

## 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, for oral use

### WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

See full prescribing information for complete boxed warning.

- Severe acute exacerbations of hepatitis B have been reported in patients coinfecting with 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 are a two-drug combination of lamivudine and tenofovir disoproxil fumarate, both nucleo(t)side reverse transcriptase inhibitors and indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients 12 years of age and older or weighing at least 35 kg. (1)

### DOSAGE AND ADMINISTRATION

- Testing: Prior to initiation and during treatment with lamivudine and tenofovir disoproxil fumarate, 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 are contraindicated in patients with previously hypersensitivity reaction to lamivudine or tenofovir disoproxil fumarate. (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)
- New Onset or Worsening Renal Impairment: Can include acute renal failure and Fanconi syndrome. Assess creatinine clearance before initiating treatment with tenofovir disoproxil fumarate, a component of lamivudine and tenofovir disoproxil fumarate. In patients at risk for renal dysfunction, assess estimated creatinine clearance, serum

phosphorus, urine glucose and urine protein before initiating treatment with tenofovir and periodically during treatment. Avoid administering lamivudine and tenofovir disoproxil fumarate with concurrent or recent use of nephrotoxic drugs. (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)
- 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. (5.5)
- Redistribution/Accumulation of Body Fat: Observed in HIV-infected patients receiving antiretroviral combination therapy. (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)
- 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 as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.9)

### ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Micro Labs USA, Inc. at 1-855-875-7814 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Didanosine: Tenofovir disoproxil fumarate increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy) when coadministered. Consider dose reductions or discontinuations of didanosine if warranted. (7.3)
- HIV-1 Protease Inhibitors: Coadministration decreases atazanavir concentrations and increases tenofovir concentrations. When coadministered with lamivudine and tenofovir disoproxil fumarate, use atazanavir and ritonavir. Coadministration of VIREAD with atazanavir and ritonavir, darunavir and ritonavir, or lopinavir/ritonavir increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity. (7.4)
- Sorbitol: Coadministration of lamivudine and sorbitol may decrease lamivudine concentrations; when possible, avoid chronic coadministration. (7.2)

### 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

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## FULL PRESCRIBING INFORMATION

### **WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B**

*See full prescribing information for complete boxed warning.*

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

## **1 INDICATIONS AND USAGE**

Lamivudine and tenofovir disoproxil fumarate are indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients 12 years of age and older or weighing at least 35 kg.

## **2 DOSAGE AND ADMINISTRATION**

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

Prior to initiation of lamivudine and tenofovir disoproxil fumarate, 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 and during therapy in all patients as clinically appropriate [see Warnings and Precautions (5.3)].

### **2.2 Recommended Dose for Adults and Pediatric Patients 12 Years of Age and Older or Weighing at Least 35 kg**

Lamivudine and tenofovir disoproxil fumarate are a two-drug fixed-dose combination product containing 300 mg of lamivudine (3TC) and 300 mg of tenofovir disoproxil fumarate (TDF). The recommended dose of lamivudine and tenofovir disoproxil fumarate in HIV-1-infected adults and pediatric patients 12 years of age and older or weighing at least 35 kg (77 lb) is one tablet taken orally once daily with or without food.

### **2.3 Not Recommended in Renal Impairment**

Because lamivudine and tenofovir disoproxil fumarate are a fixed-dose combination formulation and cannot be adjusted, it is not recommended for patients with renal impairment (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 300 mg/300 mg tablets are white to off-white colored, capsule shaped, biconvex, film-coated tablet debossed with 'T' on one side and '49' on the other side.

### **4 CONTRAINDICATIONS**

Lamivudine and tenofovir disoproxil fumarate are contraindicated in patients with previously hypersensitivity reaction to lamivudine or tenofovir disoproxil fumarate.

### **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 Co-infected 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 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 (lamivudine) tablets. EPIVIR-HBV (lamivudine) was developed for patients with chronic hepatitis B. The formulation and dosage of 3TC in EPIVIR-HBV (lamivudine) 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 (lamivudine), 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 New Onset or Worsening Renal Impairment**

TDF, a component of lamivudine and tenofovir disoproxil fumarate 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 creatinine clearance be calculated 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 TDF, and periodically during TDF therapy.

Avoid lamivudine and tenofovir disoproxil fumarate with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)) [*see Drug Interactions (7.6)*]. 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.

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

### **5.5 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)*].

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

The effects of 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 (5.3)*].

## **5.6 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.

## **5.7 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.

## 5.9 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. 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 >6). See the complete prescribing information for interferon and ribavirin.

