

CIPLA

LAMIVUDINE AND ZIDOVUDINE TABLETS FOR ORAL SUSPENSION 30 MG/60 MG

MODULE 1: ADMINISTRATIVE INFORMATION AND PRESCRIBED INFORMATION

1.3. Product Information

1.3.1- Summary of Product Characteristics (SmPC)

Product is in-line with USFDA (PEPFAR) approval hence enclosed USFDA approved Pack insert is enclosed

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Lamivudine and Zidovudine Tablets for Oral Suspension safely and effectively. See full prescribing information for Lamivudine and Zidovudine, Tablets for Oral Suspension.

Lamivudine and Zidovudine Tablets for Oral Suspension 30 mg/60 mg

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

See full prescribing information for complete boxed warning.

- Hematologic toxicity including neutropenia and anemia have been associated with the use of zidovudine, one of the components of Lamivudine and Zidovudine Tablets for Oral Suspension (5.1)
- Symptomatic myopathy associated with prolonged use of zidovudine (5.2)
- Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues including zidovudine. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.3)
- 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, a component of Lamivudine and Zidovudine tablets for Oral Suspension. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.4)

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

Lamivudine and Zidovudine tablets for Oral Suspension, a combination of two nucleoside analogue reverse transcriptase inhibitors, are indicated in combination with other antiretroviral agents for the treatment of HIV - 1 infection. (1)

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

- Pediatrics: Dosage should be based on body weight. 2.1
- Lamivudine and zidovudine, a fixed-dose product, should not be prescribed for pediatric patients who are less than 3 months of age, or patients requiring dosage adjustment, such as those with renal or hepatic impairment, or patients experiencing dose-limiting adverse reactions. (2.2)

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

Tablets for Oral Suspension: Scored 30 mg Lamivudine and 60 mg Zidovudine (3)

-----CONTRAINDICATIONS-----

Lamivudine and Zidovudine Tablets for Oral Suspension are contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., anaphylaxis, Stevens-Johnson syndrome). (4)

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

- See boxed warning for information about the following: hematologic toxicity, symptomatic myopathy, lactic acidosis and severe hepatomegaly, and severe acute exacerbations of hepatitis B. (5.1, 5.2, 5.3, 5.4)
- Lamivudine and Zidovudine Tablets for Oral Suspension should not be administered with other lamivudine- or zidovudine-containing products or emtricitabine-containing products. (5.5)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with/without ribavirin. Discontinue Lamivudine and Zidovudine Tablets for Oral Suspension as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.6)
- Exacerbation of anemia has been reported in HIV-1/HCV coinfecting patients receiving ribavirin and zidovudine. Coadministration of ribavirin and zidovudine is not advised. (5.6)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.7)
- Immune reconstitution syndrome (5.8) and redistribution/accumulation of body fat (5.9) have been reported in patients treated with combination antiretroviral therapy.
- Inform patients with phenylketonuria that lamivudine and zidovudine tablets for oral suspension contain phenylalanine, a component of aspartame (5.10)

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

- The most commonly reported adverse reactions (incidence greater than or equal to 15%) in adult and pediatric HIV-1 clinical studies of combination lamivudine and zidovudine were headache, nausea, malaise, fatigue, nasal signs and symptoms, diarrhea, and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cipla Ltd. at 1-866-604-3268 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**DRUG INTERACTIONS**-----

- Concomitant use with the following drugs should be avoided: stavudine (7.1), zalcitabine (7.1), doxorubicin (7.2).
- Bone marrow suppressive/cytotoxic agents: May increase the hematologic toxicity of zidovudine. (7.3)

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

- Nursing Mothers: HIV-1 infected mothers should not breastfeed to avoid potential postnatal transmission of HIV-1. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

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FULL PRESCRIBING INFORMATION

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 *Warnings and Precautions* (5.1)].

Myopathy: Prolonged use of zidovudine has been associated with symptomatic myopathy [see *Warnings and Precautions* (5.2)].

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 Warnings and Precautions (5.3)].

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

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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 Warnings and Precautions (5.4)].

1 INDICATIONS AND USAGE

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.

