultation should be obtained.

Mineralization Defects: Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of TDF [see *Adverse Reactions (6.2)*]. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing TDF [see *Warnings and Precautions (5.5)*].

5.7 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including 3TC and TDF. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

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

5.8 Early Virologic Failure

Clinical trials in HIV-infected subjects have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTI) are generally less effective than triple drug regimens containing two NRTIs in combination with either a non-nucleoside reverse

transcriptase inhibitor or a HIV-1 protease inhibitor. In particular, early virological failure and high rates of resistance substitutions have been reported. Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

6 ADVERSE REACTIONS

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

- Lactic Acidosis and Severe Hepatomegaly with Steatosis [see *Warnings and Precautions (5.1)*].
- Exacerbations of Hepatitis B [see *Boxed Warning, Warnings and Precautions (5.2)*].
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C [see *Warnings and Precautions (5.3)*].
- Pancreatitis [see *Warnings and Precautions (5.4)*].
- New Onset or Worsening Renal Impairment [see *Warnings and Precautions (5.5)*].
- Bone Effects [see *Warnings and Precautions (5.6)*].
- Immune Reconstitution Syndrome [see *Warnings and Precautions (5.7)*].

6.1 Clinical Trials Experience

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

Lamivudine and Tenofovir Disoproxil Fumarate

Treatment-Naïve Patients

Study 903 - Adverse Reactions: The most common adverse reactions seen in a double-blind comparative controlled study in which 600 treatment-naïve subjects received TDF (N = 299) or stavudine (d4T) (N = 301) in combination with 3TC and EFV for 144 weeks 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 moderate to severe adverse reactions are summarized in Table 1.

Table 1. Selected Adverse Reactions^a (Grades 2 to 4) Reported in $\geq 5\%$ in Any Treatment Group in Study 903 (0 to 144 Weeks)

	TDF + 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 TDF (19% and 1%) respectively, laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir disoproxil fumarate and stavudine treatment arms. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 2.

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

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

Pancreatitis

Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric subjects receiving 3TC alone or in combination with other antiretroviral agents [see *Warnings and Precautions* (5.4)].

Changes in Bone Mineral Density

In HIV-1-infected adult subjects in Study 903, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving TDF + 3TC + EFV ($-2.2\% \pm 3.9$) compared with subjects receiving d4T + 3TC + EFV ($-1.0\% \pm 4.6$) through 144 weeks. Changes in BMD at the hip were similar between the two treatment groups ($-2.8\% \pm 3.5$ in the TDF group vs. $-2.4\% \pm 4.5$ in the d4T 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 TDF-treated subjects vs. 21% of the d4T-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 TDF group and 6 subjects in the d4T group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide) and higher serum parathyroid hormone levels and 1,25 Vitamin D levels in the TDF group relative to the d4T group; however, except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range [see *Warnings and Precautions* (5.6)].

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use for each of the individual components of lamivudine and tenofovir disoproxil fumarate tablets. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to 3TC and TDF.

Lamivudine

Body as a Whole: Redistribution/accumulation of body fat

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 [see *Warnings and Precautions* (5.1)], posttreatment exacerbation of hepatitis B [see *Warnings and Precautions* (5.2)].

Hypersensitivity: Anaphylaxis, urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Skin: Alopecia, pruritus.

Tenofovir Disoproxil Fumarate

Immune System Disorders: allergic reaction, including angioedema.

Metabolism and Nutrition Disorders: lactic acidosis, hypokalemia, hypophosphatemia.

Respiratory, Thoracic, and Mediastinal Disorders: dyspnea.

Gastrointestinal Disorders: pancreatitis, increased amylase, abdominal pain.

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: renal insufficiency, acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria [see Warnings and Precautions (5.6)].

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

7.1 Drugs Affecting Renal Function

Since tenofovir is primarily eliminated by the kidneys [see *Clinical Pharmacology* (12.3)], coadministration of lamivudine and tenofovir disoproxil fumarate tablets with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs [see Warnings and Precautions (5.5)].

7.2 HIV-1 Protease Inhibitors

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

Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir coadministered with ritonavir have been shown to increase tenofovir concentrations [see *Clinical Pharmacology* (12.3)]. Patients receiving lamivudine and tenofovir disoproxil fumarate tablets concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir should be monitored for tenofovir-associated adverse reactions. Lamivudine and tenofovir disoproxil fumarate tablets should be discontinued in patients who develop tenofovir-associated adverse reactions.

7.3 Hepatitis C Antiviral Agents

Coadministration of TDF, a component of lamivudine and tenofovir disoproxil fumarate tablets, and sofosbuvir/velpatasvir or ledipasvir/sofosbuvir has been shown to increase tenofovir exposure [see *Clinical Pharmacology* (12.3)].

In patients receiving lamivudine and tenofovir disoproxil fumarate tablets concomitantly with sofosbuvir/velpatasvir, monitor for adverse reactions associated with TDF.

In patients receiving lamivudine and tenofovir disoproxil fumarate tablets concomitantly with ledipasvir/sofosbuvir without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, monitor for adverse reactions associated with TDF.

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

7.4 Drugs Inhibiting Organic Cation Transporters

3TC, a component of lamivudine and tenofovir disoproxil fumarate tablets, 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) [see *Clinical Pharmacology* (12.3)]. No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of 3TC.