## 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)*].
- New Onset or Worsening Renal Impairment [see *Warnings and Precautions (5.3)*].
- Pancreatitis [see *Warnings and Precautions (5.4)*].
- Bone Effects [see *Warnings and Precautions (5.5)*].
- Fat Redistribution [see *Warnings and Precautions (5.6)*].
- Immune Reconstitution Syndrome [see *Warnings and Precautions (5.7)*].
- Hepatic Decompensation in Patients Co-Infected with HIV-1 and Hepatitis C [see *Warnings and Precautions (5.9)*].

### 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 efavirenz (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<sup>a</sup> (Grades 2-4) Reported in  $\geq 5\%$  in Any Treatment Group in Study 903 (0-144 Weeks)**

	TDF+ 3TC + EFV	d4T + 3TC + EFV
	N = 299	N = 301
<b>Body as a Whole</b>		
Headache	14%	17%
Pain	13%	12%
Fever	8%	7%
Abdominal pain	7%	12%
Back pain	9%	8%
Asthenia	6%	7%
<b>Digestive System</b>		
Diarrhea	11%	13%
Nausea	8%	9%
Dyspepsia	4%	5%
Vomiting	5%	9%
<b>Metabolic Disorders</b>		
Lipodystrophy <sup>b</sup>	1%	8%
<b>Musculoskeletal</b>		
Arthralgia	5%	7%
Myalgia	3%	5%
<b>Nervous System</b>		
Depression	11%	10%
Insomnia	5%	8%
Dizziness	3%	6%
Peripheral neuropathy <sup>c</sup>	1%	5%
Anxiety	6%	6%
<b>Respiratory</b>		
Pneumonia	5%	5%

<b>Skin and Appendages</b>		
Rash event <sup>d</sup>	18%	12%

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

<sup>b</sup> Lipodystrophy represents a variety of investigator-described adverse events not a protocol-defined syndrome.

<sup>c</sup> Peripheral neuropathy includes peripheral neuritis and neuropathy.

<sup>d</sup> 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 d4T group (40% and 9%) compared with TDF (19% and 1%) respectively, laboratory abnormalities observed in this study occurred with similar frequency in the TDF and d4T 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  $\geq$  1% of Lamivudine- and Tenofovir Disoproxil Fumarate-Treated Patients in Study 903 (0-144 Weeks)**

	<b>TDF + 3TC + EFV</b>	<b>d4T + 3TC + EFV</b>
	<b>N = 299</b>	<b>N = 301</b>
Any $\geq$ 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 <sup>3</sup> )	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. In an open-label dose-escalation trial (NUCA2002), 14 subjects (14%) developed pancreatitis while receiving monotherapy with 3TC. Three of these subjects died of complications of pancreatitis. In a second open-label trial (NUCA2005), 12 subjects (18%) developed pancreatitis. In Trial ACTG300, pancreatitis was not observed in 236 subjects randomized to 3TC plus zidovudine. Pancreatitis was observed in 1 subject in this trial who received open-label 3TC in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy [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 24-48 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 (5.5)*].

Clinical trials in HIV-1 infected children and adolescents evaluated BMD changes. In Study 321 (12 to less than 18 years), the mean rate of BMD gain at Week 48 was less in the TDF compared to the placebo treatment group. Six TDF 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 TDF for 96 weeks. In this trial, skeletal growth (height) appeared to be unaffected [*see Warnings and Precautions (5.5)*].

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use for each of the individual components of lamivudine and tenofovir disoproxil fumarate. 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 [*see Warnings and Precautions (5.6)*].

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 Warnings and Precautions (5.1, 5.2)*].

Hypersensitivity: Anaphylaxis, urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Skin: Alopecia, pruritus.

*Tenofovir Disoproxil Fumarate:*

Immune System Disorders: Allergic reaction, including angioedema

Metabolism and Nutrition Disorders: Lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, and Mediastinal Disorders: Dyspnea

Gastrointestinal Disorders: Pancreatitis, increased amylase, abdominal pain

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, increased creatinine, proteinuria, polyuria [*see Warnings and Precautions (5.3)*].

General Disorders and Administration Site Conditions Asthenia

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

## **7 DRUG INTERACTIONS**

No drug interaction trials have been conducted using lamivudine and tenofovir disoproxil fumarate tablets. Drug interaction trials have been conducted with 3TC and TDF, the components of lamivudine and tenofovir disoproxil fumarate. This section describes clinically relevant drug interactions observed with 3TC and TDF [*see Clinical Pharmacology (12.3)*].

### **7.1 Drugs Inhibiting Organic Cation Transporters**

3TC, a component of lamivudine and tenofovir disoproxil fumarate, 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.

