

1.14 Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LAMIVUDINE tablets, for oral use

Initial U.S. Approval: 1995

**WARNING: LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY,
EXACERBATIONS OF HEPATITIS B, and
DIFFERENT FORMULATIONS OF LAMIVUDINE TABLETS**

See full prescribing information for complete boxed warning

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.1)
- Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued Lamivudine Tablets. Monitor hepatic function closely in these patients and, If appropriate, initiate anti-hepatitis B treatment. (5.2)
- Patients with HIV-1 infection should receive only dosage forms of Lamivudine Tablets appropriate for treatment of HIV-1. (5.2)

-----RECENT MAJOR CHANGES-----

Warnings and Precautions, Patients with Hepatitis B Virus Co-infection (5.2)	09/2015
Warnings and Precautions, Lower Virologic Suppression Rates and Increased Risk of Viral Resistance with Oral Solution (5.6)	07/2016

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

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

Limitations of Use: The dosage of this product is for HIV-1 and not for HBV. (1)

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

- Adults: 300 mg daily, administered as either 150 mg twice daily or 300 mg once daily. (2.1)
- Pediatric Patients Aged 3 Months and Older: Administered twice daily. Dose should be calculated on body weight (kg) and should not exceed 300 mg daily. (2.2)
- Patients with Renal Impairment: Doses of Lamivudine tablets must be adjusted in accordance with renal function. (2.3)

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

- Tablets: 150 mg Scored (3)

-----CONTRAINDICATIONS-----

1.14 Labeling

Lamivudine Tablets are contraindicated in patients with previous hypersensitivity reaction to Lamivudine (4)

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

- Co-infected HIV-1/HBV Patients: Emergence of lamivudine-resistant HBV variants associated with Lamivudine-containing antiretroviral regimens has been reported. (5.2)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co- infected patients receiving interferon and ribavirin-based regimens. Monitor for treatment-associated toxicities. Discontinue lamivudine 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 treatment as clinically appropriate. (5.4)
- Immune reconstitution syndrome and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy. (5.5, 5.7)
- Lower virologic suppression rates and increased risk of viral resistance were observed in pediatric subjects who received lamivudine oral solution concomitantly with other antiretroviral oral solution compared with those who received tablets (5.6)

-----**ADVERSE REACTIONS**-----

- The most common reported adverse reactions (incidence greater than or equal to 15%) in adults were headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough. (6.1)
- The most common reported adverse reactions (incidence greater than or equal to 15%) in pediatric subjects were fever and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Centaur Pharmaceuticals Pvt. Ltd. or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Lactation: Breastfeeding not recommended. (8.2)

Additional pediatric use information for patients aged 3 months and above is approved for ViiV Healthcare Company's EPIVIR® (lamivudine) tablets and oral solution. However, due to ViiV Healthcare Company's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

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

Revised: 11/2016

1.14 Labeling

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, EXACERBATIONS OF HEPATITIS B, and DIFFERENT FORMULATIONS OF LAMIVUDINE TABLETS.

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Adult Patients

2.2 Recommended Dosage for Pediatric Patients

2.3 Patients with Renal impairment

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis and Severe Hepatomegaly with Steatosis

5.2 Patient with Hepatitis B Virus Co-infection

5.3 Use with Interferon- and Ribavirin- Based Regimens

5.4 Pancreatitis

5.5 Immune Reconstitution Syndrome

5.6 Lower Virologic Suppression Rates and Increased Risk of Viral Resistance with Oral Solution

5.7 Fat Redistribution.

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 Patients with Impaired Renal Function

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.3 Pharmacokinetics

12.4 Microbiology

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Adult Subjects

14.2 Pediatric Subjects

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

1.14 Labeling

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, EXACERBATIONS OF HEPATITIS B, and DIFFERENT FORMULATIONS OF LAMIVUDINE TABLETS.

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 analogues and other antiretrovirals. Discontinue lamivudine if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur [see *Warnings and Precautions (5.1)*].

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. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue lamivudine and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted [see *Warnings and Precautions (5.2)*].

Important Differences Among Lamivudine – Containing Products:

Lamivudine tablets and oral solution (used to treat HIV-1 infection) contain a higher dose of the active ingredient (lamivudine) than EPIVIR-HBV® Tablets and oral solution (used to treat chronic HBV infection). Patients with HIV-1 infection should receive only dosage forms appropriate for treatment of HIV-1 [see *Warnings and Precautions (5.2)*].

1 INDICATIONS AND USAGE

Lamivudine Tablets are a nucleoside analogue indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection.

Limitations of use:

- The dosage of this product is for HIV-1 and not for HBV.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Adult Patients

The recommended dosage of lamivudine tablets in HIV-1-infected adults is 300 mg daily, administered as either 150 mg taken orally twice daily or 300 mg taken orally once daily with or without food. If lamivudine is administered to a patient infected with HIV-1 and HBV, the dosage indicated for HIV-1 therapy should be used as part of an appropriate combination regimen [see *Warnings and Precautions (5.2)*].

1.14 Labeling

2.2 Recommended Dosage for Pediatric Patients

The recommended dosage of lamivudine oral solution in HIV-1-infected pediatric patients aged 3 months and older is 4 mg per kg taken orally twice daily (up to a maximum of 300 mg daily), administered in combination with other antiretroviral agents.

Lamivudine scored tablet is the preferred formulation for HIV-1-infected pediatric patients who weigh at least 14 kg and for whom a solid dosage form is appropriate. Before prescribing Lamivudine scored tablets, pediatric patients should be assessed for the ability to swallow tablets. For patients unable to safely and reliably swallow Lamivudine tablets, the oral solution formulation should be prescribed [see Warnings and Precautions (5.6)]. The recommended oral dosage of Lamivudine tablets for HIV-1-infected pediatric patients is presented in Table 1.

