PUBLIC ASSESSMENT REPORT

Lamivudine Tablets 150 mg and 300 mg

International Nonproprietary name (INN): **Lamivudine**

Abstract

Lamivudine Tablets 150 mg and 300 mg manufactured by Aurobindo Pharma Limited, Unit III, Survey No. 313, Bachupally, Quthubullapur Mandal, Hyderabad, Andhra Pradesh 500 072, India, was the subject of an abbreviated new drug application (ANDA) submitted to the U. S. Food and Drug Administration (USFDA) pursuant to section 505(j) of the U. S. Federal Food, Drug, and Cosmetic Act.

This ANDA was reviewed under the President's Emergency Plan for AIDS Relief (PEPFAR). Based upon the information presented to date the USFDA concluded that Lamivudine Tablets 150 mg and 300 mg are safe and effective for use as recommended in the submitted labeling. The USFDA was unable to grant final approval to this ANDA at the time of review due to existing patent protection. Therefore, the ANDA was **tentatively approved** on June 15, 2005. This determination is based upon information available to the agency (i.e., information in the ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product).

Lamivudine Tablets 150 mg and 300 mg, on the basis of USFDA **tentative approval**, were placed on the WHO Prequalification Programme list of manufacturers and suppliers whose HIV-related products have been found acceptable, in principle, for procurement by UN Agencies (Prequalification Programme: Priority Essential Medicines, 63rd Edition, 1 February 2008).

Products listed on the WHO Prequalification list with the note "USFDA" have been added to the list based on the scientific assessment and inspections conducted by the USFDA. A product listed as USFDA **tentatively approved** indicates that although existing patents and/or other marketing exclusivity prevent marketing of the product in the USA, the product meets all of USFDA's safety, efficacy, and manufacturing quality standards required for marketing in the USA, and is eligible for purchase with PEPFAR funds.

Lamivudine is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in combination with other antiretroviral agents. Detailed conditions for the use of this product are described in the Summary of Product Characteristics of this Public Assessment Report.

The active pharmaceutical ingredient (API) of Lamivudine Tablets 150 mg and 300 mg is the nucleoside analogue reverse transcriptase inhibitor (NRTI) lamivudine, a well-established and documented product for the treatment of HIV/AIDS in combination with other products.

Lamivudine has been investigated in combination therapy in several clinical trials in both treatment-naïve and treatment-experienced patients. These studies have demonstrated significant decreases in HIV-1 viral load and increases in CD4+ cell count. Clinical end-point data indicate that therapy with lamivudine in combination with other antiretroviral agents results in a significant reduction in the risk of disease progression and mortality.

The most frequent adverse reactions observed during treatment were headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough.

The most important safety problems related to Lamivudine Tablets150 mg and 300 mg include lactic acidosis and severe hepatomegaly (enlarged liver), exacerbations (worsening) of hepatitis B, pancreatitis (inflamed pancreas), immune reconstitution syndrome, and redistribution/accumulation of body fat. Lamivudine Tablets 150 mg and 300 mg should not be taken with other lamivudine- and emtricitabine- containing products or with interferon- and ribavirin-based regimens. Patients with HIV-1 infection should receive only dosage forms of lamivudine appropriate for treatment of HIV-1. Patients receiving interferon alfa with or without ribavirin and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation.

The risk/benefit profile of Lamivudine Tablets 150 mg and 300 mg showed acceptable safety and adequate antiretroviral activity. Lamivudine in any form or strength is not recommended for use as monotherapy because of rapid emergence of resistance. Lamivudine Tablets 150 mg and 300 mg must not be used in patients with clinically significant hypersensitivity to lamivudine or to any of the components contained in the formulation.

All Accepted Presentations

Status	USFDA Tentative Approval 06/15/2005
INN	Lamivudine
Strength	150 mg scored, 300 mg
Form	Tablets
Route of administration	Oral
Packaging	Bottle, blister pack
Package size	Bottles of 60 (150 mg) Bottles of 30 (300 mg) 6 x 10 unit-dose (150 mg) 3 x 10 unit-dose (300 mg)

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Lamivudine Tablets 150 mg and 300 mg

Read all of this leaflet carefully before you start taking this medicine

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

WARNING: RISK OF LACTIC ACIDOSIS, EXACERBATIONS OF HEPATITIS B IN CO-INFECTED PATIENTS UPON DISCONTINUATION OF LAMIVUDINE, DIFFERENT FORMULATIONS OF LAMIVUDINE.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine and other antiretrovirals. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur.

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.

Lamivudine tablets (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.

In this leaflet:

1. WHAT LAMIVUDINE TABLETS ARE AND WHAT THEY ARE USED FOR

Lamivudine Tablets belong to a group of anti-HIV medicines, also known as antiretrovirals or antiviral medicines, in the category known as nucleoside analogue reverse transcriptase inhibitors (NRTIs). Lamivudine Tablets are used in combination with other antiretroviral medicines for the treatment of HIV-1 (human immunodeficiency virus type 1) infection in combination with other medications. Lamivudine reduces the amount of HIV virus in your body and keeps it at a low

level. It also increases CD4+ cell counts. CD4+ cells are a type of white blood cell that plays an important role in maintaining a healthy immune system to help fight infection. Response to treatment with Lamivudine Tablets varies between patients. Your doctor or health care provider will be monitoring the effectiveness of your treatment.

Lamivudine Tablets may improve your condition but are not a cure for HIV infection. HIV infection is a disease spread by contact with blood or sexual contact with an infected individual. Treatment with Lamivudine Tablets has not been shown to reduce the risk of passing HIV infection on to others by sexual contact or by blood transfer. Therefore, you must continue to take appropriate precautions to avoid giving the virus to others.

During your treatment, other infections linked to your weakened immunity (opportunistic infections) may arise. These will require specific and sometimes preventive treatment.