## 7.2 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)*].

## 7.3 Didanosine

Coadministration of TDF 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 TDF,  $C_{\max}$  and AUC of didanosine increased significantly [see *Clinical Pharmacology (12.3)*]. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. Suppression of  $CD4^+$  cell counts has been observed in patients receiving TDF 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 TDF. In patients weighing less than 60 kg, the didanosine dose should be reduced to 200 mg once daily when it is coadministered with TDF. When coadministered, TDF and didanosine EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat). For additional information on coadministration of TDF and didanosine, please refer to the full prescribing information for didanosine.

## 7.4 HIV-1 Protease Inhibitors

TDF decreases the AUC and  $C_{\min}$  of atazanavir [see *Clinical Pharmacology (12.3)*]. When coadministered with TDF, 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)*]. TDF is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters. When TDF is coadministered with an inhibitor of these transporters, an increase in absorption may be observed. Patients receiving TDF concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir should be monitored for TDF-associated adverse reactions. TDF should be discontinued in patients who develop TDF-associated adverse reactions.

## 7.5 Hepatitis C Antiviral Agents

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

In patients receiving TDF concomitantly with sofosbuvir/velpatasvir, monitor for adverse reactions associated with TDF.

In patients receiving TDF 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 TDF 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.

## **7.6 Drugs Affecting Renal Function**

Since tenofovir is primarily eliminated by the kidneys [*see Clinical Pharmacology (12.3)*], coadministration of 3TC and TDF 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 acyclovir, cidofovir, ganciclovir, valacyclovir, and valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs [*see Warnings and Precautions (5.3)*].

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

Available data from the Antiretroviral Pregnancy Registry (APR) show no difference in the risk of 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.

The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. The

background risk for major birth defects and miscarriage for the indicated population is unknown. The APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates women and infants from a limited geographic area and does not include outcomes for births that occurred at less than 20 weeks' gestation.

## 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 3TC and overall birth defects compared with the background birth defect rate of 2.7% in the US 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 lamivudine crosses the placenta in humans. Amniotic fluid concentrations of lamivudine 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 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 breast-feed their infants to avoid risking postnatal transmission of HIV-1.**

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, 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 secreted in human milk at low levels. The impact of this exposure in breastfed infants is unknown and the effects 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.

## **8.4 Pediatric Use**

The safety and efficacy of lamivudine and tenofovir disoproxil fumarate have not been established in pediatric patients younger than 12 years of age or weighing less than 35kg.

## **8.5 Geriatric Use**

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

## **8.6 Patients with Renal Impairment**

Lamivudine and tenofovir disoproxil fumarate are not recommended for patients with renal impairment (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.

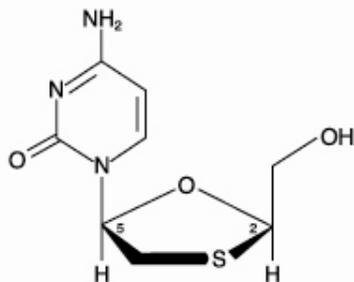
**Tenofovir Disoproxil Fumarate:** Limited clinical experience at doses higher than the therapeutic dose of TDF 300 mg is available.

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

## 11 DESCRIPTION

Lamivudine and tenofovir disoproxil fumarate tablets are fixed dose combination tablets 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. Each tablet contains the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and sodium starch glycolate. The tablets are coated with Opadry White 13B58894, which contains hypromellose, polyethylene glycol 400, polysorbate 80, and titanium dioxide.

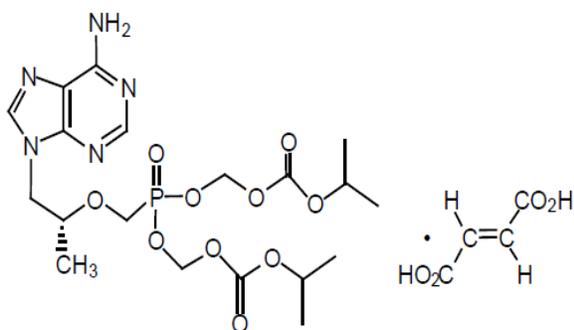
**Lamivudine:** Lamivudine (also known as 3TC) is a synthetic nucleoside analogue with activity against HIV-1 and HBV. The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine 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 is the fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. It is a prodrug 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  $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$  and a molecular weight of 635.52. It has the following structural formula:



Tenofovir disoproxil fumarate is a white to off-white crystalline powder that is freely soluble in dimethylformamide and soluble in methanol. It has an octanol/phosphate buffer (pH 6.5) partition coefficient (log p) of 1.25 at 25 °C.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

### 12.3 Pharmacokinetics in Adults

*Lamivudine and Tenofovir Disoproxil Fumarate:* Lamivudine and tenofovir disoproxil fumarate from the combination tablets (300 mg/300 mg) were comparable to that from EPIVIR tablets of ViiV Healthcare USA (containing lamivudine 300 mg) and VIREAD tablets of Gilead Sciences Inc. USA (containing tenofovir disoproxil fumarate 300 mg), respectively, when single doses were administered to healthy subjects under fasted and fed conditions.

