1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Lamivudine and Zidovudine tablets for oral suspension 30 mg/60 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains 30 mg of lamivudine, 60 mg of zidovudine

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets for Oral Suspension

Lamivudine and Zidovudine Tablets for Oral Suspension are scored, white, circular, biconvex uncoated tablets with a deep score on one side and debossed "DR" on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lamivudine and Zidovudine Tablets for Oral Suspension, a combination of two nucleoside analogues, are indicated in combination with other antiretrovirals for the treatment of HIV-1 infection.

4.2 Posology and method of administration

Paediatric Patients

The recommended oral dosage of scored Lamivudine and Zidovudine twice daily in HIV-1-infected pediatric patients at least 3 months of age and weighing greater than or equal to 5 kg is shown in Table 1. Lamivudine and Zidovudine Tablets for Oral Suspension must be administered on an empty stomach, without food.

Table 1: Recommended Pediatric Dosage of Lamivudine and Zidovudine Tablets

Body Weight Range (kg)	Dosage Regimen Using Scored Lamivudine and Zidovudine Tablets, 30 mg/60 mg		Total Daily Dose (mg)
	AM Dose (mg)	PM Dose (mg)	
5 to less than 6	1 tablet (30 mg L/60 mg Z)	1 tablet (30 mg L/60 mg Z)	60L/120Z
6 to less than 11	1.5 tablet (45 mg L/90 mg Z)	1.5 tablet (45 mg L/90 mg Z)	90L/180Z
11 to less than 14	2 tablets (60 mg L/120 mg Z)	2 tablets (60 mg L/120 mg Z)	120L/240Z

14 to less than 18	2.5 tablets (75 mg L/150 mg Z)	2.5 tablets (75 mg L/150 mg Z)	150L/300Z
18 to less than 22	3 tablets (90 mg L/180 mg Z)	3 tablets (90 mg L/180 mg Z)	180L/360Z
22 to less than 25	3.5 tablets (105 mg L/210 mg Z)	3.5 tablets (105 mg L/210 mg Z)	210L/420Z
25 to less than 28	4 tablets (120 mg L/240 mg Z)	4 tablets (120 mg L/240 mg Z)	240L/480Z
28 to less than 30	4.5 tablets (135 mg L/270 mg Z)	4.5 tablets (135 mg L/270 mg Z)	270L/540Z
30 and greater	5 tablets (150 mg L/300 mg Z)[a]	5 tablets (150 mg L/300 mg Z)[a]	300L/600Z

L = lamivudine; Z = zidovudine

a = For recommended doses of lamivudine 150 mg twice daily and zidovudine 300 mg twice daily (adult maximum daily dose), the adult formulations (lamivudine 150 mg tablet and zidovudine 300 tablet) can be used.

Safety and efficacy have not been established in patients who are less than 3 months of age.

4.3 Method of administration

For children unable to swallow tablets, the following procedure can be used

1. Place the tablet(s) in a container and add two teaspoonfuls (10 mL) of drinking water per tablet.

2. Swirl the container until the tablet(s) breaks up into pieces small enough for the child to swallow. A spoon can be used to crush the pieces, if needed.

3. Drink the mixture within 1 hour.

4. Rinse the container with an additional small amount of water and drink the contents to assure that the entire dosage is taken.

DO NOT MIX THE LAMIVUDINE AND ZIDOVUDINE TABLETS FOR ORAL SUSPENSION WITH ANY LIQUID OTHER THAN WATER. SPLIT TABLETS WHEN NEEDED. STORE UNUSED HALF TABLETS IN A SEPARATE BAG OR BOTTLE AND USE AS SOON AS PRACTICAL.

4.4 Contraindications

Lamivudine and Zidovudine Tablets for Oral Suspension are contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., anaphylaxis, Stevens-Johnson syndrome) to any of the components of the product.

4.5 Special warnings and precautions for use

WARNING: HEMATOLOGIC TOXICITY, MYOPATHY, LACTIC ACIDOSIS, EXACERBATIONS OF HEPATITIS B

Hematologic Toxicity: Zidovudine, one of the 2 active ingredients in Lamivudine and Zidovudine Tablets for Oral Suspension, has been associated with hematologic toxicity including neutropenia and anemia, particularly in patients with advanced HIV-1 disease *[see Section 4.5]*.

Myopathy: Prolonged use of zidovudine has been associated with symptomatic myopathy *[see Section 4.5]*.

Lactic Acidosis and Severe Hepatomegaly: Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine, zidovudine, and other antiretrovirals. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur *[see Section 4.5]*.

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 HIV-1 and have discontinued lamivudine, which is one component of Lamivudine and Zidovudine Tablets for Oral Suspension. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue Lamivudine and Zidovudine Tablets for Oral Suspension and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Section 4.5]*.