7.5 Sorbitol

Coadministration of single doses of 3TC and sorbitol resulted in a sorbitol dose-dependent reduction in 3TC exposures. When possible, avoid use of sorbitol-containing medicines with 3TC [see *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

Available data from the ARP show no difference in the risk of overall major birth defects for 3TC compared to the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) (*see Data*).

3TC produced embryonic toxicity in rabbits at a dose that produced similar human exposures as the recommended clinical dose. The relevance of animal findings to human pregnancy registry data is not known. There are no adequate and well-controlled studies with TDF in pregnant women. Because animal reproduction studies are not always predictive of human response, TDF should be used during pregnancy only if clearly needed.

Data

Human Data: Lamivudine: Based on prospective reports from the APR of over 11,000 exposures to 3TC during pregnancy resulting in live births (including over 4,300 exposed in the first trimester), there was no difference between lamivudine and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in the first trimester was 3.1% (95% CI: 2.6% to 3.7%).

3TC pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks gestation using 150 mg 3TC twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg 3TC twice daily with zidovudine, and 10 women at 38 weeks gestation using 3TC 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. 3TC pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. 3TC concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that 3TC crosses the placenta in humans. Amniotic fluid concentrations of 3TC were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg per mL (150 mg twice daily) and 2.1 to 5.2 mcg per mL (300 mg twice daily).

Animal Data: Lamivudine: Studies in pregnant rats showed that 3TC is transferred to the fetus through the placenta. Reproduction studies with orally administered 3TC have been performed in

rats and rabbits at doses producing plasma levels up to approximately 35 times that for the recommended adult HIV dose. No evidence of teratogenicity due to 3TC was observed. Evidence of early embryo-lethality 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.

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.

8.2 Lactation

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

Lamivudine: 3TC is excreted into human milk. Samples of breast milk obtained from 20 mothers receiving 3TC monotherapy 300 mg twice daily (2 times the dose in lamivudine and tenofovir disoproxil fumarate tablets), had measurable concentrations of 3TC. There is no information on the effects of 3TC on the breastfed infant, or the effects of 3TC on milk production.

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

Because of the potential for 1) HIV transmission (in HIV-negative infants); 2) developing viral resistance (in HIV-positive infants); and 3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving lamivudine and tenofovir disoproxil fumarate tablets.

8.4 Pediatric Use

The safety and effectiveness of lamivudine and tenofovir disoproxil fumarate tablets as a fixed-dose formulation in pediatric patients infected with HIV-1 and weighing at least 35 kg have been established based on clinical studies using the individual components (lamivudine and tenofovir disoproxil fumarate).

8.5 Geriatric Use

Clinical studies of lamivudine and tenofovir disoproxil fumarate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of lamivudine and tenofovir disoproxil fumarate tablets in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

Lamivudine and tenofovir disoproxil fumarate tablets is not recommended for patients with impaired renal function (i.e., creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis because it is a fixed-dose combination formulation that cannot be adjusted [see *Dosage and Administration* (2.3)].

10 OVERDOSAGE

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

Lamivudine: There is no known specific treatment for overdose with 3TC. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required. Because a negligible amount of 3TC 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 3TC overdose event.

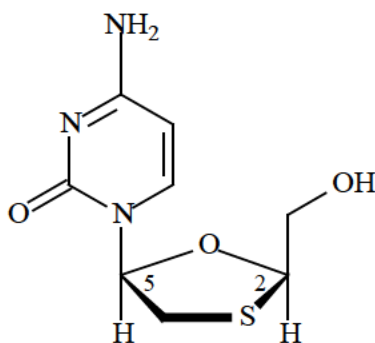
Tenofovir Disoproxil Fumarate: Limited clinical experience at doses higher than the therapeutic dose of TDF is available.

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir disoproxil fumarate, a 4-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

11 DESCRIPTION

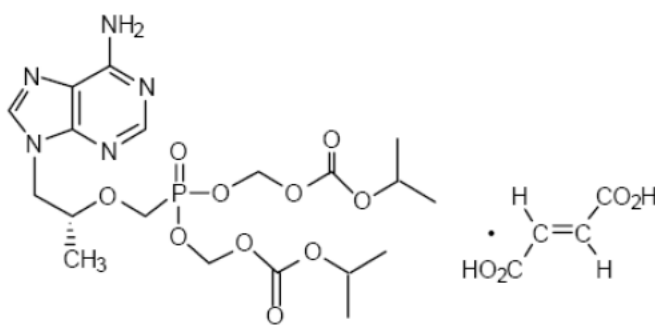
Lamivudine and tenofovir disoproxil fumarate tablets contain lamivudine (also known as 3TC), a synthetic nucleoside analogue with activity against HIV-1 and tenofovir disoproxil fumarate or tenofovir DF, a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester prodrug of tenofovir. *In vivo* tenofovir DF 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 lamivudine is (-)-1-[2R,5S)-2-Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Lamivudine is the (-)-enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of C₈H₁₁N₃O₃S and a molecular weight of 229.3 g per mol. It has the following structural formula:



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

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



Tenofovir DF is a white to off-white crystalline powder with a solubility of 13.4 mg per 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.