*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  $1.5 \pm 0.5$  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  $1.0 \pm 0.4$  hrs (mean  $\pm$  SD) and  $C_{\max}$  and AUC values were  $296 \pm 90$  ng/mL and  $2287 \pm 685$  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  $243 \pm 33$  mL/min (mean  $\pm$  SD). Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

*Effects of Food on Oral Absorption of Lamivudine and Tenofovir Disoproxil Fumarate:* The effect of food on lamivudine and tenofovir disoproxil fumarate has not been evaluated. Based on cross trial comparisons, the pharmacokinetics of lamivudine, and tenofovir is not anticipated to be significantly affected by food, hence lamivudine and tenofovir disoproxil fumarate can be administered with or without food.

#### 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.

*Gender:* There are no significant or clinically relevant gender differences in the pharmacokinetics of 3TC and TDF.

*Geriatric Patients:* The pharmacokinetics of 3TC and TDF have not been studied in patients over 65 years of age.

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

The pharmacokinetics of 3TC and tenofovir are altered in subjects with renal impairment. In subjects with creatinine clearance below 50 mL/min,  $C_{max}$  and AUC of 3TC and tenofovir were increased. Lamivudine and tenofovir disoproxil fumarate are not recommended for patients with renal impairment (i.e., creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis because it is a fixed-dose combination formulation that cannot be adjusted.

*Patients with Hepatic Impairment:* Lamivudine: The pharmacokinetic properties of 3TC 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 3TC have not been established in the presence of decompensated 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 hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects.

*Pediatric Patients:*

The pharmacokinetics of lamivudine and tenofovir disoproxil fumarate have not been established in pediatric patients younger than 12 years of age or weighing less than 35 kg.

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 (5.9)*].

*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 patients [see *Warnings and Precautions* (5.9)].

*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<sub>∞</sub>, a decrease of 29% ± 13% in 3TC 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.

*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<sub>(0-24)</sub>, 14%, 32%, and 36% in the AUC<sub>(∞)</sub>, and 28%, 52%, and 55% in the C<sub>max</sub> of lamivudine.

#### 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 TDF with other medicinal products is low.

TDF has been evaluated in healthy volunteers in combination with other antiretroviral and potential concomitant drugs. Tables 3 and 4 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of TDF on the pharmacokinetics of coadministered drug. 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<sub>max</sub> 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 4). The mechanism of this interaction is unknown.

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

**Table 3 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir<sup>a</sup> in the Presence of the Coadministered Drug**