Hemotologic Toxicity/Bone Marrow Suppression
Zidovudine, a component of Lamivudine and Zidovudine Tablets for Oral Suspension, has been associated with hematologic toxicity including neutropenia and anemia, particularly in patients with advanced HIV-1 disease. Lamivudine and Zidovudine tablets for oral suspension should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count less than 1,000 cells/mm3 or hemoglobin less than 9.5 g/dL *[see Section 4.12)]*.
Frequent blood counts are strongly recommended in patients with advanced HIV-1 disease who are treated with lamivudine and zidovudine tablets for oral suspension. Periodic blood counts are recommended for other HIV -I-infected patients. If anemia or neutropenia develops, dosage interruption may be needed.

Myopathy
Myopathy and myositis, with pathological changes similar to that produced by HIV-1 disease, have been associated with prolonged use of zidovudine, and therefore may occur with therapy with Lamivudine and Zidovudine Tablets for Oral Suspension.

Lactic Acidosis/Hepatomegaly with Steatosis
Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine, zidovudine 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 and zidovudine to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with lamivudine and zidovudine 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

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

Important Differences Among Lamivudine-Containing Products Lamivudine and Zidovudine Tablets for Oral Suspension contain a different dose of the same active ingredient (lamivudine) than EPIVIR-HBV® (lamivudine) Tablets and Oral Solution. EPIVIR-HBV was developed for treating chronic hepatitis B. Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV.

Emergence of Lamivudine-Resistant HBV In non-HIV-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. 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-, Zidovudine- and/or Emtricitabine-Containing Products Lamivudine and Zidovudine Tablets for oral Suspension are a fixed-dose combination of lamivudine and zidovudine. Lamivudine and zidovudine Tablets for oral Suspension should not be administered concomitantly with other lamivudine- or zidovudine-containing products including EPIVIR® (lamivudine), EPIVIR-HBV (lamivudine), RETROVIR® (zidovudine), COMBIVIR (lamivudine and zidovudine), EPZICOM® (abacavir sulfate and lamivudine), 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 and 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 and zidovudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when

ribavirin was co administered with lamivudine or zidovudine in HIV-l/HCV co-infected patients *[see Section 5.1)]*, hepatic decompensation (some fatal) has occurred in HIVl/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 and zidovudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia. Discontinuation of Lamivudine and Zidovudine 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 complete prescribing information for interferon & ribavirin).
Exacerbation of anemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine. Co-administration of ribavirin and zidovudine is not advised.

Pancreatitis
Lamivudine and zidovudine tablets for oral suspension should be used with caution in patients with a history of pancreatitis or other significant risk factors for the development of pancreatitis. Treatment with lamivudine and zidovudine tablets for oral suspension should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur *[see Section 4.12)]*.

Immune Reconstitution Syndrome
Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including lamivudine and zidovudine. During the initial phase of combination antiretroviral treatment, patients whose immune systems 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.

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 antiretrovira1 therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Phenylketonurics
Lamivudine and zidovudine tablets for oral suspension contain phenylalanine, a component of aspartame. Each tablet for oral suspension (30 mg of lamivudine and 60 mg of zidovudine) contains 1.7 mg phenylalanine. Phenylalanine can be harmful to patients with phenylketonuria.

4.6 Paediatric population

Lamivudine and Zidovudine Tablets for Oral Suspension should not be administered to pediatric patients who are less than 3 months of age because the safety and efficacy have not been established in this population.

4.7 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been conducted using Lamivudine and Zidovudine Tablets for Oral Suspension.

Antiretroviral Agents

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

Zidovudine
Stavudine Concomitant use of lamivudine and zidovudine with stavudine should be avoided since an antagonistic relationship with zidovudine has been demonstrated in vitro.

Nucleoside Analogues Affecting DNA Replication
Some nucleoside analogues affecting DNA replication, such as ribavirin, antagonize the in vitro antiviral activity of zidovudine against HIV-1; concomitant use of such drugs should be avoided.

Doxorubicin
Zidovudine Concomitant use of Lamivudine and Zidovudine with doxorubicin should be avoided since an antagonistic relationship with zidovudine has been demonstrated in vitro.

Hematologic/Bone Marrow Suppressive/Cytotoxic Agents
Zidovudine Coadministration of ganciclovir, interferon alfa, ribavirin, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

Interferon- and Ribavirin-Based Regimens
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, 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 *Sections 4.5*, *5.1*].

Trimethoprim/Sulfamethoxazole (TMP/SMX)
Lamivudine 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.

4.8 Additional information on special populations

Geriatric Use

Clinical studies of lamivudine and zidovudine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Lamivudine and zidovudine tablets for oral suspension are not recommended for patients with impaired renal function (i.e., creatinine clearance less than 50 mL/min) because it is a fixed-dose combination that cannot be adjusted.