Table 1. Dosing Recommendations for Lamivudine Scored (150-mg) Tablets in Pediatric Patients

Weight (kg)	Twice-Daily Dosing Regimen Using Scored 150-mg Tablet		
	AM Dose	PM Dose	Total Daily dose
14 to <20	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
≥20 to <25	½ tablet (75 mg)	1 tablet (150 mg)	225 mg
≥25	1 tablet (150 mg)	1 tablet (150 mg)	300 mg

Additional pediatric use information for patients aged 3 months and above is approved for ViiV Healthcare Company’s EPIVIR® (lamivudine) tablets and oral solution. However, due to ViiV Healthcare Company’s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

2.3 Patients with Renal Impairment

Dosing of lamivudine tablets are adjusted in accordance with renal function. Dosage adjustments are listed in Table 2 [see Clinical Pharmacology (12.3)].

Table 2. Adjustment of Dosage of Lamivudine Tablets in Adults and Adolescents (Greater than or Equal to 25 kg) in Accordance with Creatinine Clearance

Creatinine Clearance (mL/min)	Recommended Dosage of Lamivudine
≥50	150 mg twice daily or 300 mg once daily
30-49	150 mg once daily
15-29	150 mg first dose, then 100 mg once daily
5-14	150 mg first dose, then 50 mg once daily
<5	50 mg first dose, then 25 mg once daily

1.14 Labeling

No additional dosing of lamivudine Tablets is required after routine (4-hour) hemodialysis or peritoneal dialysis.

Although there are insufficient data to recommend a specific dose adjustment of lamivudine in pediatric patients with renal impairment, a reduction in the dose and/or an increase in the dosing interval should be considered.

3 DOSAGE FORMS AND STRENGTHS

- **Lamivudine Tablets, USP (scored)**

Lamivudine Tablets, USP contain 150 mg of lamivudine. White, diamond-shaped, scored film-coated tablets debossed one side with "001" on either side of scoreline.

4 CONTRAINDICATIONS

Lamivudine tablets are contraindicated in patients with previous hypersensitivity reaction to lamivudine.

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 analogues and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Caution should be exercised when administering lamivudine tablets to any patient with known risk factors for liver disease; however, cases also have been reported in patients with no known risk factors. Treatment with lamivudine tablets should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations)

5.2 Patients with Hepatitis B Virus Co-infection

Posttreatment Exacerbations of Hepatitis

Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from postmarketing experience after changes from Lamivudine-containing HIV-1 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

1.14 Labeling

Important Differences among Lamivudine-Containing Products

Lamivudine tablets and oral solution contain a higher dose of the same active ingredient (lamivudine) than EPIVIR-HBV tablets and EPIVIR-HBV oral solution. EPIVIR - HBV was developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine in EPIVIR-HBV are not appropriate for patients co-infected with HIV-1 and HBV. Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV. If treatment with EPIVIR-HBV is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV-1 infection, rapid emergence of HIV-1 resistance is likely to result because of the subtherapeutic dose and the inappropriateness of monotherapy HIV-1 treatment. If a decision is made to administer lamivudine to patients co-infected with HIV-1 and HBV, lamivudine tablets, lamivudine oral solution, or another product containing the higher dose of lamivudine should be used as part of an appropriate combination regimen.

Emergence of Lamivudine - Resistant HBV

Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in subjects dually infected with HIV-1 and HBV (see full prescribing information for EPIVIR-HBV). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected subjects who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

5.3 Use with Interferon- and Ribavirin- Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients [see *Clinical Pharmacology* (12.3)], hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of lamivudine tablets 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, lamivudine should be used with caution. Treatment with lamivudine should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur [see *Adverse Reactions* (6.1)].

1.14 Labeling

5.5 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including lamivudine tablets. During the initial phase of combination antiretroviral treatment, patients whose immune system respond 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.

5.6 Lower Virologic Suppression Rates and Increased Risk of Viral Resistance with Oral Solution

Pediatric subjects who received lamivudine oral solution concomitantly with other antiretroviral oral solutions at any time in the ARROW trial had lower rates of virologic suppression, lower plasma lamivudine exposure, and developed viral resistance more frequently than those receiving lamivudine tablets [see *Clinical Pharmacology (12.3)*, *Microbiology (12.4)*, *Clinical Studies (14.2)*].

Lamivudine scored tablet is the preferred formulation for HIV-1-infected pediatric patients who weigh at least 14 kg and for whom a solid dosage form is appropriate. Consider more frequent monitoring of HIV-1 viral load when treating with lamivudine oral solution.

5.7 Fat Redistribution

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

6 ADVERSE REACTIONS

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

- Lactic acidosis and severe hepatomegaly with steatosis [see *Boxed Warning, 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)*].
- Immune reconstitution syndrome [see *Warnings and Precautions (5.5)*].
- Fat redistribution [see *Warnings and Precautions (5.7)*].

1.14 Labeling

6.1 Clinical Trials Experience

Clinical Trials Experience in Adult Subjects

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

The safety profile of lamivudine tablets in adults is primarily based on 3,568 HIV-1-infected subjects in 7 clinical trials.

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

Selected clinical adverse reactions in greater than or equal to 5% of subjects during therapy with lamivudine tablets 150 mg twice daily plus RETROVIR® 200 mg 3 times daily for up to 24 weeks are listed in Table 3.