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters <sup>b</sup> (90% CI)		
			C <sub>max</sub>	AUC	C <sub>min</sub>
Atazanavir <sup>c</sup>	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Atazanavir/Ritonavir <sup>c</sup>	300/100 once daily	12	↑ 34 (↑ 20 to ↑ 51)	↑ 37 (↑ 30 to ↑ 45)	↑ 29 (↑ 21 to ↑ 36)
Darunavir/Ritonavir <sup>d</sup>	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 <sup>e,f</sup>	90/400 once daily × 10 days	24	↑ 47 (↑ 37 to ↑ 58)	↑ 35 (↑ 29 to ↑ 42)	↑ 47 (↑ 38 to ↑ 57)
Ledipasvir/Sofosbuvir <sup>e,g</sup>		23	↑ 64 (↑ 54 to ↑ 74)	↑ 50 (↑ 42 to ↑ 59)	↑ 59 (↑ 49 to ↑ 70)
Ledipasvir/Sofosbuvir <sup>h</sup>	90/400 once daily × 14 days	15	↑ 79 (↑ 56 to ↑ 104)	↑ 98 (↑ 77 to ↑ 123)	↑ 163 (↑ 132 to ↑ 197)
Ledipasvir/Sofosbuvir <sup>i</sup>	90/400 once daily × 10 days	14	↑ 32 (↑ 25 to ↑ 39)	↑ 40 (↑ 31 to ↑ 50)	↑ 91 (↑ 74 to ↑ 110)
Ledipasvir/Sofosbuvir <sup>j</sup>	90/400 once daily × 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 <sup>k</sup>	400 single dose	16	↑ 25 (↑ 8 to ↑ 45)	↔	↔
Sofosbuvir/Velpatasvir <sup>l</sup>	400/100 once daily	24	↑ 55 (↑ 43 to ↑ 68)	↑ 30 (↑ 24 to ↑ 36)	↑ 39 (↑ 31 to ↑ 48)
Sofosbuvir/Velpatasvir <sup>m</sup>	400/100 once daily	29	↑ 55 (↑ 45 to ↑ 66)	↑ 39 (↑ 33 to ↑ 44)	↑ 52 (↑ 45 to ↑ 59)
Sofosbuvir/Velpatasvir <sup>n</sup>	400/100 once daily	15	↑ 77 (↑ 53 to ↑ 104)	↑ 81 (↑ 68 to ↑ 94)	↑ 121 (↑ 100 to ↑ 143)
Sofosbuvir/Velpatasvir <sup>o</sup>	400/100 once daily	24	↑ 36 (↑ 25 to ↑ 47)	↑ 35 (↑ 29 to ↑ 42)	↑ 45 (↑ 39 to ↑ 51)
Sofosbuvir/Velpatasvir <sup>p</sup>	400/100 once daily	24	↑ 44 (↑ 33 to ↑ 55)	↑ 40 (↑ 34 to ↑ 46)	↑ 84 (↑ 76 to ↑ 92)
Sofosbuvir/Velpatasvir <sup>q</sup>	400/100 once daily	30	↑ 46 (↑ 39 to ↑ 54)	↑ 40 (↑ 34 to ↑ 45)	↑ 70 (↑ 61 to ↑ 79)

Tacrolimus	0.05 mg/kg twice daily × 7 days	21	↑ 13 (↑ 1 to ↑ 27)	↔	↔
Tipranavir/ Ritonavir <sup>f</sup>	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/tenofovir DF.  
m Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF.  
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/tenofovir DF.  
r Aptivus (tipranavir) Prescribing Information.

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

**Table 4 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 <sup>a</sup> (90% CI)		
			C <sub>max</sub>	AUC	C <sub>min</sub>
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	↔	NA
Atazanavir <sup>b</sup>	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir <sup>b</sup>	Atazanavir/ Ritonavir 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25 <sup>c</sup> (↓ 42 to ↓ 3)	↓ 23 <sup>c</sup> (↓ 46 to ↑ 10)

Darunavir <sup>d</sup>	Darunavir/Ritonavir 300/100 once daily	12	↑ 16 (↓ 6 to ↑ 42)	↑ 21 (↓ 5 to ↑ 54)	↑ 24 (↓ 10 to ↑ 69)
Didanosine <sup>e</sup>	250 once, simultaneously with VIREAD and a light meal <sup>f</sup>	33	↓ 20 <sup>g</sup> (↓ 32 to ↓ 7)	↔ <sup>g</sup>	NA
Emtricitabine	200 once daily × 7 days	17	↔	↔	↑ 20 (↑ 12 to ↑ 29)
Entecavir	1 mg once daily × 10 days	28	↔	↑ 13 (↑ 11 to ↑ 15)	↔
Indinavir	800 three times daily × 7 days	12	↓ 11 (↓ 30 to ↑ 12)	↔	↔
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)	↔	↔
Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	↔ ↔	↔ ↔	↔ ↔
Saquinavir Ritonavir	Saquinavir/Ritonavir 1000/100 twice daily × 14 days	32	↑ 22 (↑ 6 to ↑ 41) ↔	↑ 29 <sup>h</sup> (↑ 12 to ↑ 48) ↔	↑ 47 <sup>h</sup> (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	↔	↔	↔
Tipranavir <sup>i</sup>	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<sub>min</sub> 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<sub>min</sub> 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 the 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  $\alpha$ ,  $\beta$ , and mitochondrial DNA polymerase  $\gamma$ .

#### 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<sub>50</sub> values were in the range of 3 to 15,000 nM. (1  $\mu$ M = 0.23 mcg/mL). The median EC<sub>50</sub> 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<sub>50</sub> 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 microM) 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<sub>50</sub> (50% effective concentration) values for tenofovir were in the range of 0.04  $\mu$ M to 8.5  $\mu$ M. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC<sub>50</sub> values ranged from 0.5  $\mu$ M to 2.2  $\mu$ M) and strain-specific activity against HIV-2 (EC<sub>50</sub> values ranged from 1.6  $\mu$ M to 5.5  $\mu$ M). Please see the full prescribing information for TDF 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 the resistance was predominantly due to a methionine to valine or isoleucine (M184V/I) substitution in reverse transcriptase.