Renal Impairment

Reduction of the dosages of lamivudine and zidovudine is recommended for patients with impaired renal function. Patients with creatinine clearance less than 50 mL/min should not receive lamivudine and zidovudine tablets for oral suspension because it is a fixed-dose combination that cannot be adjusted.

Hepatic Impairment

A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. Lamivudine and zidovudine tablets for oral suspension are not recommended for patients with impaired hepatic function because it is a fixed-dose combination that cannot be adjusted.

4.9 Paediatric population

Not known

4.10 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category C:

Fetal Risk Summary:
There are no adequate and well-controlled studies of lamivudine and zidovudine in pregnant women. Clinical trial data demonstrate that maternal zidovudine treatment during pregnancy reduces vertical transmission of HIV-1 infection to the fetus. Animal reproduction studies performed with lamivudine and zidovudine showed increased embryotoxicity and fetal malformations (zidovudine), and increased embryolethality (lamivudine). Lamivudine and zidovudine tablets for oral suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations:
Treatment of HIV during pregnancy optimizes the health of both mother and fetus. Clinical trial data reviewed by FDA demonstrate that maternal zidovudine treatment significantly reduces vertical transmission of HIV-1 infection to the fetus *[see Section 5.1]*. Published data suggest that combination antiretroviral regimens may reduce the rate of vertical transmission even further.

Pharmacokinetics of lamivudine and zidovudine in pregnant women are similar to the pharmacokinetics in nonpregnant women. No dose adjustments are needed during pregnancy. In a clinical trial, adverse reactions among HIV-1-infected women were not different among untreated women and women treated with zidovudine. It is not known whether risks of adverse reactions associated with lamivudine are altered in pregnant women compared with other HIV-1 infected patients (see Human data below).

Data:

Human Data:
Lamivudine: 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 1amivudine 300 mg twice daily without other antiretrovirals.

Lamivudine pharmacokinetics in pregnant women were similar to those seen in nonpregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples.

Zidovudine: A randomized, double-blind, placebo-controlled trial was conducted in HIV-1-infected pregnant women to determine the utility of zidovudine for the prevention of maternal fetal HIV-1 transmission. Zidovudine treatment during pregnancy reduced the rate of materal fetal HIV-1 transmission from 24.9% for infants born to placebo-treated mothers to 7.8% for infants born to mothers treated with zidovudine. There were no differences in pregnancy-related adverse reactions between the treatment groups. Congenital abnormalities occurred with similar frequency between neonates born to mothers who received zidovudine and neonates born to mothers who received placebo. The observed abnormalities included problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of study drug *[see Section 5.1]*.

Zidovudine pharmacokinetics were studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation.
The pharmacokinetics of zidovudine were similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery.

Animal Data:
Lamivudine: 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, 1amivudine crosses the placenta and is transferred to the fetus *[see Section 5.3]*.

Zidovudine: Increased fetal resorptions occurred in pregnant rats and rabbits treated with doses of zidovudine that produced drug plasma concentrations 66 to 226 times (rats) and 12 to 87 times (rabbits) the mean steady-state peak human plasma concentration following a single 100-mg dose of zidovudine. There were no other reported developmental anomalies. In another developmental toxicity study, pregnant rats received zidovudine up to near-lethal doses that produced peak plasma concentrations 350 times peak human plasma concentrations (300 times the daily AUC in humans given 600 mg/day zidovudine). This dose was associated with marked maternal toxicity and an increased incidence of fetal malformations. However, there were no signs of teratogenicity at doses up to one-fifth the lethal dose *[see Section 5.3]*.

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Because of both the potential for HIV-1 transmission and serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving lamivudine and zidovudine tablets for oral suspension.

Although no studies of lamivudine and zidovudine tablets for oral suspension excretion in breast milk have been performed, lactation studies performed with lamivudine and zidovudine show that both drugs are excreted in human breast milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg 1amivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine. In another study, after administration of a single dose of 200 mg zidovudine to 13 HIV-1-infected women, the mean concentration of zidovudine was similar in human milk and serum.

4.11 Effects on ability to drive and use machines

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

4.12 Undesirable effects

The following adverse reactions are discussed in greater detail in other sections of the labeling:
• Hematologic toxicity, including neutropenia and anemia [see Boxed Warning, Section 4.5].
• Symptomatic myopathy [see Boxed Warning, Section 4.5].
• Lactic acidosis and hepatomegaly with steatosis [see Boxed Warning, Section 4.5].
• Acute exacerbations of hepatitis B [see Boxed Warning, Section 4.5].
• Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C [see Section 4.5].
• Exacerbation of anemia in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine [see Section 4.5].
• Pancreatitis [see Section 4.5].

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

Adults: Lamivudine Plus Zidovudine Administered As Separate Formulations: In 4 randomized, controlled trials of lamivudine 300 mg per day plus zidovudine 600 mg per day, the following selected adverse reactions and laboratory abnormalities were observed (see Tables 2 and 3).

