

PRESCRIBING INFORMATION

LAMIVUDINE/STAVUDINE TABLETS

(Lamivudine 150 mg and Stavudine 30 mg)

(Lamivudine 150 mg and Stavudine 40 mg)

R_x ONLY

WARNING

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING LAMIVUDINE AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

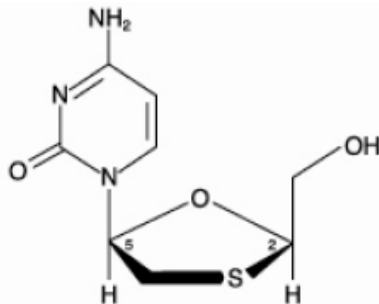
SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HIV AND HAVE DISCONTINUED LAMIVUDINE/STAVUDINE TABLETS. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE LAMIVUDINE/STAVUDINE TABLETS AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

FATAL LACTIC ACIDOSIS HAS BEEN REPORTED IN PREGNANT WOMEN WHO RECEIVED THE COMBINATION OF STAVUDINE AND DIDANOSINE WITH OTHER ANTIRETROVIRAL AGENTS. THE COMBINATION OF STAVUDINE AND DIDANOSINE SHOULD BE USED WITH CAUTION DURING PREGNANCY AND IS RECOMMENDED ONLY IF THE POTENTIAL BENEFIT CLEARLY OUTWEIGHS THE POTENTIAL RISK (SEE WARNINGS AND PRECAUTIONS: PREGNANCY).

FATAL AND NONFATAL PANCREATITIS HAVE OCCURRED DURING THERAPY WHEN STAVUDINE WAS PART OF A COMBINATION REGIMEN THAT DIDANOSINE, WITH OR WITHOUT HYDROXYUREA, IN BOTH TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION (SEE WARNINGS).

DESCRIPTION

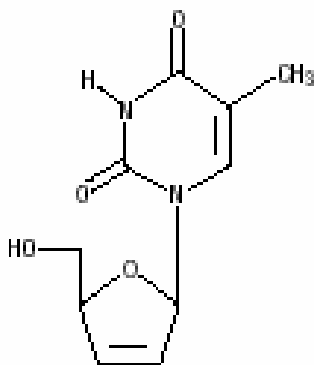
Lamivudine: Lamivudine (also known as 3TC) is a synthetic nucleoside analogue with activity against HIV-1 and HBV. The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)-enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-) 2',3'-dideoxy-3'-thiacytidine. It has a molecular formula of 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.

Stavudine: Stavudine (d4T), is a synthetic thymidine nucleoside analogue, active against the human immunodeficiency virus (HIV).

The chemical name for stavudine is 2',3'-dideohydro-3'-deoxythymidine. Stavudine has the following structural formula:



Stavudine is a white to off-white crystalline solid with the molecular formula $C_{10}H_{12}N_2O_4$ and a molecular weight of 224.2. The solubility of stavudine at 23°C is approximately 83 mg/mL in water and 30 mg/mL in propylene glycol. The n-octanol/water partition coefficient of stavudine at 23°C is 0.144.

LAMIVUDINE/STAVUDINE TABLETS: Lamivudine/stavudine tablets are supplied for oral administration in strengths of 150mg/30mg and 150mg/40mg. Each uncoated tablet also contains the inactive ingredient colloidal silicon dioxide, ferric oxide red (in 150 mg/30 mg strength tablets) or ferric oxide yellow (in 150 mg/40 mg strength tablets), magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

MICROBIOLOGY

Mechanism of Action:

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is the inhibition of

HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue into viral DNA. 3TC-TP is a weak inhibitor of mammalian DNA polymerases α , β , and γ .

Stavudine: Stavudine, a nucleoside analogue of thymidine, is phosphorylated by cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) by competing with the natural substrate thymidine triphosphate ($K_i=0.0083$ to $0.032 \mu\text{M}$) and by causing DNA chain termination following its incorporation into viral DNA. Stavudine triphosphate inhibits cellular DNA polymerases β and γ and markedly reduces the synthesis of mitochondrial DNA.

Antiviral 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. EC_{50} values (50% effective concentrations) were in the range of 0.003 to $15 \mu\text{M}$ ($1 \mu\text{M} = 0.23 \text{ mcg/mL}$). HIV from therapy-naive subjects with no mutations associated with resistance gave median EC_{50} values of $0.426 \mu\text{M}$ (range: 0.200 to $2.007 \mu\text{M}$) from Virco ($n=93$ baseline samples from COLA40263) and $2.35 \mu\text{M}$ (1.44 to $4.08 \mu\text{M}$) from Monogram Biosciences ($n=135$ baseline samples from ESS30009). The EC_{50} values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to $0.120 \mu\text{M}$, and against HIV-2 isolates from 0.003 to $0.120 \mu\text{M}$ in peripheral blood mononuclear cells. Ribavirin ($50 \mu\text{M}$) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells. In HIV-1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity.