*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 tenofovir disoproxil fumarate regimen.

### Cross-Resistance:

*Lamivudine:* Cross-resistance among NRTIs has been observed. 3TC-resistant HIV-1 isolates 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 K70 E substitutions selected by tenofovir are also selected in some HIV-1 infected subjects treated with abacavir or ddI. HIV-1 isolates with the K65R substitution also showed reduced susceptibility to emtricitabine (FTC) and 3TC. HIV-1 isolates from subjects (N = 20) whose HIV-1 expressed a mean of 3 zidovudine-associated RT 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 TDF. 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 lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) the humans 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 Tablets:**

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 18–64); 74% were male, 64% were Caucasian, and 20% were Black. The mean baseline CD4+ cell count was 279 cells/mm<sup>3</sup> (range 3–956) and median baseline plasma HIV-1 RNA was 77,600 copies/mL (range 417–5,130,000). Subjects were stratified by baseline HIV-1 RNA and CD4+ cell count. Forty-three percent of subjects had baseline viral loads >100,000 copies/mL and 39% had CD4+ cell counts <200 cells/mm<sup>3</sup>. Treatment outcomes through 48 and 144 weeks are presented in Table 5.

**Table 5. 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 <sup>a</sup>	79%	82%	68%	62%
Virologic failure <sup>b</sup>	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 <sup>c</sup>	8%	7%	14%	15%

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

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

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

Achievement of plasma HIV-1 RNA concentrations of less than 400 copies/mL at Week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (> or ≤100,000 copies/mL) and CD4+ cell count (< or ≥200 cells/mm<sup>3</sup>). 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/mm<sup>3</sup> for the TDF arm and 283 cells/mm<sup>3</sup> 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 white to off-white colored, capsule shaped, biconvex, film-coated tablet debossed with 'I' on one side and '49' on the other side. They are available as follows.

30 tablets/bottle with induction seal, desiccant, cotton coil, and child-resistant cap

NDC 42571-165-30

100 tablets/bottle with induction seal, desiccant, cotton coil, and child-resistant cap

NDC 42571-165-01

Store below 30°C (86°F).

Dispense in original container.

## 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. Treatment with lamivudine and tenofovir disoproxil fumarate 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)*].

### Post-Treatment Acute Exacerbation of Hepatitis B in Patients with HBV Co-Infection

Severe acute exacerbations of hepatitis have been reported in patients who are infected with HIV or coinfecting with HBV and HIV-1 and have discontinued 3TC and TDF, components of lamivudine and tenofovir disoproxil fumarate. Test patients with HIV-1 for Hepatitis B virus (HBV) before initiating antiretroviral therapy. In patients with chronic hepatitis B, it is important to obtain HIV antibody testing prior to initiating 3TC and TDF, components of lamivudine and tenofovir disoproxil fumarate [see *Warnings and Precautions (5.2)*].

### 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 disoproxil fumarate with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) [see *Dosage and Administration (2.3, Warnings and Precautions (5.3))*].

### Risk of Pancreatitis

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

### Risk of Hepatic Decompensation in Patients with HIV-1/HCV Co-Infection

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 (5.9)*].

### Decreases in Bone Mineral Density

Advise patients that decreases in bone mineral density have been observed with the use of 3TC and TDF, components of lamivudine and tenofovir disoproxil fumarate, in patients with HIV [see *Warnings and Precautions (5.5)*].

### Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any symptoms of infection, as in some patients with advanced HIV infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started [*see Warnings and Precautions (5.7)*].

#### Fat Redistribution

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including lamivudine and tenofovir disoproxil fumarate, and that the cause and long-term health effects of these conditions are not known at this time [*see Warnings and Precautions (5.6)*].

#### Administration Instruction

Inform patients that it is important to take lamivudine and tenofovir disoproxil fumarate once daily on a regular dosing schedule with or without food. Advise patients if a dose is missed, take it as soon as possible unless it is almost time for the next dose.

#### Lactation

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

**Patient Information**  
**Lamivudine and tenofovir disoproxil fumarate**  
**tablets**

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

**Lamivudine and tenofovir disoproxil fumarate 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:**

- feel very weak or tired
- feel cold, especially in your arms and legs
- unusual (not normal) muscle pain
- feel dizzy or lightheaded
- trouble breathing
- have a fast or irregular heartbeat
- 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). Inflammation of your liver (hepatitis) that can lead to liver failure requiring a liver transplant has been reported in some people treated with lamivudine and tenofovir disoproxil fumarate. Your healthcare provider may do blood tests to check your liver before and during treatment with lamivudine and tenofovir disoproxil fumarate.