2. BEFORE YOU TAKE LAMIVUDINE TABLETS

Do not take Lamivudine Tablets

- if you are allergic (hypersensitive) to lamivudine or any other ingredients of Lamivudine Tablets (see Part 6, “What Lamivudine Tablets contain”).

Take special care with Lamivudine Tablets

Before using this medicine, you should tell your doctor or health care provider:

- if you have kidney disease. The standard recommended dose may have to be reduced.
- if you have a history of liver disease. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver adverse events and may require blood tests for control of liver function.
- if you have a chronic hepatitis B infection, you should not stop your treatment without instructions from your doctor or health care provider, as you may have a recurrence of your hepatitis. This recurrence may be more severe if you have serious liver disease.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor or health care provider immediately.

You will need to take Lamivudine Tablets by mouth every day, in combination with other prescribed anti-HIV medications. This medicine helps to control your condition, but it is not a cure for HIV infection. You may continue to develop other infections and other illnesses associated with HIV disease. Lamivudine Tablets do not reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Tell your doctor if your child has a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis as lamivudine should be used with caution. Pediatric patients who develop severe abdominal pain or other symptoms of pancreatitis while taking lamivudine should stop treatment immediately and receive immediate medical attention.

Taking other medicines
There are other medicines that may not mix with Lamivudine Tablets. Tell your doctor, healthcare provider, or pharmacist about any other medicines you take, including those you have purchased yourself ("over the counter") medicines, prescription and non-prescription medicines, vitamins, and herbal supplements. These may affect the action of Lamivudine Tablets, or Lamivudine Tablets may affect their action. Make sure your doctor knows about all medicines you take.

The following medicines should not be taken with Lamivudine Tablets since they contain lamivudine, the active ingredient in Lamivudine Tablets:

- Epivir-HBV® Tablets
- Epivir Oral Solution
- Combivir® (lamivudine/zidovudine) Tablets
- Epzicom® (abacavir sulfate and lamivudine) Tablets
- Trizivir® (abacavir sulfate, lamivudine, and zidovudine)
- Emtricitabine-containing products such as Atripla® (efavirenz, emtricitabine, and tenofovir), Emtriva® (emtricitabine), or Truvada® (emtricitabine and tenofovir), or Complera™ (rilpivirine/emtricitabine/tenofovir).

The following medicines may need to be replaced with another medicine when taken with Lamivudine Tablets:

- Epivir-HBV® Tablets
- Epivir Oral Solution
- Combivir® (lamivudine/zidovudine) Tablets
- Epzicom® (abacavir sulfate and lamivudine) Tablets
- Trizivir® (abacavir sulfate, lamivudine, and zidovudine)
- emtricitabine-containing products such as Atripla® (efavirenz, emtricitabine, and tenofovir), Emtriva® (emtricitabine), or Truvada® (emtricitabine and tenofovir), or Complera™ (rilpivirine/emtricitabine/tenofovir)
- zalcitabine

The following medicines may require a change in the dose of either Lamivudine Tablets or the other medicine:

- Interferon alfa, ribavirin, or both.
- 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 score >6).

Tell your doctor about all medicines that you take, even nonprescription ("over the counter") medicines, vitamins, or food supplements.

Contraception (Birth Control)
For women taking Lamivudine Tablets, barrier contraception (for example, condoms) should always be used in combination with other contraceptive methods including oral ("the pill") or other hormonal contraceptives (for example, implant or injection).

Taking Lamivudine Tablets with food and drink
Lamivudine Tablets may be taken with or without food.

Pregnancy
FDA Pregnancy Category C for Lamivudine Tablets

Lamivudine Tablets are assigned this pregnancy category because there are no adequate and well-controlled studies of lamivudine in pregnant women. Lamivudine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

If you become pregnant or are planning to become pregnant, talk to your health care provider about the benefits and risks of your anti-HIV therapy for you and your child.

If you have taken Lamivudine Tablets during your pregnancy, your doctor or health care provider may request regular visits to monitor the development of your child. Such visits may include blood tests and other diagnostic tests.

In children whose mother took anti-HIV medications during pregnancy, the benefit from the reduced chance of being infected with HIV is greater than the risk of suffering from side effects.

Breastfeeding
Do not breastfeed if you are taking Lamivudine Tablets. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Driving and using machines
No information on the effects of lamivudine on the ability to drive and use machines is available.

3. HOW TO TAKE LAMIVUDINE TABLETS

Always take Lamivudine Tablets exactly as your doctor or health care provider told you. You should check with your doctor, health care provider or pharmacist if you are not sure.

Adults and Adolescents over 16 years of age
The recommended oral dose of Lamivudine Tablets for HIV-1-infected adults and adolescents over 16 years of age is 300 mg daily. This can be taken either as one 150 mg tablet twice a day approximately 12 hours apart or 300 mg once a day.

Pediatric Patients
The recommended oral dose of Lamivudine Tablets for HIV-1-infected pediatric patients 3 months to 16 years of age is 4 mg/kg twice daily (up to a maximum of 150 mg twice a day), administered in combination with other antiretroviral agents. Lamivudine Tablets 150 mg are scored for HIV-1-infected pediatric patients who weigh greater than or equal to14 kg and should receive a solid dosage form. Before prescribing Lamivudine Tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow Lamivudine Tablets, the oral solution formulation should be prescribed. The recommended oral dosage of Lamivudine Tablets for HIV-1-infected pediatric patients is in the table below.

Weight (kg)	Dosage Regimen Using Scored 150 mg Tablet		Total Daily Dose
	AM Dose	PM Dose	
14 to 21	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
>21 to <30	½ tablet (75 mg)	1 tablet (150 mg)	225 mg
>30	1 tablet (150 mg)	1 tablet (150 mg)	300 mg

Patients with Kidney Problems
If you have a kidney problem, your dose may need to be altered. Please follow the instructions of your health care provider.