Table 3. Selected Clinical Adverse Reactions (Greater than or Equal to 5% Frequency) in Four Controlled Clinical Trials (NUCA3001, NUCA3002, NUCB3001, NUCB3002)

Adverse Reaction	Lamivudine Tablets 150 mg Twice Daily plus RETROVIR (n=251)	RETROVIR^a (n=230)
Body as a Whole		
Headache	35%	27%
Malaise & fatigue	27%	23%
Fever or chills	10%	12%
Digestive		
Nausea	33%	29%
Diarrhea	18%	22%
Nausea & vomiting	13%	12%
Anorexia and/or decreased appetite	10%	7%
Abdominal pain	9%	11%
Abdominal cramps	6%	3%
Dyspepsia	5%	5%
Nervous System		
Neuropathy	12%	10%
Insomnia & other sleep disorders	11%	7%
Dizziness	10%	4%
Depressive disorders	9%	4%
Respiratory		
Nasal signs & symptoms	20%	11%
Cough	18%	13%

1.14 Labeling

Skin		
Skin rashes	9%	6%
Musculoskeletal		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

^aEither zidovudine monotherapy or zidovudine in combination with zalcitabine.

Pancreatitis: Pancreatitis was observed in 9 out of 2,613 adult subjects (0.3%) who received lamivudine in controlled clinical trials EPV20001,NUCA3001,NUCB3001, NUCA3002, NUCB3002, and NUCB3007 [see Warnings and Precautions (5.4)].

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

Selected laboratory abnormalities observed during therapy are summarized in Table 4.

Table 4. Frequencies of Selected Grade 3-4 Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Trials (NUCA3001, NUCA3002, NUCB3001, NUCB3002) and a Clinical Endpoint Trial (NUCB3007)

TEST (Threshold Level)	24-Week Surrogate Endpoint Trials ^a		Clinical Endpoint Trial ^a	
	Lamivudine plus RETROVIR	RETROV IR ^b	Lamivudine plus Current Therapy ^c	Placebo plus Current Therapy ^c
Absolute neutrophil count ($<750/\text{mm}^3$)	7.2%	5.4%	15%	13%
Hemoglobin (<8.0 g/dL)	2.9%	1.8%	2.2%	3.4%
Platelets ($<50,000/\text{mm}^3$)	0.4%	1.3%	2.8%	3.8%
ALT (>5.0 x ULN)	3.7%	3.6%	3.8%	1.9%
AST (>5.0 x ULN)	1.7%	1.8%	4.0%	2.1%
Bilirubin (>2.5 x ULN)	0.8%	0.4%	ND	ND
Amylase (>2.0 x ULN)	4.2%	1.5%	2.2%	1.1%

^a The median duration on study was 12 months.

^b Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

^c Current therapy was either zidovudine, zidovudine plus didanosine, or zidovudine plus zalcitabine.

ULN = Upper limit of normal.

ND = Not done.

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

1.14 Labeling

Clinical Trials Experience in Pediatric Subjects

Lamivudine oral solution has been studied in 638 pediatric subjects aged 3 months to 18 years in 3 clinical trials.

Selected clinical adverse reactions and physical findings with a greater than or equal to 5% frequency during therapy with lamivudine 4 mg per kg twice daily plus RETROVIR 160 mg per m² 3 times daily in therapy-naïve (less than or equal to 56 days of antiretroviral therapy) pediatric subjects are listed in Table 5.

Table 5. Selected Clinical Adverse Reactions and Physical Findings (Greater than or Equal to 5% Frequency) in Pediatric Subjects in Trial ACTG300

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

^aIncludes pain, discharge, erythema, or swelling of an ear.

Pancreatitis: Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric subjects receiving lamivudine 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 lamivudine. 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 Lamivudine plus RETROVIR. Pancreatitis was observed in 1 subject in this trial who received open-label lamivudine in combination with RETROVIR and ritonavir following discontinuation of didanosine monotherapy [see Warnings and Precautions (5.4)].

1.14 Labeling

Paresthesias and Peripheral Neuropathies: Paresthesias and peripheral neuropathies were reported in 15 subjects (15%) in Trial NUCA2002, 6 subjects (9%) in Trial NUCA2005, and 2 subjects (less than 1%) in Trial ACTG300.

Selected laboratory abnormalities experienced by therapy-naive (less than or equal to 56 days of antiretroviral therapy) pediatric subjects are listed in Table 6.

Table 6. Frequencies of Selected Grade 3-4 Laboratory Abnormalities in Pediatric Subjects in Trial ACTG300

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

ULN= Upper limit of normal.

Additional pediatric use information for patients aged 3 months and above is approved for ViiV Healthcare Company's EPIVIR[®] (lamivudine) tablets and oral solution. However, due to ViiV Healthcare Company's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

Neonates: Limited short-term safety information is available from 2 small, uncontrolled trials in South Africa in neonates receiving lamivudine with or without zidovudine for the first week of life following maternal treatment starting at Week 38 or 36 of gestation [see *Clinical Pharmacology* (12.3)]. Selected adverse reactions reported in these neonates included increased liver function tests, anaemia, diarrhea, electrolyte disturbances, hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections and sepsis; 3 neonates died (1 from gastroenteritis with acidosis and convulsions; 1 from traumatic injury, and 1 from unknown causes). Two other nonfatal gastroenteritis or diarrhea cases were reported, including 1 with convulsions; 1 infant had transient renal insufficiency associated with dehydration. The absence of control groups limits assessments of causality, but it should be assumed that perinatally exposed infants may be at risk for adverse reactions comparable to those reported in pediatric and adult HIV-1-infected patients treated with lamivudine-containing combination regimens. Long-term effects of in utero and infant lamivudine exposure are not known.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of lamivudine 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 lamivudine.

1.14 Labeling

Body as a Whole

Redistribution/accumulation of body fat [see *Warnings and Precautions (5.7)*].

Endocrine and Metabolic

Hyperglycemia.

General

Weakness.

Hemic and Lymphatic

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

Hepatic and Pancreatic

Lactic acidosis and hepatic steatosis [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.

7 DRUG INTERACTIONS

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim) [see *Clinical Pharmacology (12.3)*]. No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

1.14 Labeling

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to lamivudine during pregnancy. Physicians are encouraged to register patients by calling the Antiretroviral Pregnancy Registry at 1-800-258-4263.

Risk Summary

Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of overall major birth defects for lamivudine compared with the background rate for major birth defects of 2.7% in the US reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP).