2 DOSAGE AND ADMINISTRATION

2.1 Pediatric 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 mg tablet) can be used.

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

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Method of Preparation

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.

2.2 Patients Requiring Dosage Adjustment

Because Lamivudine and Zidovudine tablets for oral suspension are a fixed-dose combination formulation, they should not be prescribed for patients requiring dosage adjustment, such as those with reduced renal function (creatinine clearance less than 50 mL/min), patients on hemodialysis, patients with hepatic impairment, or patients experiencing dose-limiting adverse reactions.

3 DOSAGE FORMS AND STRENGTHS

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 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.

5 WARNINGS AND PRECAUTIONS

5.1 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 Adverse*

Reactions (6.1)].

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 -1-infected patients. If anemia or neutropenia develops, dosage interruption may be needed.

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5.2 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.**

5.3 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).

5.4 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.

5.5 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

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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).

5.6 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-1/HCV co-infected patients

[see *Clinical Pharmacology (12.3)*], hepatic decompensation (some fatal) has occurred in HIV-1/

HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon

alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and

lamivudine 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.

5.7 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 *Adverse Reactions (6.1)*].

5.8 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.

5.9 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.

5.10 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.

6 ADVERSE REACTIONS

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

- Hematologic toxicity, including neutropenia and anemia [*see Boxed Warning, Warnings and Precautions (5.1)*].
- Symptomatic myopathy [*see Boxed Warning, Warnings and Precautions (5.2)*].
- Lactic acidosis and hepatomegaly with steatosis [*see Boxed Warning, Warnings and Precautions (5.3)*].
- Acute exacerbations of hepatitis B [*see Boxed Warning, Warnings and Precautions (5.4)*].
- Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C [*see Warnings and Precautions (5.6)*].
- Exacerbation of anemia in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine [*see Warnings and Precautions (5.6)*].
- Pancreatitis [*see Warnings and Precautions (5.7)*].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials

of another drug and may not reflect the rates observed in practice.

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 ($\geq 5\%$ 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%

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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 Warnings and Precautions (5.7)*).

Selected laboratory abnormalities observed during therapy are listed in Table 3.

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/mm³) 7.2% (237)

Anemia (Hgb<8.0 g/dL) 2.9% (241)

Thrombocytopenia (platelets<50,000/mm³) 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 $\geq 5\%$ frequency during therapy

with lamivudine 4 mg/kg twice daily plus zidovudine 160 mg/m² three times daily compared

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with didanosine in therapy-naive (≤ 56 days of antiretroviral therapy) pediatric patients are listed

in Table 4.

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

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 Warnings and Precautions (5.7)).

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.

Adverse Reactions Lamivudine plus Zidovudine

(n = 236)

Didanosine

(n = 235)

Body as a Whole

Fever

25%

32%

Digestive

Hepatomegaly

Nausea and vomiting

Diarrhea

Stomatitis

Splenomegaly

11%

8%

8%

6%

5%

11%

7%

6%

12%

8%

Respiratory

Cough

Abnormal breath sounds/wheezing

15%

7%

18%

9%

Ear, Nose and Throat

Signs or symptoms of ears^a

Nasal discharge or congestion

7%

8%

6%

11%

Other

Skin rashes

Lymphadenopathy

12%

9%

14%

11%

53

10

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/mm³) 8% 3%

Hemoglobin (<7.0 g/dL) 4% 2%

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

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 Clinical Pharmacology (12.3)]. 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 $\geq 5\%$ 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-naïve (≤ 56 days of

antiretroviral therapy) pediatric patients are listed in Table 6.

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

Lamivudine plus

Zidovudine Didanosine

Adverse Reaction (n = 236) (n = 235)

Body as a Whole

Fever 25% 32%

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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 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.

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/mm³) 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.

6.2 Postmarketing Experience

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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 Warnings and Precautions*

(5.9)].

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, Warnings and Precautions (5.3), (5.4), (5.7)*].

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.

7 DRUG INTERACTIONS

No drug interaction studies have been conducted using **Lamivudine and Zidovudine Tablets for Oral Suspension** [*see Clinical Pharmacology (12.3)*].

7.1 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.

7.2 Doxorubicin

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

7.3 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.