Lamivudine and tenofovir disoproxil fumarate tablets are for oral administration. Each tablet contains 300 mg of lamivudine USP and 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil, as active ingredients. The tablets also include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, FD&C Blue#2, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lamivudine and tenofovir disoproxil fumarate tablets is a fixed dose combination of antiviral drugs 3TC and TDF with antiviral activity against HIV-1 [see *Microbiology* (12.4)].

12.3 Pharmacokinetics

Pharmacokinetics in Adults

Lamivudine: After oral administration of 2 mg/kg of 3TC twice a day to 9 adults with HIV-1, the peak serum 3TC concentration ($C_{\max}$) was 1.5 ± 0.5 mcg/mL (mean $\pm$ 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 and absolute bioavailability in 12 adult patients was $86\% \pm 16\%$ (mean $\pm$ SD) for the 150-mg tablet and $87\% \pm 13\%$ for the oral solution. Binding of 3TC to human plasma proteins is low ($< 36\%$). Within 12 hours after a single oral dose of 3TC in 6 HIV-1-infected adults, $5.2\% \pm 1.4\%$ (mean $\pm$ SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. The majority of 3TC is eliminated unchanged in urine by active organic cationic secretion and the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to 7 hours in most single-dose studies with serum sampling for 24 hours after dosing.

Tenofovir Disoproxil Fumarate: Following oral administration of a single 300 mg dose of TDF to HIV-1-infected subjects in the fasted state, maximum serum concentrations ($C_{\max}$) were achieved in 1.0 ± 0.4 hrs (mean $\pm$ SD) and $C_{\max}$ and AUC values were 296 ± 90 ng/mL and 2287 ± 685 ng•hr/mL, respectively. The oral bioavailability of tenofovir from TDF in fasted subjects is approximately 25%. Less than 0.7% of tenofovir binds to human plasma proteins *in vitro* and the binding is independent of concentration over the range of 0.01 to 25 mcg/mL. Approximately 70 to 80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of 243 ± 33 mL/min (mean $\pm$ SD). Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

Special Populations

Race

Lamivudine: There are no significant or clinically relevant racial differences in 3TC 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.

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

Gender: There are no significant or clinically relevant gender differences in the pharmacokinetics of lamivudine and tenofovir.

Patients with Renal Impairment: [see *Use in Specific Populations (8.6)*].

Lamivudine: The pharmacokinetics of lamivudine are altered in subjects with renal impairment

(Table 3).

Table 3. Pharmacokinetic Parameters (Mean $\pm$ SD) after a Single 300-mg Oral Dose of 3TC in Subjects with Varying Degrees of Renal Function

Parameter	Creatinine Clearance Criterion (Number of Subjects)		
	> 60 mL/min (n = 6)	10 to 30 mL/min (n = 4)	< 10 mL/min (n = 6)
Creatinine clearance (mL/min)	111 $\pm$ 14	28 $\pm$ 8	6 $\pm$ 2
C _{max} (mcg/mL)	2.6 $\pm$ 0.5	3.6 $\pm$ 0.8	5.8 $\pm$ 1.2
AUC _∞ (mcg•h/mL)	11.0 $\pm$ 1.7	48.0 $\pm$ 19	157 $\pm$ 74
Cl/F (mL/min)	464 $\pm$ 76	114 $\pm$ 34	36 $\pm$ 11

Tenofovir Disoproxil Fumarate: The pharmacokinetics of tenofovir are altered in subjects with renal impairment [see *Warnings and Precautions* (5.5)]. In subjects with creatinine clearance below 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, and AUC_{0-∞} of tenofovir were increased (Table 4).

Table 4. Pharmacokinetic Parameters (Mean $\pm$ SD) of Tenofovir in Subjects after a Single 300-mg Oral Dose of TDF in Subjects with Varying Degrees of Renal Function

Baseline Creatinine Clearance (mL/min)	> 80 (N = 3)	50 to 80 (N = 10)	30 to 49 (N = 8)	12 to 29 (N = 11)
C _{max} (μg/mL)	0.34 $\pm$ 0.03	0.33 $\pm$ 0.06	0.37 $\pm$ 0.16	0.60 $\pm$ 0.19
AUC _{0-∞} (μg•hr/mL)	2.18 $\pm$ 0.26	3.06 $\pm$ 0.93	6.01 $\pm$ 2.50	15.98 $\pm$ 7.22
CL/F (mL/min)	1043.7 $\pm$ 115.4	807.7 $\pm$ 279.2	444.4 $\pm$ 209.8	177.0 $\pm$ 97.1
CL _{renal} (mL/min)	243.5 $\pm$ 33.3	168.6 $\pm$ 27.5	100.6 $\pm$ 27.5	43.0 $\pm$ 31.2

Patients with Hepatic Impairment

Lamivudine: The pharmacokinetics of lamivudine were not altered by diminishing 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 TDF have been studied in non-HIV infected subjects with moderate to severe (Child-Pugh B to C) hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects.

Assessment of Drug Interactions: [see *Drug Interactions* (7)].

Lamivudine:

Effect of 3TC on the Pharmacokinetics of Other Agents: Based on *in vitro* study results, 3TC at therapeutic drug exposures is not expected to affect the pharmacokinetics of drugs that are substrates of the following transporters: organic anion transporter polypeptide 1B1/3 (OATP1B1/3), breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), multidrug and toxin extrusion protein 1 (MATE1), MATE2-K, organic cation transporter 1 (OCT1), OCT2, or OCT3.