Table 2. Selected Clinical Adverse Reactions (≥5% Frequency) in 4 Controlled Clinical Trials With Lamivudine 300 mg/day and Zidovudine 600 mg/day

Adverse Reaction	Lamivudine plus Zidovudine (n = 251)
Body as a whole	
Headache	35%
Malaise & fatigue	27%
Fever or chills	10%
Digestive	
Nausea	33%
Diarrhea	18%
Nausea & vomiting	13%
Anorexia and/or decreased appetite	10%
Abdominal pain	9%
Abdominal cramps	6%
Dyspepsia	5%
Nervous system	
Neuropathy	12%
Insomnia & other sleep disorders	11%
Dizziness	10%
Depressive disorders	9%
Respiratory	
Nasal signs & symptoms	20%
Cough	18%
Skin	
Skin rashes	9%
Musculoskeletal	
Musculoskeletal pain	12%
Myalgia	8%
Arthralgia	5%

Pancreatitis:

Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who received lamivudine in controlled clinical trials (see Section 4.5).

Selected laboratory abnormalities observed during therapy are listed in Table below.

Table 3. Frequencies of Selected Laboratory Abnormalities Among Adults in 4 Controlled Clinical Trials of Lamivudine 300 mg/day plus Zidovudine 600 mg/day[a]

Test (Abnormal Level)	Lamivudine plus Zidovudine % (n)
Neutropenia (ANC<750/mm^3)	7.2% (237)
Anemia (Hgb<8.0 g/dL)	2.9% (241)
Thrombocytopenia (platelets<50,000/mm^3)	0.4% (240)
ALT (>5.0 x ULN)	3.7% (241)
AST (>5.0 x ULN)	1.7% (241)
Bilirubin (>2.5 x ULN)	0.8% (241)
Amylase (>2.0 x ULN)	4.2% (72)

ULN = Upper limit of normal.
ANC = Absolute neutrophil count.
n = Number of patients assessed.
a = Frequencies of these laboratory abnormalities were higher in patients with mild laboratory abnormalities at baseline.

Pediatric Patients

Lamivudine:

Selected clinical adverse reactions and physical findings with a ≥5% frequency during therapy with lamivudine 4 mg/kg twice daily plus zidovudine 160 mg/m2 three times daily compared with didanosine in therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table below.

Table 4: Selected Clinical Adverse Reactions and Physical Findings (≥5% Frequency) in Pediatric Patients in Study ACTG300

Adverse Reactions	**Lamivudine plus Zidovudine (n = 236)**	**Didanosine (n = 235)**
Body as a Whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea and	8%	7%
vomiting Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
Respiratory		
Cough	15%	18%
Abnormal 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%

a = Includes 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 patients receiving lamivudine alone or in combination with other antiretroviral agents. In an open-label, dose-escalation study (NUCA2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with lamivudine. Three of these patients died of complications of pancreatitis. In a second open-label study (NUCA2005), 12 patients (18%) developed pancreatitis. In Study ACTG300, pancreatitis was not observed in 236 patients randomized to lamivudine plus zidovudine. Pancreatitis was observed in 1 patient in this study who received open-label lamivudine in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy (see Section 4.5).

Paresthesias and Peripheral Neuropathies:

Paresthesias and peripheral neuropathies were reported in 15 patients (15%) in Study NUCA2002, 6 patients (9%) in Study NUCA2005, and 2 patients (<1%) in Study ACTG300.

Selected laboratory abnormalities experienced by therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 5.

Table 5: Frequencies of Selected Grade 3-4 Laboratory Abnormalities in Pediatric Patients in Study ACTG300

Test (Threshold Level)	Lamivudine plus Zidovudine	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

Neonates:

Limited short-term safety information is available from 2 small, uncontrolled studies 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 Section 5.1]. 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; 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-infected patients treated with lamivudine-containing combination regimens. Long-term effects of in utero and infant lamivudine exposure are not known.

Zidovudine:
The clinical adverse reactions reported among adult recipients of zidovudine may also occur in pediatric patients.

Study ACTG 300: Selected clinical adverse reactions and physical findings with a ≥ 5% frequency during therapy with lamivudine oral suspension 4 mg/kg twice daily plus zidovudine 160 mg/m2 three times daily compared with didanosine in therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 6.

Table 6: Selected Clinical Adverse Reactions and Physical Findings (≥5% Frequency) in Pediatric Patients in Study ACTG 300

Adverse Reaction	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
Body as a Whole Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea and vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
Respiratory		
Cough	15%	18%

Abnormal breath sounds/wheezing	7%	9%
Ear, Nose, and Throat		
Signs or symptoms of earsa	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

a = Includes pain, discharge, erythema, or swelling of an ear.

Selected laboratory abnormalities experienced by therapy-naïve (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 7.