Lamivudine 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.

Data

Human Data: Based on prospective reports from the Antiretroviral Pregnancy Registry of over 11,000 exposures to lamivudine 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 US reference population of the MACDP. The prevalence of defects in the first trimester was 3.1% (95% CI: 2.6% to 3.7%).

Lamivudine 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 lamivudine tablets twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg lamivudine tablets twice daily with zidovudine, and 10 women at 38 weeks gestation using lamivudine tablets 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, 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: Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine 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 lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans.

8.2 Lactation

Risk Summary

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

1.14 Labeling

infection. Because of the potential for HIV-1 transmission, mothers should be instructed not to breastfeed.

8.4 Pediatric Use

The safety and effectiveness of lamivudine in combination with other antiretroviral agents have been established in pediatric patients aged 3 months and older. Lamivudine scored tablet is the preferred formulation for HIV-1-infected pediatric patients who weigh at least 14 kg and for whom a solid dosage form is appropriate because pediatric subjects who received lamivudine oral solution had lower rates of virologic suspension, lower plasma lamivudine exposure and developed viral resistance more frequently than those receiving EPIVIR tablets in the ARROW trial [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.6), *Adverse Reactions* (6.1), *Clinical Pharmacology* (12.3), *Clinical Studies* (14.2)].

8.5 Geriatric Use

Clinical trials of lamivudine 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 tablets in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [see *Dosage and Administration* (2.3), *Clinical Pharmacology* (12.3)].

8.6 Patients with Impaired Renal Function

Reduction of the dosage of lamivudine tablets is recommended for patients with impaired renal function [see *Dosage and Administration* (2.3), *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

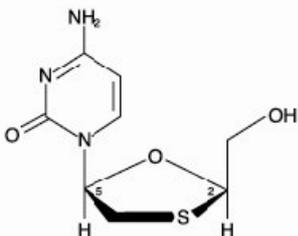
There is no known specific treatment for overdose with lamivudine. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

11 DESCRIPTION

Lamivudine (also known as 3TC) is a brand name for lamivudine, 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 C₈H₁₁N₃O₃S and a molecular weight of 229.3 g per mol. It has the following structural formula:

1.14 Labeling



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

Lamivudine tablets USP are for oral administration. Each scored 150-mg film-coated tablet contains 150 mg of lamivudine and the inactive ingredients hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lamivudine is an antiretroviral agent [see *Microbiology (12.4)*].

12.3 Pharmacokinetics

Pharmacokinetics in Adults

The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV-1-infected adult subjects after administration of single intravenous (IV) doses ranging from 0.25 to 8 mg per kg, as well as single and multiple (twice-daily regimen) oral doses ranging from 0.25 to 10 mg per kg.

The pharmacokinetic properties of lamivudine have also been studied as single and multiple oral doses ranging from 5 mg to 600 mg per day administered to HBV-infected subjects.

The steady-state pharmacokinetic properties of the lamivudine 300-mg tablet once daily for 7 days compared with the lamivudine 150-mg tablet twice daily for 7 days were assessed in a crossover trial in 60 healthy subjects. Lamivudine tablets 300 mg once daily resulted in lamivudine exposures that were similar to Lamivudine tablets 150 mg twice daily with respect to plasma AUC_{24,ss}; however, C_{max,ss} was 66% higher and the trough value was 53% lower compared with the 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to AUC_{24,ss} and C_{max24,ss}; however, trough values were lower compared with the 150-mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations.

The pharmacokinetics of lamivudine was evaluated in 12 adult HIV-1-infected subjects dosed with lamivudine tablets 150 mg twice daily in combination with other antiretroviral agents.

1.14 Labeling

The geometric mean (95% CI) for $AUC_{(0-12)}$ was 5.53 (4.58, 6.67) mcg.h per mL and for C_{max} was 1.40 (1.17, 1.69) mcg per mL.

Absorption and Bioavailability: Following oral administration, lamivudine is rapidly absorbed and extensively distributed. Absolute bioavailability in 12 adult subjects was $86\% \pm 16\%$ (mean \pm SD) for the 150-mg tablet and $87\% \pm 13\%$ for the oral solution. After oral administration of 2 mg per kg twice a day to 9 adults with HIV-1, the peak serum lamivudine concentration (C_{max}) was 1.5 ± 0.5 mcg/mL (mean \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 per kg.

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

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

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

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

Metabolism: Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite of lamivudine is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours). Serum concentrations of this metabolite have not been determined. Lamivudine is not significantly metabolized by cytochrome P450 enzymes.

Elimination: The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300-mg oral dose of lamivudine, renal clearance was 199.7 ± 56.9 mL per min (mean \pm SD). In 20 HIV-1 infected patients given a single IV dose, renal clearance was 280.4 ± 75.2 mL per min (mean \pm SD), representing $71\% \pm 16\%$ (mean \pm SD) of total clearance of lamivudine.

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

Special Populations

Renal Impairment: The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-1-infected adults with impaired renal function (Table 7).

1.14 Labeling

Table 7. Pharmacokinetic Parameters (Mean ± SD) After a Single 300-mg Oral Dose of Lamivudine in 3 Groups of Adults with Varying Degrees of Renal Function

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

T_{max} was not significantly affected by renal function. Based on these observations, it is recommended that the dosage of lamivudine be modified in patients with renal impairment [see Dosage and Administration (2.3)].

Based on a trial in otherwise healthy subjects with impaired renal function, hemodialysis increased lamivudine clearance from a mean of 64 to 88 mL per min; however, the length of time of hemodialysis (4 hours) was insufficient to significantly alter mean lamivudine exposure after a single-dose administration. Continuous ambulatory peritoneal dialysis and automated peritoneal dialysis have negligible effects on lamivudine clearance. Therefore, it is recommended, following correction of dose for creatinine clearance, that no additional dose modification be made after routine hemodialysis or peritoneal dialysis.