Effect of Other Agents on the Pharmacokinetics of 3TC: 3TC is a substrate of MATE1, MATE2-K, and OCT2 *in vitro*. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase 3TC plasma concentrations. This interaction is not considered clinically significant as no dose adjustment of 3TC is needed.

3TC is a substrate of P-gp and BCRP; however, considering its absolute bioavailability (87%), it is unlikely that these transporters play a significant role in the absorption of 3TC. Therefore, coadministration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of 3TC.

Interferon Alfa: There was no significant pharmacokinetic interaction between 3TC and interferon alfa in a trial of 19 healthy male subjects [see *Warnings and Precautions* (5.3)].

Ribavirin: *In vitro* data indicate ribavirin reduces phosphorylation of 3TC, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and 3TC (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects [see *Warnings and Precautions* (5.3)].

Sorbitol (Excipient): 3TC and sorbitol solutions were coadministered to 16 healthy adult subjects in an open-label, randomized sequence, 4-period, crossover trial. Each subject received a single 300-mg dose of 3TC oral solution alone or coadministered with a single dose of 3.2 grams, 10.2 grams, or 13.4 grams of sorbitol in solution. Coadministration of 3TC with sorbitol resulted in dose-dependent decreases of 20%, 39%, and 44% in the AUC₍₀₋₂₄₎, 14%, 32%, and 36% in the AUC_(∞), and 28%, 52%, and 55% in the C_{max} of 3TC.

Trimethoprim/Sulfamethoxazole: 3TC and TMP/SMX were coadministered to 14 HIV-1-positive subjects in a single-center, open-label, randomized, crossover trial. Each subject received treatment with a single 300 mg dose of 3TC and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of 3TC 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with 3TC resulted in an increase of 43% ± 23% (mean ± SD) in 3TC AUC_∞, a decrease of 29% ± 13% in lamivudine oral clearance, and a decrease of 30% ± 36% in 3TC renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with 3TC. There is no information regarding the effect on 3TC pharmacokinetics of higher doses of TMP/SMX such as those used in treat PCP.

Tenofovir Disoproxil Fumarate: At concentrations substantially higher (~300-fold) than those observed *in vivo*, tenofovir did not inhibit *in vitro* 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.

TDF has been evaluated in healthy volunteers in combination with other antiretroviral and

potential concomitant drugs. Tables 5 and 6 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of TDF on the pharmacokinetics of coadministered drug.

No clinically significant drug interactions have been observed between TDF and efavirenz, methadone, nelfinavir, oral contraceptives, ribavirin or sofosbuvir.

Table 5. 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}
Atazanavir ^c	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Atazanavir/ Ritonavir ^c	300/100 once daily	12	↑ 34 (↑ 20 to ↑ 51)	↑ 37 (↑ 30 to ↑ 45)	↑ 29 (↑ 21 to ↑ 36)
Darunavir/ Ritonavir ^d	300/100 twice daily	12	↑ 24 (↑ 8 to ↑ 42)	↑ 22 (↑ 10 to ↑ 35)	↑ 37 (↑ 19 to ↑ 57)
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	↔	↔
Ledipasvir/ Sofosbuvir ^{e,f}	90/400 once daily x 10 days	24	↑ 47 (↑ 37 to ↑ 58)	↑ 35 (↑ 29 to ↑ 42)	↑ 47 (↑ 38 to ↑ 57)
Ledipasvir/ Sofosbuvir ^{e,g}		23	↑ 64 (↑ 54 to ↑ 74)	↑ 50 (↑ 42 to ↑ 59)	↑ 59 (↑ 49 to ↑ 70)
Ledipasvir/ Sofosbuvir ^h	90/400 once daily x 14 days	15	↑ 79 (↑ 56 to ↑ 104)	↑ 98 (↑ 77 to ↑ 123)	↑ 163 (↑ 132 to ↑ 197)
Ledipasvir/ Sofosbuvir ⁱ	90/400 once daily x 10 days	14	↑ 32 (↑ 25 to ↑ 39)	↑ 40 (↑ 31 to ↑ 50)	↑ 91 (↑ 74 to ↑ 110)
Ledipasvir/ Sofosbuvir ^j	90/400 once daily x 10 days	29	↑ 61 (↑ 51 to ↑ 72)	↑ 65 (↑ 59 to ↑ 71)	↑ 115 (↑ 105 to ↑ 126)
Lopinavir/ Ritonavir	400/100 twice daily × 14 days	24	↔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Saquinavir/ Ritonavir	1000/100 twice daily × 14 days	35	↔	↔	↑ 23 (↑ 16 to ↑ 30)
Sofosbuvir ^k	400 single dose	16	↑ 25 (↑ 8 to ↑ 45)	↔	↔
Sofosbuvir/ Velpatasvir ^l	400/100 once daily	24	↑ 55 (↑ 43 to ↑ 68)	↑ 30 (↑ 24 to ↑ 36)	↑ 39 (↑ 31 to ↑ 48)
Sofosbuvir/ Velpatasvir ^m	400/100 once daily	29	↑ 55 (↑ 45 to ↑ 66)	↑ 39 (↑ 33 to ↑ 44)	↑ 52 (↑ 45 to ↑ 59)
Sofosbuvir/ Velpatasvir ⁿ	400/100 once daily	15	↑ 77 (↑ 53 to ↑ 104)	↑ 81 (↑ 68 to ↑ 94)	↑ 121 (↑ 100 to ↑ 143)