Table 7: Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Pediatric Patients in Study ACTG 300

Test (Abnormal Level)	Lamivudine plus Zidovudine	Didanosine
Neutropenia (ANC <400 cells/mm^3)	8%	3%
Anemia (Hgb <7.0 g/dL)	4%	2%
Thrombocytopenia (platelets <50,000/mm3)	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
ANC = Absolute neutrophil count

Macrocytosis was reported in the majority of pediatric patients receiving zidovudine 180 mg/m2 every 6 hours in open-label studies. Additionally, adverse reactions reported at an incidence of <6% in these studies were congestive heart failure, decreased reflexes, ECG abnormality, edema, hematuria, left ventricular dilation, nervousness/irritability, and weight loss.

Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during post-approval use of lamivudine, zidovudine, and the combination of Lamivudine and Zidovudine. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine and zidovudine and/or Lamivudine and Zidovudine.

Body as a Whole: Redistribution/accumulation of body fat [see Section 4.5].

Cardiovascular: Cardiomyopathy.

Endocrine and Metabolic: Gynecomastia, hyperglycemia

Gastrointestinal: Oral mucosal pigmentation, stomatitis.

General: Vasculitis, weakness.

Hemic and Lymphatic: Anemia, (including pure red cell aplasia and anemias progressing on therapy), lymphadenopathy, splenomegaly.

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment exacerbation of hepatitis B [see Boxed Warning, Section 4.5].

Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy, seizures.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome.

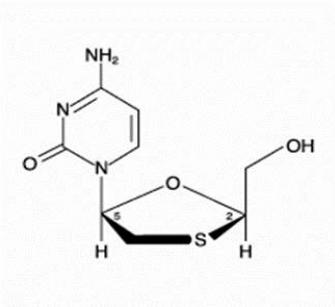
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Description:

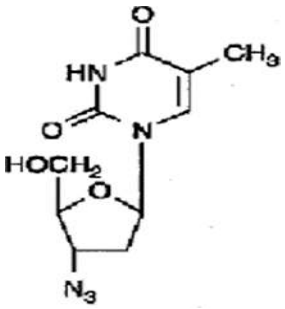
Lamivudine and Zidovudine Tablets for Oral Suspension are combination tablets containing lamivudine and zidovudine. Lamivudine and zidovudine (azidothymidine, AZT, or ZDV) are synthetic nucleoside analogues with activity against HIV-1.

Lamivudine:
The chemical name of lamivudine is (2R,cis)-4-amino-1-(2 hydroxymethyl-1,3- oxathiolan-5-yl)-(1H)-pyrmidin-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 C8H11N303S and a molecular weight of 229.3. It has the following structural formula:



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

Zidovudine:
The chemical name of zidovudine is 3'-azido-3'-deoxythymidine. It has a molecular formula of C10H13N5O4 and a molecular weight of 267.24.It has the following structural formula:



Zidovudine is a white to beige, odorless, crystalline solid with a solubility of 20.1 mg/mL in water at 25°C.

Mechanism of Action:

Lamivudine: Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC- TP). The principal mode of action of 3TC-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue. 3TC-TP is a weak inhibitor of cellular DNA polymerases α, β and γ.
Zidovudine: Intracellularly, zidovudine is phosphorylated to its active 5'-triphosphate metabolite, zidovudine triphosphate (ZDV - TP). The principal mode of action of ZDV - TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. ZDV-TP is a weak inhibitor of the cellular DNA polymerases α and γ and has been reported to be incorporated into the DNA of cells in culture.

Antiviral Activity:
Lamivudine Plus Zidovudine: In HIV-1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity.

Lamivudine: The antiviral activity of lamivudine against HIV -1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC50 values (50% effective concentrations) were in the range of 0.003 to 15 μM (1 μM = 0.23 mcg/mL). HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance gave median EC50 values of 0.429 μM (range: 0.200 to 2.007 μM) from Virco (n = 92 baseline samples from COLA40263) and 2.35 μM (1.37 to 3.68 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC50 values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM, and against

HIV-2 isolates from 0.003 to 0.120 μM in peripheral blood mononuclear cells. Ribavirin (50 μM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells.

Zidovudine: The antiviral activity of zidovudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The EC50 and EC90 values for zidovudine were 0.01 to 0.49 μM (1μM = 0.27 mcg/mL) and 0.1 to 9 μM, respectively. HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance gave median EC50 values of 0.11μM (range: 0.005 to 0.110μM) from Virco (n = 92 baseline samples from COLA40263) and 0.0017 μM (0.006 to 0.0340 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC50 values of zidovudine against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02 μM, and against HIV-2 isolates from 0.00049 to 0.004 μM. In cell culture drug combination studies, zidovudine demonstrates synergistic activity with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir, didanosine, 1amivudine, and zalcitabine; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine and nevirapine; and the protease inhibitors (PIs) indinavir, nelfinavir, ritonavir, and saquinavir; and additive activity with interferon alfa. Ribavirin has been found to inhibit the phosphorylation of zidovudine in cell culture.