Lamivudine Tablets will always be taken in combination with other antiretroviral medication; please make sure to follow the instructions within the supplied package leaflet(s).

If you take more Lamivudine Tablets than you should
If you have taken too many tablets or if someone accidentally swallows some, there is no immediate danger. However, you should contact your doctor, health care provider, or the nearest hospital emergency department for further advice.

If you forget to take Lamivudine Tablets
If you accidentally miss a dose, take the next normal dose at the scheduled time. Do not take a double dose to make up for forgotten individual doses.

If you stop taking Lamivudine Tablets
Because your medicine controls and does not cure your condition, you will normally need to take it continuously. You should not stop treatment unless your doctor or health care provider tells you to. If you stop taking Lamivudine Tablets your HIV infection may get worse. If you have any further questions on the use of this product, ask your doctor or health care provider or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Lamivudine Tablets can cause side effects, although not everybody gets them. When treating HIV-infection, it is not always possible to differentiate between unwanted effects caused by Lamivudine Tablets, and those caused by any other medicines you may be taking at the same time, and by the HIV disease. For this reason, it is important that you inform your doctor or health care provider of any change in your health.

The major side effects of Lamivudine Tablets are lactic acidosis and hepatomegaly, severe worsening of hepatitis B, hepatic decompensation, pancreatitis, immune reconstitution syndrome and redistribution/accumulation of body fat. Major side effects have also occurred in patients with HIV-1 and hepatitis B co-infection, and in patients who use other lamivudine- and emtricitabine-containing products with Lamivudine Tablets.

Very commonly reported (greater than 1 in every 10 patients treated) side effects are headache, malaise and fatigue, fever or chills, nausea and/or vomiting, diarrhea, anorexia and/or decreased appetite, neuropathy, insomnia (trouble sleeping) and other sleep disorders, dizziness, nasal signs and symptoms, cough, and musculoskeletal pain.

Commonly reported (greater than 1 in every 100 patients treated) side effects are abdominal pain or cramps, dyspepsia, depressive disorders, skin rashes, myalgia, and arthralgia.

Uncommonly reported (between 1 in 1,000 and 1 in 100 patients treated) side effects are pancreatitis.

Lactic acidosis
Combination antiretroviral therapy may cause a condition called lactic acidosis, which is a build-up of lactic acid in the body, that can cause dehydration, liver damage, and coma have been reported on rare occasions in patients taking NRTIs. Deep, rapid breathing, drowsiness, and non-

specific symptoms such as nausea, vomiting and stomach pain, may indicate the development of lactic acidosis. A majority of these cases have been in women. If you are very overweight (obese) you may be at higher risk for this rare but serious side effect. If you have liver disease or prolonged nucleoside exposure you may also be at greater risk of getting this condition. Treatment with lamivudine should be stopped if you develop symptoms or laboratory results suggestive of lactic acidosis or pronounced liver toxicity.

Fat redistribution
Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck ("buffalo hump"). The cause and long-term health effects of these conditions are not known at this time.

Immune Reconstitution Syndrome
In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started (see "Take special care with Lamivudine Tablets").

Important Differences among Lamivudine-Containing Products
Lamivudine Tablets contain a higher dose of the same active ingredient (lamivudine) than in Epivir-HBV Tablets and Oral Solution. If a decision is made to include Lamivudine Tablets 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, Combivir® (lamivudine/zidovudine) Tablets, Epzicom® (abacavir sulfate and lamivudine) Tablets, or Trizivir® (abacavir sulfate, lamivudine, and zidovudine) Tablets should be used as part of an appropriate combination regimen.

Patients with HIV-1 and Hepatitis B Virus Co-infection
Deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Discuss any changes in regimen with your health care provider.

Patients with HIV-1 and Hepatitis C Virus Co-infection
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.

Use with Other Lamivudine- and Emtricitabine-Containing Products
Lamivudine Tablets should not be coadministered with drugs containing lamivudine or emtricitabine, including Combivir (lamivudine/zidovudine) Tablets, Epzicom (abacavir sulfate and lamivudine) Tablets, Trizivir (abacavir sulfate, lamivudine, and zidovudine), Atripla® (efavirenz, emtricitabine, and tenofovir), Emtriva® (emtricitabine), Truvada® (emtricitabine and tenofovir), or Complera™ (rilpivirine/emtricitabine/tenofovir).

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started (see "Take special care with Lamivudine Tablets").

Combination antiretroviral therapy may also cause increased levels of lactic acid and sugar in the blood, hyperlipidemia (increased fats in the blood), hypertriglyceridemia (increased triglycerides in the blood), and an increased resistance to insulin.

Pediatric Patients
Very commonly reported (greater than 1 in every 10 patients treated) side effects are fever, hepatomegaly (enlarged liver), cough, and skin rashes.

The most commonly reported (greater than 1 in every 100 pediatric patients treated) side effects are nausea and vomiting, diarrhea, stomatitis (inflammation in the mouth), splenomegaly (enlarged spleen), abnormal breath sounds such as wheezing, ear pain, discharge, erythema (redness), or swelling of an ear, nasal discharge or congestion, and lymphadenopathy (disease/swelling of lymph nodes).

Pancreatitis risk in Pediatric Patients
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.

Paresthesias and Peripheral Neuropathies in Pediatric Patients
In pediatric patients, paresthesias and peripheral neuropathies have been reported in clinical trials.

Neonates
Limited short-term safety information is available in neonates receiving lamivudine with or without zidovudine for the first week of life. Selected adverse reactions reported in these neonates included increased liver function tests, anemia, diarrhea, electrolyte disturbances, hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, and sepsis. Long-term effects of *in utero* and infant lamivudine exposure are not known.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or health care provider or pharmacist as soon as possible.

5. HOW TO STORE LAMIVUDINE TABLETS

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F).

Keep out of the reach and sight of children.

Do not use Lamivudine Tablets after the expiration date which is stated on the bottle or carton. The expiration date refers to the last day of the month listed.