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters ^b (90% CI)		
			C _{max}	AUC	C _{min}
Sofosbuvir/Velpatasvir ^o	400/100 once daily	24	↑ 36 (↑ 25 to ↑ 47)	↑ 35 (↑ 29 to ↑ 42)	↑ 45 (↑ 39 to ↑ 51)
Sofosbuvir/Velpatasvir ^p	400/100 once daily	24	↑ 44 (↑ 33 to ↑ 55)	↑ 40 (↑ 34 to ↑ 46)	↑ 84 (↑ 76 to ↑ 92)
Sofosbuvir/Velpatasvir ^q	400/100 once daily	30	↑ 46 (↑ 39 to ↑ 54)	↑ 40 (↑ 34 to ↑ 45)	↑ 70 (↑ 61 to ↑ 79)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↑ 13 (↑ 1 to ↑ 27)	↔	↔
Tipranavir/Ritonavir ^r	500/100 twice daily	22	↓ 23 (↓ 32 to ↓ 13)	↓ 2 (↓ 9 to ↑ 5)	↑ 7 (↓ 2 to ↑ 17)
	750/200 twice daily (23 doses)	20	↓ 38 (↓ 46 to ↓ 29)	↑ 2 (↓ 6 to ↑ 10)	↑ 14 (↑ 1 to ↑ 27)

a. Subjects received TDF 300 mg once daily.

b. Increase = ↑; Decrease = ↓; No Effect = ↔

c. Reyataz (atazanavir) Prescribing Information.

d. Prezista (darunavir) Prescribing Information.

e. Data generated from simultaneous dosing with HARVONI (ledipasvir/sofosbuvir). Staggered administration (12 hours apart) provide similar results.

f. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/TDF.

g. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/TDF.

h. Study conducted with ATRIPLA (efavirenz/emtricitabine/tenofovir DF) coadministered with HARVONI.

i. Study conducted with COMPLERA (emtricitabine/rilpivirine/tenofovir DF) coadministered with HARVONI.

j. Study conducted with TRUVADA (emtricitabine/tenofovir DF) + dolutegravir coadministered with HARVONI.

k. Study conducted with ATRIPLA coadministered with SOVALDI[®] (sofosbuvir).

l. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/TDF.

m. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/TDF.

n. Study conducted with ATRIPLA coadministered with EPCLUSA (sofosbuvir/velpatasvir).

o. Study conducted with STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir DF) coadministered with EPCLUSA.

p. Study conducted with COMPLERA coadministered with EPCLUSA.

q. Administered as raltegravir + emtricitabine/TDF.

r. Aptivus (tipranavir) Prescribing Information.

Coadministration of TDF with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Concomitant dosing of TDF with didanosine significantly increases the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with TDF, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions (Table 6). The mechanism of this interaction is unknown.

No effect on the pharmacokinetic parameters of the following coadministered drugs was observed with TDF: abacavir, didanosine (buffered tablets), emtricitabine, entecavir, and lamivudine.

Table 6. Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of TDF

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)
Darunavir ^d	Darunavir/Ritonavir 300/100 once daily	12	↑ 16 (↓ 6 to ↑ 42)	↑ 21 (↓ 5 to ↑ 54)	↑ 24 (↓ 10 to ↑ 69)
Didanosine ^e	250 once, simultaneously with TDF and a light meal ^f	33	↓ 20 ^g (↓ 32 to ↓ 7)	↔ ^g	NA
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	↔	↔	↔
Saquinavir Ritonavir	Saquinavir/Ritonavir 1000/100 twice daily x 14 days	32	↑ 22 (↑ 6 to ↑ 41)	↑ 29 ^h (↑ 12 to ↑ 48)	↑ 47 ^h (↑ 23 to ↑ 76)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↔	↔	↔
Tipranavir ⁱ	Tipranavir/Ritonavir 500/100 twice daily	22	↓ 17 (↓ 26 to ↓ 6)	↓ 18 (↓ 25 to ↓ 9)	↓ 21 (↓ 30 to ↓ 10)
	Tipranavir/Ritonavir 750/200 twice daily (23 doses)	20	↓ 11 (↓ 16 to ↓ 4)	↓ 9 (↓ 15 to ↓ 3)	↓ 12 (↓ 22 to 0)

a. Increase = ↑; Decrease = ↓; No Effect = ↔; NA = Not Applicable

b. Reyataz (atazanavir) Prescribing Information.

c. In HIV-infected subjects, addition of TDF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.

- d. Prezista (darunavir) Prescribing Information.
- e. Videx EC Prescribing Information. Subjects received didanosine enteric-coated capsules.
- f. 373 kcal, 8.2 g fat
- g. Compared with didanosine (enteric-coated) 400 mg administered alone under fasting conditions.
- h. 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.
- i. Aptivus (tipranavir) Prescribing Information.

12.4 Microbiology

Mechanism of Action

Lamivudine: 3TC is a synthetic nucleoside analogue with activity against HIV-1 and HBV. Intracellularly, 3TC is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue.