Resistance:
Lamivudine Plus Zidovudine Administered As Separate Formulations: In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of amino acid substitutions conferring resistance to zidovudine.
HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients after prolonged Lamivudine and Zidovudine therapy. Dual resistance required the presence of multiple amino acid substitutions the most essential of which may be G333E. The incidence of dual resistance and the duration of combination therapy required before dual resistance occurs are unknown.

Lamivudine: Lamivudine-resistant isolates of HIV-1 have been selected in cell culture and have also been recovered from patients treated with lamivudine or lamivudine plus zidovudine. Genotypic analysis of isolates selected in cell culture and recovered from lamivudine-treated patients showed that the resistance was due to a specific amino acid substitution in the HIV -1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine (M184V/I).

Zidovudine: HIV-1 isolates with reduced susceptibilty to zidovudine have been selected in cell culture and were also recovered from patients treated with zidovudine. Genotypic analyses of the isolates selected in cell culture and recovered from zidovudine-treated patients showed substitutions in the HIV-1 RT gene resulting in 6 amino acid substitutions (M41L, D67N, K70R, L210W, T215Y or F, and K219Q) that confer zidovudine resistance. In general, higher levels of resistance were associated with greater number of amino acid substitutions.

Cross-Resistance: Cross-resistance has been observed among NRTIs.

Lamivudine Plus Zidovudine: Cross-resistance between lamivudine and zidovudine has not been reported. In some patients treated with lamivudine alone or in combination with zidovudine, isolates have emerged with a substitution at codon 184, which confers resistance to lamivudine. Cross-resistance to abacavir, didanosine, tenofovir, and zalcitabine has been observed in some patients harboring lamivudine-resistant HIV-1 isolates. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple drugs, including 1amivudine, have emerged (see under Zidovudine below).

Lamivudine: See Lamivudine Plus Zidovudine (above)

Zidovudine: In a study of 167 HIV-1-infected patients, isolates (n = 2) with multi drug resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were recovered from patients treated for ≥ 1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The pattern of resistance-associated amino acid substitutions with such combination therapies was different (A62V, V75I, F77L, Fl16Y, Q151M) from the pattern with zidovudine monotherapy, with the Q151M substitution being most commonly associated with multi-drug resistance. The substitution at codon 151 in combination with substitutions at 62, 75, 77, and 116 results in a virus with reduced susceptibility to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine. Thymidine analogue mutations (TAMs) are selected by zidovudine and confer cross- resistance to abacavir, didanosine, stavudine, tenofovir, and zalcitabine.

Clinical Studies

Adults

Clinical Endpoint Study:

Lamivudine Plus Zidovudine: The NUCB3007 (CAESAR) study was conducted using lamivudine 150-mg Tablets (150 mg twice daily) and zidovudine 100-mg Capsules (2 x 100 mg 3 times daily). CAESAR was a multi-center, 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 or lamivudine plus an investigational non-nucleoside reverse transcriptase inhibitor, randomized 1:2:1. A total of 1,816 HIV-1-infected adults with 25 to 250 (median 122) CD4 cells/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 study was 12 months. Results are summarized in Table below.

Table 8. Number of Patients (%) With At Least 1 HIV-1 Disease-Progression Event or Death

Endpoint	Current Therapy (n = 460)	Lamivudine plus Current Therapy (n = 896)	Lamivudine plus a 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%)

a An investigational non-nucleoside reverse transcriptase inhibitor not approved in the United States.

Pediatric Patients

Clinical Endpoint Study:

ACTG 300 was a multi-center, randomized, double-blind study that provided for comparison of lamivudine plus zidovudine with didanosine monotherapy. A total of
471 symptomatic, HIV-infected therapy-naive (≤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/mm3 (mean: 1,060 cells/mm3 and range: 0 to 4,650 cells/mm3 for patients ≤5 years of age; mean 419 cells/mm3 and range: 0 to 1,555 cells/mm3 for patients >5 years of age) and the mean baseline plasma HIV-1 RNA was 5.0 log10 copies/mL. The median duration on study was 10.1 months for the patients receiving lamivudine plus zidovudine and 9.2 months for patients receiving didanosine monotherapy. Results are summarized in Table below.

Table 9. Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	**Lamivudine plus Zidovudine (n=236)**	**Didanosine (n=235)**
HIV disease progression or death (total)	15 (6.4%)	37 (15.7%)
Physical growth failure	7 (3.0%)	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

Pharmacokinetics in Adults:
Lamivudine and zidovudine combination tablets for oral suspension (30 mg/60 mg) were bioequivalent to COMBIVIR Tablets of GlaxoSmithKline USA containing lamivudine 150 mg and zidovudine 300mg when administered to healthy volunteers under fasting conditions at a dose of lamivudine 150 mg and zidovudine 300 mg (five combination tablets).