7.4 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 Warnings and Precautions (5.5), Clinical Pharmacology (12.3)*].

7.5 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.

8 USE IN SPECIFIC POPULATION

8.1 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 embryoletality (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 Clinical Studies (14.2)*]. 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 lamivudine 300 mg twice daily without other antiretrovirals.

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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 maternal-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 Clinical Studies (14.2)*].

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 embryo lethality 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 [*see Nonclinical Toxicology (13.2)*].

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 Nonclinical Toxicology (13.2)*].

8.3 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.

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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 lamivudine 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.

8.4 Pediatric Use

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.

8.5 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.

8.6 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.

8.7 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.

10 OVERDOSAGE

Lamivudine and zidovudine: There is no known antidote for lamivudine and zidovudine tablets for oral suspension.

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 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.

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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.

Zidovudine: Acute overdoses of zidovudine have been reported in pediatric patients and adults.

These involved exposures up to 50 grams. The only consistent findings were nausea and vomiting. Other reported occurrences included headache, dizziness, drowsiness, lethargy,

confusion, and 1 report of a grand mal seizure. Hematologic changes were transient. All patients recovered. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, while elimination of its primary metabolite, 3'-azido-3'-deoxy-5'-O-β-D-glucopyranuronosylthymidine (GZDV), is enhanced.

11 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 and Zidovudine Tablets for Oral Suspension are for oral administration.

Each uncoated tablet contains 30 mg of lamivudine, 60 mg of zidovudine, and the inactive ingredients aspartame, colloidal silicon dioxide, flavor orange permaseal PHS-131987, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and starch.

Lamivudine: The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue

of cytidine. Lamivudine has also been referred to as (-) 2',3' -dideoxy, 3'-thiacytidine. It has a

molecular formula of C₈H₁₁N₃O₃S and a molecular weight of 229.3. 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lamivudine and Zidovudine are antiviral agents [*see Clinical Pharmacology (12.4)*].

12.3 Pharmacokinetics

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 8. 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 8. 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.

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Table 8. 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
distribution (L/kg)

1.3 ± 0.4 N = 20 1.6 ± 0.6 n = 8

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 \pm 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 Use in Specific Populations (8.1).

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 Specific Populations (8.3).

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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 $66\% \pm 26\%$ (mean \pm SD),

which was less than the $86\% \pm 16\%$ (mean \pm SD) observed in adults. The mechanism for the

diminished absolute bioavailability 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, C_{max} 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 \pm SD of $14.2\% \pm 7.9\%$) of the concentration in a simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to 0.3 mcg/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 *Adverse Reactions (6.1)*].

Zidovudine:

Zidovudine pharmacokinetics has been evaluated in HIV-infected pediatric patients (Table 9).

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 9: 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 *Drug Interactions* (7).

No drug interaction studies have been conducted using **Lamivudine and Zidovudine** Tablets for

Oral Suspension. However, Table 10 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

64
21

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

12 hr).

Table 10. Effect of Coadministered Drugs on Lamivudine and Zidovudine AUC_a

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

AUC Variability Drug

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

⁶⁵

22

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/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected patients [see *Warnings and Precautions (5.5)*].

12.4 Microbiology

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 μ M (1 μ M = 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 μ M (range: 0.200 to 2.007 μ M) from Virco (n = 92 baseline samples from COLA40263) and 2.35 μ M (1.37 to 3.68 μ M) 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 μ M, and against HIV-2 isolates from 0.003 to 0.120 μ M in peripheral blood mononuclear cells. Ribavirin (50 μ M) 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 μ M (1 μ M = 0.27 mcg/mL) and 0.1 to 9 μ M, respectively. HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance gave median EC₅₀ values of 0.11 μ M (range: 0.005 to 0.110 μ M) from Virco (n = 92 baseline samples from COLA40263) and 0.0017 μ M (0.006 to 0.0340 μ M) 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 μ M, and against HIV-2 isolates from 0.00049 to 0.004 μ M. In cell culture drug combination studies, zidovudine demonstrates

synergistic activity with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir, didanosine, lamivudine, 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 susceptibility 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.