Tenofovir Disoproxil Fumarate: TDF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. TDF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. 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 3TC against HIV-1 was assessed in a number of cell lines including monocytes and fresh human peripheral blood lymphocytes (PBMCs) using standard susceptibility assays. EC_{50} values were in the range of 3 to 15,000 nM. (1 μ M = 0.23 mcg/mL). The median EC_{50} values of 3TC were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B), respectively. The EC_{50} values against HIV-2 isolates (n = 4) ranged from 3 to 120 nM in PBMCs. 3TC was not antagonistic to all tested anti-HIV agents. Ribavirin (50 μ M) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of 3TC by 3.5-fold in MT-4 cells.

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 μ M to 8.5 μ M. 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 μ M to 2.2 μ M) and strain-specific activity against HIV-2 (EC_{50} values ranged from 1.6 μ M to 5.5 μ M). Please see the full prescribing information for VIREAD® for information regarding the inhibitory activity of TDF against HBV.

Resistance

Lamivudine: 3TC-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis showed that resistance was predominantly due to a methionine to valine or isoleucine (M184V/I).

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 addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to tenofovir. K65R substitutions developed in some subjects failing a TDF regimen.

Cross-Resistance

Lamivudine: Cross-resistance among NRTIs has been observed. 3TC-resistant HIV-1 isolate were cross-resistant in cell culture to didanosine (ddI). Cross-resistance is also expected with abacavir and emtricitabine as these select M184V substitutions.

Tenofovir Disoproxil Fumarate: Cross-resistance among NRTIs has been observed. The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1 infected subjects treated with abacavir or didanosine. HIV-1 isolates with the K65R substitution also showed reduced susceptibility to emtricitabine and 3TC. HIV-1 isolates from subjects (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated reverse transcriptase amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir.

Subjects whose virus expressed an L74V substitution without zidovudine resistance associated substitutions (N=8) had reduced response to VIREAD. Limited data are available for patients whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4), all of whom had a reduced response.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lamivudine: Long-term carcinogenicity studies with 3TC in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) the human exposures at the recommended dose of 300 mg.

3TC was not mutagenic in a microbial mutagenicity assay, in an *in vitro* cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in assay for unscheduled DNA synthesis in rat liver. 3TC showed no evidence of *in vivo* genotoxic activity in

the rat at oral doses of up to 2000 mg per kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection.

In a study of reproductive performance, 3TC administered to rats at doses up to 4,000 mg per kg per day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

Tenofovir Disoproxil Fumarate: Long-term oral carcinogenicity studies of TDF 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.

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

There were no effects on fertility, mating performance or early embryonic development when TDF 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 Disoproxil Fumarate

Tenofovir and TDF 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

Trial 903

Data through 144 weeks are reported for Trial 903, a double-blind, active-controlled multicenter trial comparing EFV 600 mg + 3TC 300 mg + TDF 300 mg vs. EFV 600 mg + 3TC 300 mg + stavudine (d4T) 40 mg 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 7.

Table 7 Outcomes of Randomized Treatment at Week 48 and 144 (Study 903)

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

^a Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48 and 144.

^b Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48 and 144.

^c Includes lost to follow-up, subject's withdrawal, noncompliance, protocol violation and other reasons.

Achievement of plasma HIV-1 RNA concentrations of less than 400 copies/mL at Week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (> or ≤100,000 copies/mL) and CD4⁺ cell count (< or ≥200 cells/mm³). Through 144 weeks of therapy, 62% and 58% of subjects in the TDF 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 TDF arm and 283 cells/mm³ for the stavudine arm.

Through 144 weeks, 11 subjects in the TDF 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 blue colored, oval shaped, beveled edge, biconvex, film-coated tablets debossed with 'J' on one side and '27' on the other side. They are supplied as follows:

Bottles of 30 tablets with desiccant, induction seal and child-resistant cap NDC 65862-543-30

Store below 30°C (86°F)

Store in the original container and keep the bottle tightly closed. Do not remove desiccant.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Lactic Acidosis and Severe Hepatomegaly

Inform patients that lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Lamivudine and tenofovir disoproxil fumarate tablets should be suspended in any patient who develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) [see *Warnings and Precautions* (5.1)].

Patients with Hepatitis B or C Co-infection

Inform patients co-infected with HIV-1 and HBV that deterioration of liver disease has occurred in some cases when treatment with lamivudine and tenofovir disoproxil fumarate were discontinued. Advise patients to discuss any changes in regimen with their healthcare provider [see *Warnings and Precautions* (5.2)].

Inform patients with HIV-1/HCV co-infection that hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin [see *Warnings and Precautions* (5.3)].

Risk of Pancreatitis

Advise parents or guardians to monitor pediatric patients for signs and symptoms of pancreatitis [see *Warnings and Precautions* (5.4)].

New Onset or Worsening Renal Impairment

Inform patients that renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported. Advise patients with impaired renal function (i.e., creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis to avoid lamivudine and tenofovir disoproxil fumarate tablets with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) for patients [see *Dosage and Administration* (2.3), *Warnings and Precautions* (5.5)].

Decreases in Bone Mineral Density

Inform patients that decreases in bone mineral density have been observed with the use of TDF, a component of lamivudine and tenofovir disoproxil fumarate tablets, in patients with HIV [see *Warnings and Precautions* (5.6)].