Do not use Lamivudine Tablets if you notice visible signs of deterioration (discoloration, thickening, caking, etc.).

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Lamivudine Tablets contain
The active ingredient is lamivudine. Each tablet contains 150 mg or 300 mg of lamivudine. In addition, each tablet contains the following inactive ingredients: hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

What Lamivudine Tablets 150 mg and 300 mg look like and contents of the packaging
Each Lamivudine Tablet, 150 mg, is a scored, white to off-white, film-coated, oval shaped tablet with 'C' on one side and '63' on the other side.

Each Lamivudine Tablet, 300 mg, is white to off-white, film-coated, oval shaped tablet with 'C' on one side and '64' on the other side.

Lamivudine Tablets are packaged in bottles of 60 (150 mg), bottles of 30 (300 mg), and in unit-dose packages: 6 x 10 unit-dose tablets (150 mg) and 3 x 10 unit-dose tablets (300 mg).

For further information about this medicinal product, please contact the supplier:
Aurobindo Pharma Limited
Unit III, Survey No. 313
Bachupally, Quthubullapur Mandal
Hyderabad, Andhra Pradesh 500 072, India

SUMMARY OF PRODUCT CHARACTERISTICS

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lamivudine Tablets 150 mg and 300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 150 mg tablet contains 150 mg of lamivudine.
Each 300 mg tablet contains 300 mg of lamivudine.

For a full list of excipients, see Part 6.1.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lamivudine is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

4.2 Posology and method of administration

Oral use.

Therapy should be prescribed by a physician experienced in the diagnosis and management of HIV-1 infection.

Adults
The recommended oral dose of lamivudine in adults and adolescents greater than 16 years of age is 300 mg daily, administered as either 150 mg twice daily or 300 mg once daily, in combination with other antiretroviral agents. If lamivudine is administered to patients infected with HIV-1 and HBV, the dosage indicated for HIV-1 therapy should be used as part of an appropriate combination regimen.

Pediatric Patients
The recommended oral dose of Epivir Oral Solution in HIV-1-infected pediatric patients 3 months to 16 years of age is 4 mg/kg twice daily (up to a maximum of 150 mg twice a day), administered in combination with other antiretroviral agents.

Lamivudine is also available as a scored tablet for HIV-1-infected pediatric patients who weigh greater than or equal to14 kg and for whom a solid dosage form is appropriate. Before prescribing Lamivudine Tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow Lamivudine Tablets, the oral solution formulation should be prescribed.

The recommended oral dose of Lamivudine Tablets for HIV-infected pediatric patients is presented below:

Dosage Recommendations for Lamivudine Tablets in Pediatric Patients			
Weight (kg)	Dosage Regimen Using Scored 150 mg Tablet		Total Daily Dose
	AM Dose	PM Dose	
14 to 21	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
> 21 to < 30	½ tablet (75 mg)	1 tablet (150 mg)	225 mg
≥ 30	1 tablet (150 mg)	1 tablet (150 mg)	300 mg

Lamivudine may be taken with or without food.

Renal Impairment
Dosing of Lamivudine Tablets is adjusted in accordance with renal function. Dosage adjustments are described below:

Adjustment of Dosage of Lamivudine Tablets in Adults and Adolescents (greater than or equal to 30 kg) in Accordance with Creatinine Clearance	
Creatinine clearance (mL/min)	Recommended Dosage of Lamivudine Tablets
Greater than or equal to 50	150 mg twice daily or 300 mg once daily
30 to 49	150 mg once daily
15 to 29	150 mg first dose, then 100 mg once daily
5 to 14	100 mg first dose, then 50 mg once daily
Less than 5	50 mg first dose, then 25 mg once daily

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.

4.3 Contraindications

Lamivudine Tablets are contraindicated in patients with clinically significant hypersensitivity to lamivudine or to any of the components in the formulation (see Part 6.1 for a list of excipients).

4.4 Special warnings and special precautions for use

Transmission of HIV
Antiretroviral therapy has not been proven to prevent the risk of transmission of HIV to others through sexual contact or contamination with blood.

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

Patients With HIV-1 and Hepatitis B Virus Co-Infection:
Post-treatment Exacerbations of Hepatitis
In clinical trials in non-HIV-infected patients treated with lamivudine for chronic hepatitis B, clinical and laboratory evidence show that 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 lamivudine-containing HIV treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of post-treatment exacerbations of hepatitis.

Patients with HIV-1 and Hepatitis B Virus Co-Infection:
Important Differences among Lamivudine-Containing Products
Lamivudine Tablets 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 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, Epivir Oral Solution, Combivir® (lamivudine/zidovudine) Tablets, Epzicom® (abacavir sulfate and lamivudine) Tablets, or Trizivir® (abacavir sulfate, lamivudine, and zidovudine) Tablets should be used as part of an appropriate combination regimen.

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

Use with Other Lamivudine- and Emtricitabine-Containing Products
Lamivudine should not be administered concomitantly with other lamivudine-containing products including Epivir-HBV Tablets, Epivir Oral Solution, Combivir (lamivudine/zidovudine) Tablets, Epzicom (abacavir sulfate and lamivudine) Tablets, or Trizivir (abacavir sulfate, lamivudine, and zidovudine) or emtricitabine-containing products, including Atripla® (efavirenz, emtricitabine, and tenofovir), Emtriva® (emtricitabine), Truvada® (emtricitabine and tenofovir), or Complera™ (rilpivirine/emtricitabine/tenofovir).

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 pharmacodynamics

interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of lamivudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh >6). See the complete prescribing information for interferon and ribavirin.

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 Tablets should be used with caution. Treatment with Lamivudine Tablets should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur.

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 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 Guillian-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.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Interferon- and Ribavirin-Based Regimens
Although no evidence of a pharmacokinetic or pharmacodynamics interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin.