The effects of renal impairment on lamivudine pharmacokinetics in pediatric patients are not known.

Hepatic Impairment: The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

Pregnancy: Lamivudine pharmacokinetics were studied in 36 pregnant women during 2 clinical trials conducted in South Africa. Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples.

Pediatric Patients: The pharmacokinetics of lamivudine have been studied after either single or repeat doses of Lamivudine in pediatric subjects. Pediatric subjects receiving lamivudine oral solution according to the recommended dosage regimen achieved approximately 25% lower plasma concentrations of lamivudine compared with HIV-1-infected adults. Pediatric subjects receiving lamivudine oral tablets achieved plasma concentrations comparable to or slightly higher than those observed in adults. The absolute bioavailability of both Lamivudine tablets & oral solution are lower in children than adults. The relative bioavailability of lamivudine oral solution is approximately 40% lower than tablets containing lamivudine in pediatric subjects despite no difference in adults. The mechanisms for the diminished

1.14 Labeling

absolute bioavailability of lamivudine and relative bioavailability of lamivudine solution are unknown.

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

Limited, uncontrolled pharmacokinetic and safety data are available from administration of lamivudine (and zidovudine) to 36 infants aged up to 1 week in 2 trials in South Africa. In these trials, lamivudine clearance was substantially reduced in 1-week-old neonates relative to pediatric subjects (aged over 3 months) studied previously. There is insufficient information to establish the time course of changes in clearance between the immediate neonatal period and the age-ranges over 3 months old. [see *Adverse Reactions* (6.1)]

Additional pediatric use information for patients aged 3 months and above is approved for ViiV Healthcare Company's EPIVIR[®] (lamivudine) tablets and oral solution. However, due to ViiV Healthcare Company's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

Geriatric Patients: The pharmacokinetics of lamivudine after administration of lamivudine tablets to subjects over 65 years have not been studied [see *Use in Specific Populations* (8.5)].

Gender: There are no significant or clinically relevant gender differences in lamivudine pharmacokinetics.

Race: There are no significant or clinically relevant racial differences in lamivudine pharmacokinetics.

Drug Interactions

Interferon Alfa: There was no significant pharmacokinetics interaction between lamivudine 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 lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects [see *Warnings and Precautions* (5.3)].

Trimethoprim/Sulfamethoxazole: Lamivudine 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 lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine tablets 300 mg with the fifth dose in a crossover design.

1.14 Labeling

Coadministration of TMP/SMX with lamivudine resulted in an increase of $43\% \pm 23\%$ (mean \pm SD) in lamivudine AUC_{∞} , a decrease of $29\% \pm 13\%$ in lamivudine oral clearance, and a decrease of $30\% \pm 36\%$ in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used in treat PCP.

Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult subjects given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg every 12 hours).

12.4 Microbiology

Mechanism of Action

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

Antiviral Activity

The antiviral activity of lamivudine 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 0.003 to 15 microM (1 microM = 0.23 mcg per mL). The median EC_{50} values of lamivudine 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 0.003 to 0.120 microM in PBMCs. Lamivudine 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 lamivudine by 3.5-fold in MT-4 cells.

Resistance

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

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from subjects. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In subjects receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most subjects became phenotypically and genotypically resistant to lamivudine within 12 weeks.

Genotypic and Phenotypic Analysis of On-Therapy HIV-1 Isolates from Subjects with Virologic Failure

Trial EPV20001: Fifty-three of 554 (10%) subjects enrolled in EPV20001 were identified as virological failures (plasma HIV-1 RNA level greater than or equal to 400 copies per mL) by Week 48. Twenty-eight subjects were randomized to the lamivudine once-daily treatment group and 25 to the lamivudine twice-daily treatment group. The median baseline plasma

1.14 Labeling

HIV-1 RNA levels of subjects in the lamivudine once-daily group and lamivudine twice-daily group were 4.9 log₁₀ copies per mL and 4.6 log₁₀ copies per mL, respectively.

Genotypic analysis of on-therapy isolates from 22 subjects identified as virologic failures in the lamivudine once-daily group showed that isolates from 8 of 22 subjects contained a treatment-emergent lamivudine resistance-associated substitution (M184V or M184I), isolates from 0 of 22 subjects contained treatment-emergent amino acid substitutions associated with zidovudine resistance (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E), and isolates from 10 of 22 subjects contained treatment-emergent amino acid substitutions associated with efavirenz resistance (L100I, K101E, K103N, V108I, or Y181C).

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

Phenotypic analysis of baseline- matched on-therapy HIV-1 isolates from subjects (n = 13) receiving lamivudine once daily showed that isolates from 7 of 13 subjects showed an 85- to 299-fold decrease in susceptibility to lamivudine, isolates from 12 of 13 subjects were susceptible to zidovudine, and isolates from 8 of 13 subjects exhibited a 25- to 295-fold decrease in susceptibility to efavirenz.

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

Trial EPV40001: Fifty subjects received lamivudine tablets 300 mg once daily plus zidovudine 300 mg twice daily plus abacavir 300 mg twice daily and 50 subjects received lamivudine tablets 150 mg plus zidovudine 300 mg plus abacavir 300 mg all twice-daily. The median baseline plasma HIV-1 RNA levels for subjects in the 2 groups were 4.79 log₁₀ copies per mL and 4.83 log₁₀ copies per mL, respectively. Fourteen of 50 subjects in the lamivudine once-daily treatment group and 9 of 50 subjects in the lamivudine twice-daily group were identified as virologic failures.

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

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

Phenotypic analysis of on-therapy isolates from subjects (n = 4) receiving lamivudine twice daily showed that HIV-1 isolates from 1 subject exhibited a 45-fold decrease in susceptibility to lamivudine and a 4.5-fold decrease in susceptibility to zidovudine.