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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 lamivudine, 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, F116Y, 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 crossresistance to abacavir, didanosine, stavudine, tenofovir, and zalcitabine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity: Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) 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.

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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.

13.2 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 embryoletality 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.

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14 CLINICAL STUDIES

14.1 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, placebocontrolled 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 11.

Table 11. 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%)

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

14.2 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 12.

Table 12. 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%)

70

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CDC Clinical Category C 2 (0.8%) 8 (3.4%)

Death 2 (0.8%) 11 (4.7%)

16 HOW SUPPLIED/STORAGE AND HANDLING

Lamivudine and Zidovudine Tablets for oral suspension, containing 30 mg lamivudine and 60

mg zidovudine, are scored, white, circular, biconvex uncoated tablets with a deep score on one

side and debossed "DR" on other side. They are available as follows:

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

Do not store above 30° C.

17 PATIENT COUNSELING INFORMATION

17.1 Advice for the Patient

Neutropenia and Anemia: Patients should be informed that the important toxicities associated

with zidovudine are neutropenia and/or anemia. They should be told of the extreme importance

of having their blood counts followed closely while on therapy, especially for patients with

advanced HIV-1 disease [*see Boxed Warning, Warnings and Precautions (5.1)*].

Myopathy: Patients should be informed that myopathy and myositis with pathological changes,

similar to that produced by HIV-1 disease, have been associated with prolonged use of

zidovudine [*see Boxed Warning, Warnings and Precautions (5.2)*].

Lactic Acidosis/Hepatomegaly: Patients should be informed that some HIV medicines, including

lamivudine and zidovudine, can cause a rare, but serious condition called lactic acidosis with

liver enlargement (hepatomegaly) [*see Boxed Warning, Warnings and Precautions (5.3)*].

HIV-1/HBV Co-infection: Patients co-infected with HIV-1 and HBV should be informed that

deterioration of liver disease has occurred in some cases when treatment with lamivudine was

discontinued. Patients should be advised to discuss any changes in regimen with their physician

[*see Warnings and Precautions (5.4)*].

HIV-1/HCV Co-Infection: Patients with HIV-1/HCV co-infection should be informed that

hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving

combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin [*see*

Warnings and Precautions (5.6)].

Drug Interactions: Patients should be cautioned about the use of other medications, including

ganciclovir, interferon alfa, and ribavirin, which may exacerbate the toxicity of zidovudine [*see*

Drug Interactions (7.3)].

Redistribution/Accumulation of Body Fat: Patients should be informed that redistribution or

accumulation of body fat may occur in patients receiving antiretroviral therapy and that the

cause and long-term health effects of these conditions are not known at this time
[see Warnings and Precautions (5.9)].

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Use With Other Lamivudine-, Zidovudine-, and/or Emtricitabine-Containing Products:

Lamivudine and Zidovudine Tablets for Oral Suspension should not be coadministered with drugs containing lamivudine, zidovudine, or emtricitabine, including EPIVIR (lamivudine), EPVIR-HBV (lamivudine), RETROVIR (zidovudine), COMBIVIR (lamivudine and zidovudine), EPZICOM (abacavir sulfate and lamivudine), TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine), ATRIPLA (efavirenz, emtricitabine, and tenofovir), EMTRIVA (emtricitabine), TRUVADA (emtricitabine and tenofovir) or COMPLERA (rilpivirine, emtricitabine and tenofovir) *[see Warnings and Precautions (5.5)].*

Phenylketonurics: Inform patients with phenylketonuria that lamivudine and zidovudine tablets for oral suspension contain phenylalanine, a component of aspartame *[see Warnings and Precautions (5.10)].*

Information About HIV-1 Infection: **Lamivudine and Zidovudine Tablets for Oral Suspension** are not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV -1 infection, including opportunistic infections. Patients should remain under the care of a physician when using **Lamivudine and Zidovudine** tablets for oral suspension. Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

Do not share needles or other injection equipment.

Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.

Do not have any kind of sex without protection. Always practice safe sex by using a latex or

polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Do not breastfeed. Lamivudine and zidovudine are excreted in human breast milk.

Mothers with

HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Patients should be informed to take all HIV medications exactly as prescribed.

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