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

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

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

4.6 Pregnancy and lactation

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

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical studies conducted in South Africa. The study assessed pharmacokinetics in: 16 women at 36 weeks gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation using lamivudine 300 mg twice daily without other antiretrovirals. These studies were not designed or powered to provide efficacy information. Lamivudine pharmacokinetics in the pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, lamivudine amniotic fluid specimens were collected following natural rupture of membranes. Amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg/mL (150 mg twice daily) and 2.1 to 5.2 mcg/mL (300 mg twice daily). It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared with other HIV-1-infected patients.

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

Placental and breast milk transmission
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 infection. Because of the potential for serious adverse reactions in nursing infants and HIV-1 transmission, mothers should be instructed not to breastfeed if they are receiving lamivudine.

Lamivudine is excreted in human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg

lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The following adverse events have been reported in controlled clinical trials and case series during treatment of HIV-1 infection with Lamivudine Tablets. With many of these it is unclear whether they are related to Lamivudine Tablets, other medications taken concurrently, or are a result of the underlying disease process.

The most common adverse reactions are headache, nausea, malaise, fatigue, nasal signs and symptoms, diarrhea and cough. See also sections 4.4 and 4.5.

The adverse events considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1000 to <1/100), rare (>1/10,000 to <1/1000), very rare (<1/10,000).

Metabolic and nutritional disorders
Very common: anorexia and/or decreased appetite
Common: increased serum amylase

Blood and lymphatic systems
Very common: Reduced absolute neutrophil count
Common: Reduced platelet count, reduced hemoglobin, increased serum amylase

Nervous system
Very common: Neuropathy, insomnia and other sleep disorders, dizziness
Common: Depressive disorders

Respiratory
Very common: Nasal signs and symptoms, cough

Gastrointestinal
Very common: Nausea, diarrhea, nausea and vomiting
Common: Abdominal pain, abdominal cramps, dyspepsia
Uncommon: Pancreatitis

Hepatobiliary
Common: Increased ALT, AST, and amylase
Uncommon: Increased bilirubin

Skin and subcutaneous tissue
Common: Skin rashes

Musculoskeletal and connective tissue
Very common: Musculoskeletal pain
Common: Myalgia, arthralgia

General
Very common: Headache, malaise and fatigue, fever or chills

Combination antiretroviral therapy has been associated with metabolic abnormalities such as elevated cholesterol and/or triglyceride levels, insulin resistance, hyperglycemia, and lactic acidosis.

The following adverse reactions have been identified during post-approval use of Lamivudine Tablets. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness, frequency of reporting, causal connection to Lamivudine Tablets, or a combination of these factors.

Metabolic and nutritional disorders: Redistribution/accumulation of body fat, hyperglycemia
Blood and lymphatic system disorders: anemia (including pure red blood cell aplasia and severe anemia progressing on therapy
Nervous system: none
Respiratory: none
Gastrointestinal: none
Hepatobiliary: lactic acidosis and hepatic steatosis, post-treatment exacerbation of hepatitis B
Skin and subcutaneous tissue: alopecia, pruritis
Musculoskeletal and connective tissue: muscle weakness, CPK elevation, rhabdomyolysis
Hypersensitivity: anaphylaxis, urticaria
General: weakness

4.9 Overdose

There is no known antidote for lamivudine. One case of an adult ingesting 6 grams of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Two cases of pediatric overdose were reported in Study ACTG300. One case was a single dose of 7 mg/kg of lamivudine; the second case involved use of 5 mg/kg of lamivudine twice daily for 30 days. There were no clinical signs or symptoms noted in either case. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleoside analogue reverse transcriptase inhibitor (NRTI)
ATC Code: J05AF05

Lamivudine Tablets (also known as 3TC) is a synthetic nucleoside analogue with activity against HIV-1 and HBV. Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principle mode of action of 3TC-TP is the

inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue into viral DNA. Because phosphorylation of lamivudine depends on cellular rather than viral enzymes, conversion of the drug to the active triphosphate derivative occurs in both virus-infected and uninfected cells.

Lamivudine triphosphate inhibits the activity of HIV-1 reverse transcriptase by two known mechanisms: (1) by competing with the natural substrate deoxythymidine triphosphate and (2) by its incorporation into viral DNA causing a termination of DNA chain elongation because lamivudine lacks the essential 3'-OH group.

Several clinical studies have been performed with Lamivudine Tablets administered in HIV-1-infected patients in combination regimens with other antiretroviral agents, including the following:

- NUCB3007 (CAESAR) was a multicenter, double-blind, placebo-controlled study comparing continued current therapy (zidovudine alone [62% of patients] or zidovudine with didanosine or zalcitabine [38% of patients]) to the addition of Lamivudine Tablets or Lamivudine Tablets 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/mm^3 (median = 122 cells/mm^3) at baseline were enrolled: median age was 36 years, 87% were male, 84% were nucleoside-experienced, and 16% were therapy-naïve. The median duration on study was 12 months.

  Endpoints were HIV progression event or death, or death alone. Current therapy (n= 460) resulted in HIV progression or death for 90 patients (19.6%), and death alone for 27 patients (5.9%). Lamivudine Tablets added to current therapy (n=896) resulted in HIV progression or death for 86 patients (9.6%), and death alone for 23 patients (2.6%). Lamivudine Tablets plus an NNRTI plus current therapy (n=460) resulted in HIV progression or death for 41 patients (8.9%), and death alone for 14 patients (3.0%).

- EPV20001 was a multicenter, double-blind, controlled study in which patients 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-naïve HIV-1-infected adults enrolled: male (79%), Caucasian (50%), median age of 35 years, baseline $CD4^+$ cell counts of 69 to 1,089 cells/mm^3 (median = 362 cells/mm^3), and median baseline plasma HIV-1 RNA of 4.66 $\log_{10}$ copies/mL.