1.14 Labeling

Pediatrics: Pediatric subjects receiving lamivudine oral solution concomitantly with other antiretroviral oral solutions (abacavir, nevirapine/efavirenz, or zidovudine) in ARROW developed viral resistance more frequently than those receiving tablets. Dosing of lamivudine plus abacavir, 13% of subjects who started on tablets and 32% of subjects who started on solution had resistance substitutions. The resistance profile observed in pediatrics is similar to that observed in adults in terms of the genotypic substitutions detected and relative frequency, with the most commonly detected substitutions at M184 (V or I) [see *Clinical Studies (14.2)*].

Cross-Resistance

Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors (NRTIs). Lamivudine-resistant HIV-1 mutants were cross-resistant in cell culture to didanosine (ddI). Cross-resistance is also expected with abacavir and emtricitabine as these select M184V substitutions.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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 human exposures at the recommended dose of 300 mg.

Mutagenesis

Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine 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 an assay for unscheduled DNA synthesis in rat liver. Lamivudine showed no evidence of in vivo genotoxic activity in the rat at oral doses of up to 2,000 mg per kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection.

Impairment of Fertility

In a study of reproductive performance, lamivudine 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.

14 CLINICAL STUDIES

The use of lamivudine is based on the results of clinical trials in HIV-1 infected subjects in combination regimens with other antiretroviral agents. Information from trials with clinical endpoints or a combination of CD4+ cell counts and HIV-1 RNA measurements is included below as documentation of the contribution of lamivudine to a combination regimen in controlled trials.

1.14 Labeling

14.1 Adult Subjects

Clinical Endpoint Trial

NUCB3007 (CAESAR) was a multicenter, double-blind, placebo-controlled trial comparing continued current therapy (zidovudine alone [62% of subjects] or zidovudine with didanosine or zalcitabine [38% of subjects]) to the addition of lamivudine or lamivudine plus an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI), randomized 1:2:1. A total of 1,816 HIV-1-infected adults with 25 to 250 CD4+ cells per mm³ (median = 122 cells per mm³) at baseline were enrolled: median age was 36 years, 87% were male, 84% were nucleoside-experienced, and 16% were therapy-naive. The median duration on trial was 12 months. Results are summarized in Table 9.

Table 9. Number of Subjects (%) with at Least One HIV-1 Disease Progression Event or Death

Endpoint	Current Therapy (n= 460)	Lamivudine plus Current Therapy (n= 896)	Lamivudine plus an NNRTI^a plus Current Therapy (n= 460)
HIV-1 progression or death	90 (19.6%)	86 (9.6%)	41 (8.9%)
Death	27 (5.9%)	23 (2.6%)	14 (3.0%)

^aAn investigational non-nucleoside reverse transcriptase inhibitor not approved in the United States.

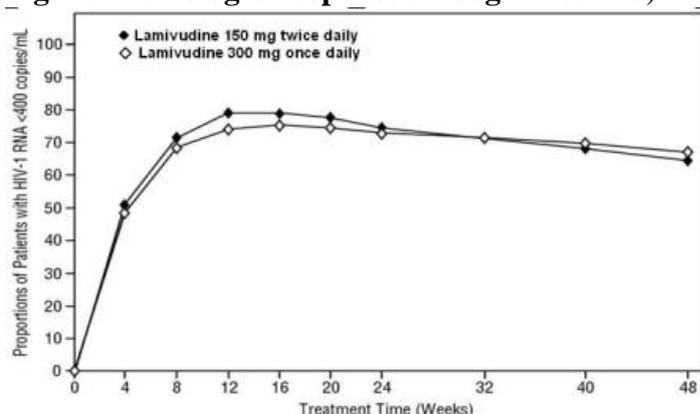
Surrogate Endpoint Trials

Dual Nucleoside Analogue Trials: Principal clinical trials in the initial development of lamivudine compared lamivudine/zidovudine combinations with zidovudine monotherapy or with zidovudine plus zalcitabine. These trials demonstrated the antiviral effect of lamivudine in a 2-drug combination. More recent uses of lamivudine in treatment of HIV-1 infection incorporate it into multiple- drug regimens containing at least 3 antiretroviral drugs for enhanced viral suppression.

Dose Regimen Comparison Surrogate Endpoint Trials in Therapy-Naive Adults: EPV20001 was a multicenter, double-blind, controlled trial in which subjects were randomized 1:1 to receive lamivudine tablets 300 mg once daily or lamivudine tablets 150 mg twice daily, in combination with zidovudine 300 mg twice daily and efavirenz 600 mg once daily. A total of 554 antiretroviral treatment-naive HIV-1-infected adults enrolled: male (79%), white (50%), median age of 35 years, baseline CD4+ cell counts of 69 to 1,089 cells per mm (median = 362 cells per mm), and median baseline plasma HIV-1 RNA of 4.66 log copies per mL. Outcomes of treatment through 48 weeks are summarized in Figure 1 and Table 10.

1.14 Labeling

Figure 1. Virologic Response through Week 48, EPV20001^{a,b} (Intent-to-Treat)



^a Roche AMPLICOR HIV-1 MONITOR.

^b Responders at each visit are subjects who had achieved and maintained HIV-1 RNA <400 copies/mL without discontinuation by that visit.

Table 10. Outcomes of Randomized Treatment through 48 Weeks (Intent-to-Treat)

Outcome	Lamivudine Tablets 300 mg Once daily plus RETROVIR plus Efavirenz (n=278)	Lamivudine Tablets 150 mg Twice Daily plus RETROVIR plus Efavirenz (n= 276)
Responder ^a	67%	65%
Virologic failure ^b	8%	8%
Discontinued due to clinical progression	<1%	0%
Discontinued due to adverse events	6%	12%
Discontinued due to other reasons ^c	18%	14%

^a Achieved confirmed plasma HIV-1 RNA less than 400 copies per mL and maintained through 48 weeks.