Lamivudine: The pharmacokinetic properties of lamivudine in fasting patients are summarized in Table 10. Following oral administration, lamivudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours).

Zidovudine: The pharmacokinetic properties of zidovudine in fasting patients are summarized in Table 10. Following oral administration, zidovudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Zidovudine is eliminated primarily by hepatic metabolism. The major metabolite of zidovudine is GZDV. GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74% of the dose following oral administration, respectively. A second metabolite, 3□-amino-3□-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one-fifth of the zidovudine AUC.

Table 10: Pharmacokinetic Parameters[a] for Lamivudine and Zidovudine in Adults

Parameter	Lamivudine		Zidovudine	
Oral bioavailability (%)	86 ±16	N = 12	64 ±10	n = 5
Apparent volume of	1.3 ±0.4	N = 20	1.6 ±0.6	n = 8
distribution (L/kg)				
Plasma protein binding (%)	<36		<38	
CSF:plasma ratio[b]	0.12 [0.04 to 0.47]	n = 38[c]	0.60 [0.04 to 2.62]	N = 39[d]
Systemic clearance (L/hr/kg)	0.33 ±0.06	N = 20	1.6 ±0.6	n = 6
Renal clearance (L/hr/kg)	0.22 ±0.06	N = 20	0.34 ±0.05	n = 9
Elimination half-life (hr)[e]	5 to 7		0.5 to 3	

a Data presented as mean ± standard deviation except where noted.
b Median [range].
c Children.
d Adults.
e Approximate range.

Effect of Food on Absorption of lamivudine and zidovudine tablets for oral suspension:

The effect of food on lamivudine and zidovudine tablets for oral suspension was not determined; therefore, this product must be administered on an empty stomach, without food.

Special Populations:

Pregnancy: See Section 4.10.

Lamivudine and Zidovudine: No data are available.

Zidovudine: Zidovudine pharmacokinetics has been studied in a Phase 1 study 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. The pharmacokinetics of zidovudine was similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery.

Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear to alter zidovudine pharmacokinetics. In a nonpregnant adult population, a potential for interaction has been identified.

Nursing Mothers: See Use in Specifc Populations.

Pediatric Patients:

Lamivudine and Zidovudine tablets for oral suspension: Lamivudine and Zidovudine tablets for oral suspension should not be administered to pediatric patients who are less than 3 months of age.

Lamivudine:
In Study NUCA2002, the 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 I.V. 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 bioavailabilty of lamivudine in infants and children is unknown.
Systemic clearance decreased with increasing age in pediatric patients, as shown in Figure 1.

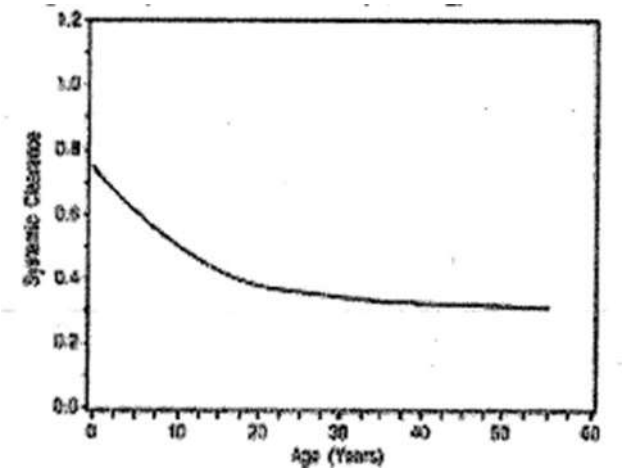


Figure 1: Systemic Clearance (L/hr.kg) of Lamivudine in Relation to Age

After oral administration of lamivudine 4 mg/kg twice daily to 11 pediatric patients ranging from 4 months to 14 years of age, Cmax was 1.1 ± 0.6 mcg/mL and the half-life was 2.0 ± 0.6 hours. (In adults with similar blood sampling, the half-life was 3.7 ± 1 hour.) 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 the 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 [see Section 4.12].

Zidovudine:
Zidovudine pharmacokinetics has been evaluated in HIV-infected pediatric patients (Table 11). Patients 3 Months to 12 Years: Overall, zidovudine pharmacokinetics in pediatric patients greater than 3 months of age are similar to those in adult patients. Proportional increases in plasma zidovudine concentrations were observed following administration of oral solution from 90 to 240 mg/m2 every 6 hours. Oral bioavailability, terminal half-life, and oral clearance were comparable to adult values. As in adult patients, the major route of elimination was by metabolism to GZDV. After intravenous dosing, about 29% of the dose was excreted in the urine unchanged, and about 45% of the dose was excreted as GZDV.