  The proportions of patients with HIV-1 RNA <50 copies/mL (via Roche Ultrasensitive assay) through Week 48 were 61% for patients 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/mm^3 at Week 48 in patients receiving Lamivudine Tablets 300 mg once daily and 146 cells/mm^3 for patients receiving Lamivudine Tablets 150 mg twice daily.

- A small, randomized, open-label pilot study, EPV40001, was conducted in Thailand. A total of 159 treatment-naïve adult patients (male 32%, Asian 100%, median age 30 years, baseline median $CD4^+$ cell count 380 cells/mm^3, median plasma HIV-1 RNA 4.8 $\log_{10}$ copies/mL) were enrolled. Two of the treatment arms in this study 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/mL were 61% (33/54) in the group randomized to once-daily lamivudine and 75% (39/52) in the group randomized to receive all 3 drugs twice daily; the proportions with HIV-1 RNA below 50 copies/mL were 54% (29/54) in the once-daily lamivudine group and 67% (35/52) in the all-twice-daily group; and the median increases in $CD4^+$ cell counts were 166 cells/mm^3 in the once-daily lamivudine group and 216 cells/mm^3 in the all-twice-daily group.

Pediatric Patients: ACTG300 was a multi-center, randomized, double-blind study that provided for comparison of Lamivudine Tablets 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 patients 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-Caucasian. The mean baseline $CD4^+$ cell count was 868 cells/mm^3 (mean: 1,060 cells/mm^3 and range: 0 to 4,650 cells/mm^3 for patients less than or equal to 5 years of age; mean: 419 cells/mm^3 and range: 0 to 1,555 cells/mm^3 for patients greater than 5 years of age) and the mean baseline plasma HIV-1 RNA was 5 $\log_{10}$ copies/mL. The median duration on study was 10.1 months for the patients receiving Lamivudine Tablets plus Retrovir (zidovudine) and 9.2 months for patients receiving didanosine monotherapy. Results are summarized below.

Number of Pediatric Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)		
Endpoint	**Lamivudine Tablets 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%)	6 (2.6%)
Central nervous system deterioration	4 (1.7%)	12 (5.1%)
CDC Clinical Category C	2 (0.8%)	8 (3.4%)
Death	2 (0.8%)	11 (4.7%)

5.2 Pharmacokinetic properties

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

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

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 study in 60 healthy volunteers. Lamivudine 300 mg once daily resulted in lamivudine exposures that were similar to Lamivudine 150 mg twice daily with respect to plasma $AUC_{24,ss}$; however, $C_{max,ss}$ was 66% higher and the trough value was 53% lower compared with the 150 mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to $AUC_{24,ss}$ and $C_{max24,ss}$; however, trough values were lower compared with the 150 mg twice-daily regimen. Inter-subject variability was greater

for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations. The clinical significance of observed differences for both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations is not known.

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

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

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

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

Metabolism:
Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose of lamivudine in 6 HIV-1-infected adults, 5.2% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfide metabolite in the urine. Serum concentration of this metabolite has not been determined.

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

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

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. Exposure (AUC_{∞}), C_{max}, and half-life increased with diminishing renal function (as expressed by creatinine clearance). Apparent total clearance (Cl/F) of lamivudine decreased as creatinine clearance decreased. 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 Summary of Product Characteristics, Part 4.2 for renal dosing recommendations).

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

After oral administration of lamivudine 4 mg/kg twice daily to 11 pediatric patients ranging from 4 months to 14 years of age, C_{max} was 1.1 ± 0.6 mcg/mL and half-life was 2 ± 0.6 hours. (In adults with similar blood sampling, the half-life was 3.7 ± 1 hours.) Total exposure to lamivudine, as reflected by mean AUC values, was comparable between pediatric patients receiving an 8 mg/kg/day dose and adults receiving a 4-mg/kg/day dose.

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

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

Geriatric Patients: The pharmacokinetics of lamivudine after administration of Lamivudine Tablets to patients over 65 years of age have not been studied.

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

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

5.3 Preclinical safety data

Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV-1 infection. Lamivudine was not active in a microbial mutagenicity screen or an *in vitro* cell transformation assay, but showed weak *in vitro*

mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2,000 mg/kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection. In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F).

6.5 Nature and contents of container

Each Lamivudine Tablet, 150 mg, is a scored, white to off-white, film-coated, oval shaped tablet with ‘C’ on one side and ‘63’ on the other side.

Each Lamivudine Tablet, 300 mg, is white to off-white, film-coated, oval shaped tablet with ‘C’ on one side and ‘64’ on the other side.

Lamivudine Tablets are packaged in bottles of 60 (150 mg), bottles of 30 (300 mg), and in unit-dose packages: 6 x 10 unit-dose tablets (150 mg) and 3 x 10 unit-dose tablets (300 mg).

6.6 Instructions for use and handling and disposal

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. SUPPLIER

Aurobindo Pharma Limited
Unit III, Survey No. 313
Bachupally, Quthubullapur Mandal
Hyderabad, Andhra Pradesh 500 072, India

8. DATE OF USFDA TENTATIVE APPROVAL

June 15, 2005

LABELING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Lamivudine Tablets 150 mg, Lamivudine Tablets 300 mg

1. NAME OF THE MEDICINAL PRODUCT

Lamivudine Tablets

2. STATEMENT OF ACTIVE SUBSTANCE

Each 150 mg lamivudine scored tablet contains 150 mg of lamivudine.
Each 300 mg lamivudine tablet contains 300 mg of lamivudine.

3. LIST OF EXCIPIENTS

Hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Each Lamivudine Tablet, 150 mg, is a scored, white to off-white, film-coated, oval shaped tablet with ‘C’ on one side and ‘63’ on the other side.

Each Lamivudine Tablet, 300 mg, is white to off-white, film-coated, oval shaped tablet with ‘C’ on one side and ‘64’ on the other side.