^b Achieved suppression but rebounded by Week 48, discontinued due to virologic failure, insufficient viral response according to the investigator, or never suppressed through Week 48.

^c Includes consent withdrawn, lost to follow-up, protocol violation, data outside the trial-defined schedule, and randomized but never initiated treatment.

The proportions of subjects with HIV-1 RNA less than 50 copies per mL (via Roche Ultrasensitive assay) through Week 48 were 61% for subjects receiving lamivudine tablets 300 mg once daily and 63% for patients receiving lamivudine tablets 150 mg twice daily. Median increases in CD4+ cell counts were 144 cells per mm³ at Week 48 in subjects receiving lamivudine tablets 300 mg once daily and 146 cells per mm³ for subjects receiving lamivudine tablets 150 mg twice daily.

A small, randomized, open-label pilot trial, EPV40001, was conducted in Thailand. A total of 159 treatment-naïve adult subjects (male 32%, Asian 100%, median age 30 years, baseline median CD4+ cell count 380cells per mm³, median plasma HIV-1 RNA 4.8 log₁₀ copies per

1.14 Labeling

mL) were enrolled. Two of the treatment arms in this trial provided a comparison between lamivudine tablets 300 mg once daily (n = 54) and lamivudine tablets 150 mg twice daily (n = 52), each in combination with zidovudine 300 mg twice daily and abacavir 300 mg twice daily. In intent-to-treat analyses of 48-week data, the proportions of patients with HIV-1 RNA below 400 copies per mL were 61% (33 of 54) in the group randomized to once-daily lamivudine and 75% (39 of 52) in the group randomized to receive all 3 drugs twice daily; the proportions with HIV-1 RNA below 50 copies per mL were 54% (29 of 54) in the once-daily lamivudine group and 67% (35 of 52) in the all-twice-daily group; and the median increases in CD4+ cell counts were 166 cells per mm³ in the once-daily lamivudine group and 216 cells per mm³ in the all-twice-daily group.

14.2 Pediatric Subjects

Clinical Endpoint Trial

ACTG300 was a multicenter, randomized, double-blind trial that provided for comparison of lamivudine plus RETROVIR (zidovudine) with didanosine monotherapy. A total of 471 symptomatic, HIV-1-infected therapy-naïve (less than or equal to 56 days of antiretroviral therapy) pediatric subjects were enrolled in these 2 treatment arms. The median age was 2.7 years (range: 6 weeks to 14 years), 58% were female, and 86% were non-white. The mean baseline CD4+ cell count was 868 cells per mm³ (mean: 1,060 cells per mm³ and range: 0 to 4,650 cells per mm³ for subjects aged less than or equal to 5 years; mean: 419 cells per mm³ and range: 0 to 1,555 cells per mm³ for subjects aged over 5 years) and the mean baseline plasma HIV-1 RNA was 5.0 log₁₀ copies per mL. The median duration on trial was 10.1 months for the subjects receiving lamivudine tablets plus RETROVIR and 9.2 months for subjects receiving didanosine monotherapy. Results are summarized in Table 11.

Table 11. Number of Subjects (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	Lamivudine plus RETROVIR (n=236)	Didanosine (n=235)
HIV-1 disease progression or death (total)	15 (6.4%)	37 (15.7%)
Physical growth failure	7 (3.0%)	6 (2.6%)
Central nervous deterioration	4 (1.7%)	12 (5.1%)
CDC Clinical Category C	2 (0.8%)	8 (3.4%)
Death	2 (0.8%)	11 (4.7%)

Additional pediatric use information for patients aged 3 months and above is approved for ViiV Healthcare Company's EPIVIR[®] (lamivudine) tablets and oral solution. However, due to ViiV Healthcare Company's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

16 HOW SUPPLIED/STORAGE AND HANDLING

Lamivudine Tablets USP contain 150 mg of Lamivudine, are white, diamond-shaped, scored film-coated tablets, debossed one side with "001" on either side of scoreline. Packaged as follows:

1.14 Labeling

Bottle of 60 tablets (NDC 64330-001-01) with child-resistant closure.

Recommended Storage:

Store Lamivudine Tablets USP at 20° to 25°C (68° to 77°F) excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

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

Lactic Acidosis/Hepatomegaly

Advise patients that lactic acidosis and severe hepatomegaly with steatosis have been reported with use of nucleoside analogues and other antiretrovirals. Advise patients to stop taking lamivudine tablets if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity [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 was 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)].

Differences in Formulations of Lamivudine

Advise patients that Lamivudine tablets contain a higher dose of the same active ingredient (lamivudine) as EPIVIR -HBV tablets. If a decision is made to include lamivudine in the HIV-1 treatment regimen of a patient co-infected with HIV-1 and HBV, the formulation and dosage of lamivudine in lamivudine tablets (not EPIVIR -HBV) should be used [see *Warnings and Precautions* (5.2)].

Risk of Pancreatitis

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

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any signs and symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when lamivudine is started [see *Warnings and Precautions* (5.5)].

Redistribution/Accumulation of Body Fat

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time [see *Warnings and Precautions* (5.7)].

Pregnancy Registry

1.14 Labeling

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Lamivudine during pregnancy [*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, to take it as soon as they remember. Advise patients not to double their next dose or take more than the prescribed dose [*see Dosage and Administration (2)*].

EPIVIR and RETROVIR are registered trademarks of the ViiV Healthcare group of companies.

EPIVIR-HBV is a trademark licensed to the GSK group of companies.

Manufactured By:

Centaur Pharmaceuticals Private Limited
Plot No. 4, International Biotech Park, Phase II,
Hinjewadi, Pune-411 057,
INDIA

Manufactured For:

Centaur Pharmaceuticals Private Limited.
'Centaur House', Near Grand Hyatt,
Shanti Nagar, Vakola, Santacruz (East)
Mumbai, Maharashtra, 400055, India

Revised: 11/2016

1.14 Labeling

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION
Lamivudine (la-miv'-ue-deen) Tablets USP

What is the most important information I should know about lamivudine tablets?