Stavudine: The in vitro antiviral activity of stavudine was measured in peripheral blood mononuclear cells, monocytic cells, and lymphoblastoid cell lines. The concentration of drug necessary to inhibit HIV-1 replication by 50% (IC_{50}) ranged from 0.009 to $4 \mu\text{M}$ against laboratory and clinical isolates of HIV-1. In vitro, stavudine exhibited additive to antagonistic activity in combination with zidovudine. Stavudine in combination with either abacavir, didanosine, tenofovir, or zalcitabine exhibited additive to synergistic anti-HIV-1 activity. Ribavirin, at the 9 - $45 \mu\text{M}$ concentrations tested, reduced the anti-HIV-1 activity of stavudine by 2.5- to 5-fold. The relationship between in vitro susceptibility of HIV-1 to stavudine and the inhibition of HIV-1 replication in humans has not been established.

Drug Resistance

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

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. 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 mutations conferring resistance to zidovudine.

Mutations in the HBV polymerase YMDD motif have been associated with reduced susceptibility of HBV to lamivudine in cell culture. In studies of non-HIV-infected patients with chronic hepatitis B, HBV isolates with YMDD mutations were detected in some patients who received lamivudine daily for 6 months or more, and were associated with evidence of diminished treatment response; similar HBV mutants have been reported in HIV-infected patients who received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus (see PRECAUTIONS).

Stavudine: HIV-1 isolates with reduced susceptibility to stavudine have been selected in vitro (strain-specific) and were also obtained from patients treated with stavudine. Phenotypic analysis of HIV-1 isolates from 61 patients receiving prolonged (6-29 months) stavudine monotherapy showed that post-therapy isolates from four patients exhibited IC₅₀ values more than 4-fold (range 7- to 16-fold) higher than the average pretreatment susceptibility of baseline isolates. Of these, HIV-1 isolates from one patient contained the zidovudine-resistance-associated mutations T215Y and K219E, and isolates from another patient contained the multiple-nucleoside-resistance-associated mutation Q151M. Mutations in the RT gene of HIV-1 isolates from the other two patients were not detected. The genetic basis for stavudine susceptibility changes has not been identified.

Cross-Resistance:

Lamivudine: Lamivudine-resistant HIV-1 mutants were cross-resistant to didanosine (ddI) and zalcitabine (ddC). In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Stavudine: Cross-resistance among HIV-1 reverse transcriptase inhibitors has been observed. Several studies have demonstrated that prolonged stavudine treatment can select and/or maintain mutations associated with zidovudine resistance. HIV-1 isolates with one or more zidovudine-resistance-associated mutations (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) exhibited reduced susceptibility to stavudine in vitro.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults:

Matrix Laboratories fixed dose combination tablets containing lamivudine 150 mg and stavudine 40 mg are bioequivalent to Epivir[®] tablets (lamivudine 150 mg) of GlaxoSmithKline and Zerit[®] capsules (stavudine 40 mg) of Bristol-Myers Squibb Company when administered together in healthy volunteers under both fasting and fed conditions (high fat, high calorie meal).

Lamivudine:

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

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

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

Elimination: The majority of lamivudine is eliminated unchanged in urine. In 9 healthy subjects given a single 300-mg oral dose of lamivudine, renal clearance was 199.7 ± 56.9 mL/min (mean ± SD). In most single-dose studies in HIV-infected patients, HBV-infected patients, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to 7 hours. In HIV-infected patients, total clearance was 398.5 ± 69.1 mL/min (mean ± SD).

Stavudine:

Absorption: Following oral administration, stavudine is rapidly absorbed, with peak plasma concentrations occurring within 1 hour after dosing. The systemic exposure to stavudine is the same following administration as capsules or

solution. Steady-state pharmacokinetic parameters of stavudine in HIV-infected adults are shown in Table 1.

Parameter	Stavudine 40 mg BID Mean \pm SD (n=8)
AUC (ng·h/mL) ^a	2568 \pm 454
C _{max} (ng/mL)	536 \pm 146
C _{min} (ng/mL)	8 \pm 9
^a from 0 to 24 hours AUC=area under the curve over 24 hours. C _{max} = maximum plasma concentration. C _{min} =trough or minimum plasma concentration.	

Distribution: Binding of stavudine to serum proteins was negligible over the concentration range of 0.01 to 11.4 μ g/mL. Stavudine distributes equally between red blood cells and plasma. Volume of distribution is shown in Table 2.