Lamivudine Tablets are packaged in bottles of 60 (150 mg), bottles of 30 (300 mg), and in unit-dose packages: 6 x 10 unit-dose tablets (150 mg) and 3 x 10 unit-dose tablets (300 mg).

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

8. EXPIRATION (EXPIRY) DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store Lamivudine Tablets at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F).

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

11. NAME AND ADDRESS OF THE SUPPLIER

Aurobindo Pharma Limited
Unit III, Survey No. 313
Bachupally, Quthubullapur Mandal
Hyderabad, Andhra Pradesh 500 072, India

12. MANUFACTURER'S BATCH NUMBER

<Batch> <Lot> <number>

13. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

14. INSTRUCTIONS ON USE

SCIENTIFIC DISCUSSION

DISCUSSION

Name of the Finished Pharmaceutical Product:	Lamivudine Tablets 150 mg Lamivudine Tablets 300 mg
Supplier:	Aurobindo Pharma Limited
Active Pharmaceutical Ingredient(s) (API):	Lamivudine
International Non-proprietary Name:	Lamivudine
Pharmaco-therapeutic group (ATC Code):	J05AF05
Therapeutic indication:	Indicated for the treatment of human immunodeficiency virus (HIV-1) infection in combination with other antiretroviral agents.

1. Introduction

Lamivudine Tablets 150 mg and 300 mg are indicated for the treatment of human immunodeficiency virus (HIV-1) infection in combination with other antiretroviral agents. Lamivudine Tablets are not indicated for use in patients with clinically significant hypersensitivity to lamivudine or any of the components contained in the formulation.

It is recommended that therapy be initiated only on the advice of a physician or healthcare professional experienced in the diagnosis and management of HIV-1 infection and related disease.

2. Assessment of Quality

Introduction
The assessment was conducted by the USFDA as an abbreviated new drug application (ANDA) reviewed under the President's Emergency Plan for AIDS Relief (PEPFAR).

Composition
Lamivudine Tablets 150 mg are tablets containing 150 mg lamivudine as the active pharmaceutical ingredient (API).

Lamivudine Tablets 300 mg are tablets containing 300 mg lamivudine as the active pharmaceutical ingredient (API).

Lamivudine Tablets 150 mg and 300 mg are generic versions of Epivir Tablets 150 mg and 300 mg.

Control of active pharmaceutical ingredient (API)
Lamivudine Tablets are controlled as per specifications in the application and cGMPs, and are consistent with general USP requirements and product- and process-specific needs and information.

Control testing of the finished medicinal product
The release and shelf-life specifications are in line with requirements of major internationally used pharmacopoeias and guidelines for tablets. The test methods have been adequately validated. Critical process variables were optimized during the pharmaceutical R&D stage. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Stability
Stability studies have been conducted and results show that the product conforms to the proposed end of shelf life specification of 36 months including description, disintegration time, dissolution, assay, and degradation products. Stability data for this product in the proposed marketing containers conforms to specifications. Based on the stability data provided, the proposed expiration dating is acceptable.

3. Assessment of Bioequivalence

The manufacturer presented fasting bioequivalence (BE) studies comparing the test product, Lamivudine Tablets 150 mg and 300 mg, to the reference listed drug (RLD), EPIVIR® Tablets 150 mg and 300 mg manufactured by ViiV Healthcare, and comparative dissolution data on both products. Statistical analyses of plasma concentration data for Lamivudine Tablets demonstrate bioequivalence. The USFDA Office of Generic Drugs Division of Bioequivalence found the data and application acceptable with no deficiencies.

4. Summary of Product Safety and Efficacy

Introduction

Background
Lamivudine Tablets 150 mg and 300 mg have been shown to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator's product. According to the submitted data on quality and bioavailability it is pharmacologically and therapeutically equivalent and thus interchangeable with the innovator product Epivir Tablets 150 mg and 300 mg, for which benefits have been proven in terms of clinical efficacy.

Product Design
The development strategy for Lamivudine Tablets 150 mg and 300 mg focused on the compatibility of the active ingredient with the excipients identified to match the dissolution profile of the innovator, thus producing a robust formulation.

Approved Indication
Lamivudine Tablets 150 mg and 300 mg are indicated for the treatment of human immunodeficiency virus (HIV-1) infection in combination with other antiretroviral agents.

Clinical Pharmacology

Pharmacodynamics

Lamivudine Tablets (also known as 3TC) is a synthetic nucleoside analogue with activity against HIV-1 and HBV. Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principle mode of action of 3TC-TP is the inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue into viral DNA. Because phosphorylation of lamivudine depends on cellular rather than viral enzymes, conversion of the drug to the active triphosphate derivative occurs in both virus-infected and uninfected cells.

Lamivudine triphosphate inhibits the activity of HIV-1 reverse transcriptase by two known mechanisms: (1) by competing with the natural substrate deoxythymidine triphosphate and (2) by its incorporation into viral DNA causing a termination of DNA chain elongation because lamivudine lacks the essential 3'-OH group.

See the Summary of Product Characteristics Part 5.1 "Pharmacodynamic properties" for further and related discussion of Lamivudine Tablets pharmacodynamics.

Pharmacokinetics

Absorption and Bioavailability:
Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute bioavailability in 12 adult patients was 86% ± 16% (mean ± SD) for the 150 mg tablet and 87% ± 13% for the oral solution. Absorption of lamivudine was slower in the fed state (T_{max}: 3.2 ± 1.3 hours) compared with the fasted state (T_{max}: 0.9 ± 0.3 hours). C_{max} in the fed state was 40% ± 23% (mean ± SD) lower than in the fasted states; therefore, Lamivudine Tablets may be administered with or without food.

Distribution:
The apparent volume of distribution after IV administration of lamivudine to 20 patients was 1.3 ± 0.4 L/kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight. Binding of lamivudine to human plasma proteins is low (<36%) and independent of concentration.