Lamivudine can cause serious side effects, including:

- **Build-up of an acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take lamivudine tablets. Lactic acidosis is a serious medical emergency that can cause death. **Call 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 light-headed
 - trouble breathing
 - have a fast or irregular heartbeat
 - stomach pain with nausea and vomiting
- **Serious liver problems** can happen in people who take lamivudine tablets. In some cases these serious 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 :**
 - 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
 - light-colored stools (bowel movements)
 - pain, aching, or tenderness on the right side of your stomach area

You may be more likely to get lactic acidosis or serious liver problems if you are female, very overweight (obese), or have been taking nucleoside analog medicines for a long time.

- **Worsening of hepatitis B virus in people who have HIV-1 infection.** If you have HIV-1 (Human Immunodeficiency Virus type 1) and hepatitis B virus (HBV) infection, your HBV may get worse (flare-up) if you stop taking lamivudine tablets. A “flare-up” is when your HBV infection suddenly returns in a worse way than before. Worsening liver disease can be serious and may lead to death.

1.14 Labeling

- Do not run out of lamivudine tablets. Refill your prescription or talk to your healthcare provider before your lamivudine tablets are all gone.
 - Do not stop lamivudine tablets without first talking to your healthcare provider.
 - If you stop taking lamivudine tablets, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver.
- **Resistant Hepatitis B Virus (HBV).** If you have HIV-1 and hepatitis B, the hepatitis B virus can change (mutate) during your treatment with lamivudine tablets and become harder to treat (resistant).
 - **Use with interferon and ribavirin-based regimens.** Worsening of liver disease that has caused death has happened in people infected with both HIV-1 and hepatitis C virus who are taking antiretroviral medicines and are also being treated for hepatitis C with interferon with or without ribavirin. If you are taking lamivudine tablets and interferon with or without ribavirin, tell your healthcare provider if you have any new symptoms.

What is Lamivudine?

Lamivudine is a prescription medicine used together with other antiretroviral medicines to treat Human Immunodeficiency Virus (HIV-1) infection.

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

Lamivudine tablets (used to treat HIV-1 infection) contain a higher dose of the same active ingredient (lamivudine) than is in the medicine lamivudine-HBV tablets (used to treat HBV). If you have both HIV-1 and HBV, you should not use lamivudine-HBV to treat your infections.

The safety and effectiveness of lamivudine tablets have not been established in children under 3 months of age.

Who should not take lamivudine tablets?

Do not take lamivudine tablets if you are allergic to lamivudine or any of the ingredients in lamivudine tablets. See the end of this Patient Information leaflet for a complete list of ingredients in lamivudine tablets.

What should I tell my healthcare provider before taking lamivudine tablets?

Before you take lamivudine tablets, tell your healthcare provider if you:

- have or have had liver problems, including hepatitis B or C virus infection.
- have kidney problems.
- have diabetes
- are pregnant or plan to become pregnant. Taking lamivudine tablets during pregnancy has not been associated with an increased risk of birth defects. Talk to your healthcare provider if you are pregnant or plan to become pregnant.

1.14 Labeling

Pregnancy Registry. There is a pregnancy registry for women who take antiretroviral medicines 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 tablets.**
- You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
- Talk with 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 medications interact with lamivudine. 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.

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 tablets with other medicines.

How should I take lamivudine tablets?

- **Take lamivudine tablets exactly as your healthcare provider tells you to take it.**
- If you miss a dose of lamivudine 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 a healthcare provider during treatment with lamivudine tablets.
- Lamivudine tablets may be taken with or without food.
- For children 3 months and older, your healthcare provider will prescribe a dose of lamivudine tablets based on your child's body weight.
- Tell your healthcare provider if you or your child has trouble swallowing tablets. Lamivudine also comes as a liquid (oral solution)
- Do not run out of lamivudine 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 tablets, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of lamivudine tablets?

- **Lamivudine tablets can cause serious side effects including:**
- See **“What is the most important information I should know about lamivudine tablets?”**
- **Risk of inflammation of the pancreas (pancreatitis).** Children may be at risk for developing pancreatitis during treatment with lamivudine tablets if they:
 - have taken nucleoside analogue
 - have a history of pancreatitis

1.14 Labeling

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 tablets 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 right away if you start having new symptoms after you start taking lamivudine tablets.
- **Changes in body fat** can happen in people who take HIV-1 medicines. These changes may include an increased amount of fat in the upper back and neck (“buffalo hump”), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.

The most common side effects of lamivudine tablets in adults include:

- headache
- nausea
- generally not feeling well
- tiredness
- nasal signs and symptoms
- diarrhea
- cough

The most common side effects of lamivudine tablets in children include fever and cough.

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

These are not all the possible side effects of lamivudine tablets. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store lamivudine tablets?

- Store lamivudine tablets at room temperature between 68°F to 77°F (20°C to 25°C).

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

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

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

You can ask your healthcare provider or pharmacist for information about lamivudine tablets that is written for health professionals.

What are the ingredients in lamivudine tablets?

Active ingredient: lamivudine

Inactive ingredients:

Lamivudine scored 150-mg film-coated tablets: hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

Lamivudine Tablets USP 150mg
ANDA# 203586

1.14 Labeling

Manufactured By:

Centaur Pharmaceuticals Private Limited
Plot No. 4, International Biotech Park, Phase II,
Hinjewadi, Pune-411 057,
INDIA

Manufactured For:

Centaur Pharmaceuticals Private Limited.
'Centaur House', Near Grand Hyatt,
Shanti Nagar, Vakola, Santacruz (East)
Mumbai, Maharashtra, 400055,India

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

Revised: 11/2016