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

- your skin or the white part of your eyes turns yellow (jaundice)
- loss of appetite for several days or longer
- dark or “tea-colored” urine
- nausea and vomiting
- light-colored stools (bowel movements)
- pain, aching, or tenderness on the right side of your stomach-area
- confusion
- weakness
- tiredness
- stomach (abdomen) swelling

- **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. 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.

- It is not known if lamivudine and tenofovir disoproxil fumarate are safe and effective in people who have both HIV-1 and HBV infection.
- Do not run out of lamivudine and tenofovir disoproxil fumarate. Refill your prescription or talk to your healthcare provider before your lamivudine and tenofovir disoproxil fumarate are all gone.

- **Do not stop lamivudine and tenofovir disoproxil fumarate without first talking to your healthcare provider.** If you stop taking lamivudine and tenofovir disoproxil fumarate, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver.
  - **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. 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.
- For more information about side effects, see “What are the possible side effects of lamivudine and tenofovir disoproxil fumarate?”**

**What are lamivudine and tenofovir disoproxil fumarate?**

Lamivudine and tenofovir disoproxil fumarate are a prescription medicine that is used with other antiviral medicines to treat Human Immunodeficiency Virus-1 (HIV-1) in adults and children 12 years of age and older or weighing at least 35 kg.

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

Lamivudine and tenofovir disoproxil fumarate contain the prescription medicines lamivudine and tenofovir disoproxil fumarate.

Lamivudine and tenofovir disoproxil fumarate are not for use in children less than 12 years of age or weighing less than 35 kg.

**Do not take lamivudine and tenofovir disoproxil fumarate if you:**

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

**Before you take lamivudine and tenofovir disoproxil fumarate, tell your healthcare provider about all of your medical conditions, including if you:**

- have liver problems, including hepatitis B or C 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 lamivudine and tenofovir disoproxil fumarate will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. Do not breastfeed if you take lamivudine and tenofovir disoproxil fumarate.
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 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 over-the-counter medicines, vitamins and herbal supplements.

Some medicines interact with lamivudine and tenofovir disoproxil fumarate. Lamivudine and tenofovir disoproxil fumarate may affect the way other medicines work, and other medicines may affect how lamivudine and tenofovir disoproxil fumarate work. 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.

- 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 with other medicines.

#### **How should I take lamivudine and tenofovir disoproxil fumarate?**

- Take lamivudine and tenofovir disoproxil fumarate exactly as your healthcare provider tells you to take it.
- For adults and children 12 years of age and older or weighing at least 35 kg, the usual dose of lamivudine and tenofovir disoproxil fumarate is one tablet by mouth each day with or without food.
- Tell your healthcare provider if your child has problems with swallowing tablets.
- Do not miss a dose of lamivudine and tenofovir disoproxil fumarate. If you miss a dose, take the missed dose as soon as you remember. If it is almost time for your next dose of lamivudine and tenofovir disoproxil fumarate, do not take the missed dose. Take the next dose at your regular time.
- Stay under the care of your healthcare provider during treatment with lamivudine and tenofovir disoproxil fumarate.
- Do not run out of lamivudine and tenofovir disoproxil fumarate. 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, go to the nearest hospital emergency room right away.

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

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

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

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

- See “**What is the most important information I should know about lamivudine and tenofovir disoproxil fumarate?**”
- **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 and interferon alfa with or without ribavirin, tell your healthcare provider if you have any new symptoms.
- **Bone problems** can happen in some people who take lamivudine and tenofovir disoproxil fumarate. 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.
- **Risk of inflammation of the pancreas (pancreatitis).** Children may be at risk for developing pancreatitis during treatment with lamivudine and tenofovir disoproxil fumarate if they:
  - have taken nucleoside analogue medicines in the past
  - have a history of pancreatitis
  - 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 to your child if their symptoms and blood test results show that your child may have pancreatitis.

- **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 starting your HIV-1 medicine.
- **Changes in body fat** can happen in some people who take HIV-1 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.

The most common side effects of lamivudine and tenofovir disoproxil fumarate are headache, pain, depression, diarrhea, and 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. 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?**

- Store lamivudine and tenofovir disoproxil fumarate tablets below 30°C (86°F).
- Keep lamivudine and tenofovir disoproxil fumarate in the original container.
- Do not use lamivudine and tenofovir disoproxil fumarate if the seal over the bottle opening is broken or missing.
- Keep the bottle tightly closed.
- Keep lamivudine and tenofovir disoproxil fumarate and all medicines out of the reach of children.