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any signs or symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy [*see Warnings and Precautions (5.7)*].

Pregnancy Registry

Advise patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes in women exposed to lamivudine and tenofovir disoproxil fumarate tablets [*see Use in Specific Populations (8.1)*].

Lactation

Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk [*see Use in Specific Populations (8.2)*].

Missed Dosage

Instruct patients that if they miss a dose of lamivudine and tenofovir disoproxil fumarate tablets, to take it as soon as they remember. Advise patients not to double their next dose or take more than the prescribed dose.

Storage

Instruct patients to store lamivudine and tenofovir disoproxil fumarate tablets in the original package and keep the bottle tightly closed. Do not remove desiccant.

All brands listed are the trademarks of their respective owners and are not trademarks of Aurobindo Pharma Limited.

Patient Information
Lamivudine and Tenofovir Disoproxil Fumarate Tablets

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:

- **Too much lactic acid in your blood (lactic acidosis).** Lactic acidosis is a serious medical emergency that can lead to death.

Tell your healthcare provider right away if you get any of the following symptoms that could be signs of lactic acidosis:

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

- **Severe liver problems.** In some cases, severe liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis).

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

- | | |
|--|--|
| o your skin or the white part of your eyes turns yellow (jaundice) | o loss of appetite for several days or longer |
| o dark or "tea-colored" urine | o nausea |
| o light-colored stools (bowel movements) | o pain, aching, or tenderness on the right side of your stomach area |

- **Worsening of hepatitis B infection.** If you have Human Immunodeficiency Virus type 1 (HIV-1) and hepatitis B Virus (HBV) infection, your HBV may get worse (flare-up) if you stop taking lamivudine and tenofovir disoproxil fumarate tablets. A "flare-up" is when your HBV infection suddenly returns in a worse way than before. Your healthcare provider will test you for HBV infection before you start treatment with lamivudine and tenofovir disoproxil fumarate tablets.

- o It is not known if lamivudine and tenofovir disoproxil fumarate tablets is safe and effective in people who have both HIV-1 and HBV infection.
 - o Do not run out of lamivudine and tenofovir disoproxil fumarate tablets. Refill your prescription or talk to your healthcare provider before your lamivudine and tenofovir disoproxil fumarate tablets is all gone.
 - o **Do not stop 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 blood tests regularly for several months to check your liver.

- **Use with interferon and ribavirin-based regimens.** Worsening of liver disease that has caused death has happened in people infected with HIV-1 and hepatitis C virus who were taking antiretroviral medicines for HIV-1 and were also being treated for hepatitis C with interferon alfa with or without ribavirin. If you are taking lamivudine and tenofovir disoproxil fumarate tablets and interferon alfa with or without ribavirin, tell your healthcare provider if you have any new symptoms.

For more information about side effects, see "What are the possible side effects of lamivudine and tenofovir disoproxil fumarate tablets?"

What is lamivudine and tenofovir disoproxil fumarate tablets?

Lamivudine and tenofovir disoproxil fumarate tablets is a prescription medicine that is used with other antiretroviral medicines to treat Human Immunodeficiency Virus-1 (HIV-1) in adults and children weighing at least 77 pounds (35 kg).

HIV-1 is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

Lamivudine and tenofovir disoproxil fumarate tablets contains the prescription medicines lamivudine and tenofovir disoproxil fumarate.

Who should not take lamivudine and tenofovir disoproxil fumarate tablets?**Do not take lamivudine and tenofovir disoproxil fumarate tablets if you:**

- are allergic to lamivudine, tenofovir disoproxil fumarate, or any of the ingredients in lamivudine and tenofovir disoproxil fumarate tablets. See the end of this Patient Information leaflet for a complete list of ingredients in lamivudine and tenofovir disoproxil fumarate tablets.

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 about all of your medical conditions, including if you:**

- have or have had liver problems, including hepatitis B or C virus infection
- have kidney problems, including end-stage renal disease (ESRD) that requires dialysis
- have bone problems, including a history of bone fractures
- are pregnant or plan to become pregnant. It is not known if lamivudine and tenofovir disoproxil fumarate tablets will harm your unborn baby.

Pregnancy Registry. There is a pregnancy registry for women who take lamivudine and tenofovir disoproxil fumarate tablets during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. Do not breastfeed if you take lamivudine and tenofovir disoproxil fumarate tablets.
 - o You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
 - o 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 over-the-counter medicines, vitamins and herbal supplements.

Some medicines interact with lamivudine and tenofovir disoproxil fumarate tablets. Lamivudine and tenofovir disoproxil fumarate tablets may affect the way other medicines work, and other medicines may affect how lamivudine and tenofovir disoproxil fumarate tablets works. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with lamivudine and tenofovir disoproxil fumarate tablets.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take lamivudine and tenofovir disoproxil fumarate tablets with other medicines.

How should I take 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 1 time each day with or without food.
- If you miss a dose of lamivudine and tenofovir disoproxil fumarate tablets, take it as soon as you remember. Do not take 2 doses at the same time or take more than what your healthcare provider tells you to take.

- Stay under the care of your healthcare provider during treatment with lamivudine and tenofovir disoproxil fumarate tablets.
- Do not run out of lamivudine and tenofovir disoproxil fumarate tablets. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy.
- If you take too much lamivudine and tenofovir disoproxil fumarate tablets, go to the nearest hospital emergency room right away.