Table 11: Zidovudine Pharmacokinetic Parameters in Pediatric Patients[a]

Parameter	Aged 3 Months to 12 Years
Oral bioavailability (%)	65 ± 24 (n = 18)
CSF: Plasma ratio	0.68 [0.03 to 3.25][b] (n = 38)
CL (L/hr/kg)	1.85 ± 0.47 (n = 20)
Elimination half-life (hr)	1.5 ± 0.7 (n = 21)

a = Data presented as mean ± standard deviation except where noted
b = Median (range)

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

Gender: A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed no gender differences in zidovudine exposure (AUC∞) or lamivudine AUC∞ normalized for body weight.

Race: Lamivudine: There are no significant racial differences in lamivudine pharmacokinetics. Zidovudine: The pharmacokinetics of zidovudine with respect to race have not been determined.

Drug Interactions: See Section 4.7.
No drug interaction studies have been conducted using Lamivudine and Zidovudine Tablets for Oral Suspension. However, Table 12 presents drug interaction information for the individual components of Lamivudine and Zidovudine tablets for Oral Suspension.

Lamivudine Plus Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult patients given a

single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr).

Table 12: Effect of Coadministered Drugs on Lamivudine and Zidovudine AUCa
Note: ROUTINE DOSE MODIFICATION OF LAMIVUDINE AND ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.

Drugs That May Alter Lamivudine Blood Concentrations					
Coadministered Drug and Dose	**Lamivudine Dose**	**n**	**Lamivudine Concentrations**		**Concentration of Coadministered Drug**
			AUC	**Variability**	
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 150 mg	11	↑AUC 10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	single 300 mg	14	↑AUC 43%	90% CI: 32% to 55%	↔
Drugs That May Alter Zidovudine Blood Concentrations					
Coadministered Drug and Dose	**Zidovudine Dose**	**n**	**Zidovudine Concentrations**		**Concentration of Coadministered Drug**
			AUC	**Variability**	
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	↑AUC 31%	Range 23% to 78%[b]	↔
Clarithromycin 500 mg twice daily	100 mg q 4 hr x 7 days	4	↓AUC 12%	Range ↓34% to ↑14%	Not Reported
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑AUC 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑AUC 43%	Range 16% to 64%[b]	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 200 mg	11	↓AUC 35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑AUC 106%	Range 100% to 170%[b]	Not Assessed
Rifampin 600 mg daily x 14 days	200 mg q 8 hr X 14 days	8	↓AUC 47%	90% CI: 41% to 53%	Not Assessed
Ritonavir 300 mg q 6 hr x 4 days	200 mg q 8 hr x 4 days	9	↓AUC 25%	95% CI: 15% to 34%	↔

Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑AUC 80%	Range 64% to 130%b	Not Assessed

↑=Increase; ↓= Decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.
a This table is not all inclusive.
b Estimated range of percent difference.

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-l/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-l/HCV co-infected patients [see Section 4.5].

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity: Lamivudine: Long-term carcinogenicity studies with 1amivudine 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.

Zidovudine: Zidovudine was administered orally at 3 dosage levels to separate groups mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on day 279. In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species.

At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Mutagenicity: Lamivudine: Lamivudine was mutagenic in an L5178Y/TK+/- mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was negative 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.

Zidovudine: Zidovudine was mutagenic in an L5178Y/TK+/- mouse lymphoma assay, positive in an in vitro cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.

Impairment of Fertility: Lamivudine: In a study of reproductive performance, lamivudine administered to male and female rats at doses up to 130 times the usual adult dose based on body surface area considerations, revealed no evidence of impaired fertility (judged by conception rates) and no effect on the survival, growth, and development to weaning of the offspring.

Zidovudine: Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area considerations, had no effect on fertility judged by conception rates.

Reproductive and Developmental Toxicology Studies
Lamivudine: Reproduction studies have been performed in rats and rabbits at orally administered doses up to 4,000 mg/g/day and 1,000 mg/g/day, respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels up to 35 times those in humans. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

Zidovudine: Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/Kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one-sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours).In an in vitro experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/Kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. (Estimated area under the curve (AUC) in rats at this dose level was 300 times the daily AUC in humans given 600 mg/day.) No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each uncoated tablet contains the inactive ingredients aspartame, colloidal silicon dioxide, flavor orange permaseal PHS-131987, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and starch.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

60 Tablets per bottle with silica gel dessicant 1000 Tablets per bottle with silica gel dessicant
Unit Dose Pack of 60 in PVC/PE/PVDC/Aluminum blisters

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

Cipla Ltd.
Mumbai Central,
Mumbai, India.

8. MARKETING AUTHORISATION NUMBER
Rwanda FDA-HMP-MA- 0685

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION
15.12.2023

10. DATE OF REVISION OF THE TEXT

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