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

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use lamivudine and tenofovir disoproxil fumarate for a condition for which it was not prescribed. Do not give lamivudine and tenofovir disoproxil fumarate 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 that is written for health professionals.

#### **What are the ingredients in lamivudine and tenofovir disoproxil fumarate?**

**Active ingredient:** lamivudine and tenofovir disoproxil fumarate

**Inactive ingredients:** croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and sodium starch glycolate. The tablets are coated with Opadry White 13B58894, which contains hypromellose, polyethylene glycol 400,

polysorbate 80, and titanium dioxide.

The brands listed are trademarks of their respective owners and are not trademarks of Micro Labs Ltd. The makers of these brands are not affiliated with and do not endorse Micro Labs Ltd., or its products.

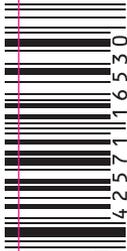
Manufactured by:  
Micro Labs Limited  
Goa-403 722, INDIA.

Manufactured for:  
Micro Labs USA Inc.  
Basking Ridge, NJ 07920

This Patient Information has been approved by the U.S. Food and Drug Administration.  
Revised: January 2018

 <b>MICRO LABS LIMITED</b> Bangalore, INDIA	1) Product : Lamivudine and Tenofovir Disoproxil Fumarate Tablets 30's Count - USA 2) Strength : 300 mg/300 mg 3) Component : Container Label 4) No of colours : 4 5) Dimension : 120 x 50 mm 6) Artwrok Code : NA 7) Pharma code : NA 8) Font type and Size : Helvetica condensed, 7 pt 9) Technical specification : NA				<b>Colours used</b>  Pantone Reflex Blue C  Pantone 300C  Black  Red  <b>Colours not for Printing</b>  Keylines	
	Code No. : $\frac{WOA}{WA}$ ✓		M. L. No. : 651		Revision: 00	
	Reason for change		NA		Date : 23-09-2013	
Approved By	Contract Giver/ PL holder	Regulatory Affairs	Packaging Development	Production Head (Site)	Head QC (Site)	Head QA (Site)
Sign/ Date						

120 mm



7  
301130642571  
3

**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.**

Store in a safe place out of the reach of children.

NDC 42571-165-30

## Lamivudine and Tenofovir Disoproxil Fumarate Tablets

**300 mg/300 mg**

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

**Rx Only**  
30 Tablets



Manufactured by:  
**Micro Labs Limited**  
 Goa-403 722, INDIA.  
  
 M. L. No. : 651  
 Manufactured for:  
**Micro Labs USA Inc.**  
 Princeton, NJ 08540

Artwork Code

50 mm

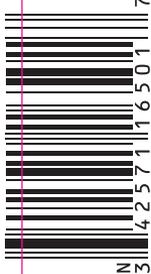
Unvarnished area for batch details  
 Lot: XXXXXXX & Exp: MM/YYYY  
 will be printed online  
 32 x 17 mm

Area for Pharmacode

120 x 50 mm

 <b>MICRO LABS LIMITED</b> Bangalore, INDIA	1) Product : Lamivudine and Tenofovir Disoproxil Fumarate Tablets 100's Count - USA 2) Strength : 300 mg/300 mg 3) Component : Container Label 4) No of colours : 4 5) Dimension : 130 x 55 mm 6) Artwrok Code : NA 7) Pharma code : NA 8) Font type and Size : Helvetica condensed, 7.2 pt 9) Technical specification : NA		<u>Colours used</u>  Pantone Reflex Blue C  Pantone 300C  Black  Red  <u>Colours not for Printing</u>  Keylines			
	Code No. : $\frac{WOA}{WA \checkmark}$	M. L. No. : 651	Revision: 00			
	Reason for change	NA	Date : 23-09-2013			
Approved By	Contract Giver/ PL holder	Regulatory Affairs	Packaging Development	Production Head (Site)	Head QC (Site)	Head QA (Site)
Sign/ Date						

55 mm
130 mm



N 3  
4 2 5 7 1 1 6 5 0 1 7

**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.**

Store in a safe place out of the reach of children.

NDC 42571-165-01

## Lamivudine and Tenofovir Disoproxil Fumarate Tablets

300 mg/300 mg

**PHARMACIST: Dispense the Medication Guide provided separately to each patient.**

**Rx Only**

**100 Tablets**



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Unvarnished area for batch details  
Lot: XXXXXXX & Exp: MM/YYYY will be printed online  
34 x 18 mm

130 x 55 mm