What should I avoid while taking lamivudine and tenofovir disoproxil fumarate tablets?

You should avoid taking medicines that contain sorbitol during treatment with lamivudine and tenofovir disoproxil fumarate tablets.

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

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

- **See “What is the most important information I should know about lamivudine and tenofovir disoproxil fumarate tablets?”**
- **Risk of inflammation of the pancreas (pancreatitis).** Children may be at risk for developing pancreatitis during treatment with lamivudine and tenofovir disoproxil fumarate tablets if they:
 - o have taken nucleoside analogue medicines in the past
 - o have a history of pancreatitis
 - o have other risk factors for pancreatitis

Call your healthcare provider right away if your child develops signs and symptoms of pancreatitis including severe upper stomach-area pain, with or without nausea and vomiting. Your healthcare provider may tell you to stop giving lamivudine and tenofovir disoproxil fumarate tablets to your child if their symptoms and blood test results show that your child may have pancreatitis.
- **New or worse kidney problems, including kidney failure.** Your healthcare provider may do blood and urine tests to check your kidneys before and during treatment with lamivudine and tenofovir disoproxil fumarate tablets. Tell your healthcare provider if you get signs and symptoms of kidney problems, including bone pain that does not go away or worsening bone pain, pain in your arms, hands, legs or feet, broken (fractured) bones, muscle pain or weakness.
- **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 tests to check your bones. Tell your healthcare provider if you have any bone pain, pain in your hands or feet, or muscle pain or weakness during treatment with lamivudine and tenofovir disoproxil fumarate tablets.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 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 you start taking lamivudine and tenofovir disoproxil fumarate tablets.

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

- headache
- pain
- depression
- diarrhea
- rash

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.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store lamivudine and tenofovir disoproxil fumarate tablets?

- Store lamivudine and tenofovir disoproxil fumarate tablets below 30°C (86°F).

- Keep lamivudine and tenofovir disoproxil fumarate tablets in the original bottle.
- The bottle has a child-resistant cap. Keep the bottle tightly closed.
- The bottle contains a desiccant packet to help keep your medicine dry (protect it from moisture). Do not remove the desiccant packet from the bottle.

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

General information about the safe and effective use of lamivudine and tenofovir disoproxil fumarate tablets.

Medicines are sometimes prescribed for purposes other than those listed in a 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 symptoms that you have. It may harm them. 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 tablets 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: colloidal silicon dioxide, croscarmellose sodium, FD&C Blue#2, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

All trademarks referenced herein are the property of their respective owners.

Distributed by: **Aurobindo Pharma USA, Inc.** 279 Princeton-Hightstown Road East Windsor, NJ 08520

Manufactured by: **Aurobindo Pharma Limited** Hyderabad-500 038, India

For more information, call Aurobindo Pharma USA, Inc. at 1-866-850-2876.

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

Issued: May 2018

NDC 65862-543-30

Rx only

Lamivudine and Tenofovir Disoproxil Fumarate Tablets

300 mg/300 mg

 AUROBINDO

30 Tablets

Each film-coated tablet contains:
300 mg of lamivudine USP and 300 mg
of tenofovir disoproxil fumarate, which
is equivalent to 245 mg of tenofovir
disoproxil.

Usual Dosage: See package insert for
Dosage and Administration.

Store below 30°C (86°F)
Store in the original bottle and keep
bottle tightly closed. Do not remove
desiccant.

This bottle is child-resistant.
Do not use if seal over bottle opening is
broken or missing.

Distributed by:
Aurobindo Pharma USA, Inc.
279 Princeton-Hightstown Road
East Windsor, NJ 08520

Made in India

Code: TS/DRUGS/22/2009



P1417010

*

***Over Printing Zone**

(Batch Details shall be printed online during packing)

Example: LOT XXXXXXXXX-A

EXP MMM/YYYY



***Over Printing Zone**
(Batch Details shall be printed online during packing)

Example:
GTIN 10365862543308
S. No XXXXXXXXXXXXXXXX
EXP MMM/YYYY
LOT XXXXXXXXX-A

P1025493

NDC 65862-543-30

**Lamivudine and
Tenofovir Disoproxil
Fumarate Tablets**

300 mg/300 mg

Rx only

30 Tablets



Each film-coated tablet contains:
300 mg of lamivudine USP and 300 mg of
tenofovir disoproxil fumarate, which is
equivalent to 245 mg of tenofovir disoproxil.

Usual Dosage: See package insert for Dosage
and Administration.

Store below 30°C (86°F)

Store in the original bottle and keep bottle
tightly closed. Do not remove desiccant.

The enclosed bottle is child-resistant.

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

NDC 65862-543-30

**Lamivudine and
Tenofovir Disoproxil
Fumarate Tablets**

300 mg/300 mg

Rx only

30 Tablets



Distributed by:
Aurobindo Pharma USA, Inc.
279 Princeton-Hightstown Road
East Windsor, NJ 08520

Made in India

Code: TS/DRUGS/22/2009



N
3 65862 54330 1

NDC 65862-543-30

**Lamivudine and
Tenofovir Disoproxil
Fumarate Tablets**

300 mg/300 mg

Rx only

30 Tablets



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEFFREY S MURRAY
05/15/2018