Metabolism /Elimination:
Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In most single-dose studies in HIV-infected patients, HBV-infected patients, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to 7 hours. Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range from 0.25 to 10 mg/kg.

Refer to the Summary of Product Characteristics, Part 5.2 “Pharmacokinetic Properties” for a more extensive discussion of absorption, bioavailability, distribution, metabolism, and elimination data for Lamivudine Tablets.

Drug Interactions, related side effects, and contraindications

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

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

Because of overlapping resistance and lack of additive antiretroviral effects, lamivudine should not be co-administered with emtricitabine or other lamivudine contain products.

Patients receiving interferon alfa with or without ribavirin and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of lamivudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh >6). See the complete prescribing information for interferon and ribavirin.

See the Summary of Product Characteristics, Part 4.5 "Interaction with other medicinal products and other forms of interaction" for a more extensive discussion of drug interactions and other forms of interaction.

Contraindications
Lamivudine Tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the products (see the Summary of Product Characteristics, Part 6.1 "List of excipients").

Clinical Efficacy

Lamivudine Tablets 150 mg and 300 mg have been shown to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator's product. According to the submitted data on quality and bioavailability it is pharmacologically and therapeutically equivalent and thus interchangeable with the innovator product EPIVIR® Tablets 150 mg and 300 mg, for which benefits have been proven in terms of clinical efficacy.

Clinical efficacy of Lamivudine Tablets is discussed at length in the Summary of Product Characteristics, Part 5.1 "Pharmacodynamic Properties".

Clinical studies in special populations

Renal Impairment (Adults and Adolescents)
Dosing of Lamivudine Tablets is adjusted in accordance with renal function. Dosage adjustments are described below:

Adjustment of Dosage of Lamivudine Tablets in Adults and Adolescents (greater than or equal to 30 kg) in Accordance with Creatinine Clearance	
Creatinine clearance (mL/min)	Recommended Dosage of Lamivudine Tablets
Greater than or equal to 50	150 mg twice daily or 300 mg once daily
30 to 49	150 mg once daily
15 to 29	150 mg first dose, then 100 mg once daily
5 to 14	100 mg first dose, then 50 mg once daily
Less than 5	50 mg first dose, then 25 mg once daily

Renal Impairment (Children)
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.

Impaired Hepatic Function (Adults)
No dose adjustment for lamivudine is required for patients with impaired hepatic function. 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.

Clinical Safety

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

See the Summary of Product Characteristics, Part 4.4 "Special warnings and special precautions for use" for complete boxed warning

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur.**
- **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.**
- **Patients with HIV-1 infection should receive only dosage forms of Lamivudine Tablets appropriate for treatment of HIV-1.**

The following adverse events have been reported in controlled clinical trials and case series during treatment of HIV-1 infection with Lamivudine Tablets.

The adverse events considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1000 to <1/100), rare (>1/10,000 to <1/1000), very rare (<1/10,000).

Metabolic and nutritional disorders
Very common: anorexia and/or decreased appetite
Common: increased serum amylase

Blood and lymphatic systems
Very common: Reduced absolute neutrophil count
Common: Reduced platelet count, reduced hemoglobin

Nervous system
Very common: Neuropathy, insomnia and other sleep disorders, dizziness
Common: Depressive disorders

Respiratory
Very common: Nasal signs and symptoms, cough

Gastrointestinal
Very common: Nausea, diarrhea, nausea and vomiting
Common: Abdominal pain, abdominal cramps, dyspepsia
Uncommon: Pancreatitis

Hepatobiliary
Common: Transient elevated ALT, AST, and amylase

Skin and subcutaneous tissue
Common: Skin rashes

Musculoskeletal and connective tissue
Very common: Musculoskeletal pain
Common: Myalgia, arthralgia

General
Very common: Headache, malaise and fatigue, fever or chills

The clinical safety of this product is considered to be acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration.

See Summary of Product Characteristics, Part 4 "Clinical Particulars" for discussion of clinical safety including contraindications, special precautions, pregnancy, overdose, interactions, and adverse events associated with use of Lamivudine Tablets.

Overdose

Limited data are available on the consequences of ingestion of acute overdoses in humans. No fatalities occurred and the patients recovered. A negligible amount of Lamivudine Tablets can be removed via hemodialysis.

There is no known antidote for lamivudine. One case of an adult ingesting 6 grams of Lamivudine Tablets was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Two cases of pediatric overdose were reported in Study ACTG300. One case was a single dose of 7 mg/kg of Lamivudine Tablets; the second case involved use of 5 mg/kg of Lamivudine Tablets twice daily for 30 days. There were no clinical signs or symptoms noted in either case. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

5. Overall Conclusion and benefit risk assessment

Quality
The quality of Lamivudine Tablets 150 mg and 300 mg is considered to be acceptable when used in accordance with the conditions defined in the Summary of Product Characteristics of this Public Assessment Report. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence
Lamivudine Tablets 150 mg and 300 mg have been shown to be bioequivalent to the comparator product, EPIVIR® Tablets 150 mg and 300 mg.

Efficacy and Safety
Regarding clinical efficacy and safety, Lamivudine Tablets are considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics of this Public Assessment Report are taken into consideration.

Benefit Risk Assessment

Based on USFDA assessment of data on quality, bioequivalence, safety, and efficacy, the benefit risk profile of Lamivudine Tablets 150 mg and 300 mg was considered acceptable for the following indication: treatment of HIV-1 infection in combination with other antiretroviral agents.

Products added to the WHO prequalification list on the basis of USFDA tentative approval rely on scientific assessment and inspections conducted by the USFDA. A product listed as USFDA **tentatively approved** indicates that although existing patents and/or other marketing exclusivity prevent marketing of this product in the USA, the product meets all of USFDA's safety, efficacy, and manufacturing quality standards required for marketing in the USA, and is eligible for purchase with PEPFAR funds.

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