Metabolism: The metabolism of stavudine has not been elucidated in humans.

Elimination: In humans, renal elimination accounts for about 40% of the overall clearance regardless of the route of administration (Table 2). The mean renal clearance was about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration. The remaining 60% of the drug is presumably eliminated by endogenous pathways.

Parameter	Mean \pm SD	N
Oral bioavailability (%)	86.4 \pm 18.2	25
Volume of distribution (L) ^a	46 \pm 21	44
Total body clearance (mL/min) ^a	594 \pm 164	44
Apparent oral clearance (mL/min) ^b	560 \pm 182 ^c	113
Renal clearance (mL/min) ^a	237 \pm 98	39
Elimination half-life, IV dose (h) ^a	1.15 \pm 0.35	44
Elimination half-life, oral dose (h) ^b	1.6 \pm 0.23	8
Urinary recovery of Stavudine (% of dose) ^{a,d}	42 \pm 14	39
^a following 1-hour IV infusion. ^b following single oral dose. ^c assuming a body weight of 70 kg. ^d over 12-24 hours.		

Special Populations:

Adults with Impaired Renal Function:

Reduction of the dosage of both stavudine and lamivudine is required in patients with a creatinine clearance of 50 ml/min or less. Therefore,

Lamivudine/Stavudine combination tablets cannot be used in this patient population.

Adults With Impaired Hepatic Function:

Lamivudine: The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function; therefore, no dose adjustment for lamivudine is required for patients with impaired hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

Stavudine: Stavudine pharmacokinetics were not altered in five non-HIV-infected patients with hepatic impairment secondary to cirrhosis (Child-Pugh classification B or C) following the administration of a single 40-mg dose.

Gender:

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

Stavudine: A population pharmacokinetic analysis of data collected during a controlled clinical study in HIV-infected patients showed no clinically important differences between males (n=291) and females (n=27).

Pregnancy: See PRECAUTIONS: Pregnancy

No data are available on pharmacokinetics of stavudine during pregnancy.

Nursing Mothers: See PRECAUTIONS: Nursing Mothers

Lamivudine: 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.

Stavudine: No data is available on pharmacokinetics of stavudine in nursing mothers. It is not known whether stavudine is excreted in breast milk.

Race:

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

Stavudine: A population pharmacokinetic analysis of data collected during a controlled clinical study in HIV-infected patients showed no clinically important differences between races (n=233 Caucasian, 39 African-American, 41 Hispanic, 1 Asian, and 4 other).

Pediatric Patients:

The pharmacokinetics of Lamivudine/Stavudine Tablets have not been studied in pediatric patients. Because it is a fixed-dose combination that cannot be adjusted for this patient population, Lamivudine/ Stavudine Tablets should not be administered to pediatric patients who weigh less than 30 kg or who are younger than 12 years of age.

Geriatric:

Stavudine:

Stavudine pharmacokinetics have not been studied in patients >65 years of age. (See **PRECAUTIONS: Geriatric Use.**)

Drug Interactions (see **PRECAUTIONS: Drug Interactions):**

Lamivudine:

No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr).

Lamivudine and trimethoprim/sulfamethoxazole (TMP/SMX) were coadministered to 14 HIV-positive patients in a single-center, open-label, randomized, crossover study. Each patient received treatment with a single 300-mg dose of lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with lamivudine resulted in an increase of $43\% \pm 23\%$ (mean \pm SD) in lamivudine AUC_{∞} , a decrease of $29\% \pm 13\%$ in lamivudine oral clearance, and a decrease of $30\% \pm 36\%$ in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine.

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

There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a study of 19 healthy male subjects.

Stavudine:

Zidovudine: Zidovudine competitively inhibits the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with stavudine should be avoided.

Doxorubicin: In vitro data indicate that the phosphorylation of stavudine is inhibited at relevant concentrations of doxorubicin.

Stavudine does not inhibit the major cytochrome P450 isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways. Because stavudine is not protein-bound, it is not expected to affect the pharmacokinetics of protein-bound drugs.

Tables 3 and 4 summarize the effects on AUC and C_{max}, with a 95% confidence interval (CI) when available, following coadministration of stavudine with didanosine, lamivudine, and nelfinavir. No clinically significant pharmacokinetic interactions were observed.

Drug	Stavudine Dosage	n ^a	AUC of Stavudine (95% CI)	C _{max} of Stavudine (95% CI)
Didanosine, 100mg q12h for 4 days	40 mg q12h for 4 days	10	↔	↑17%
Lamivudine, 150 mg single dose	40 mg single dose	18	↔ (92.7-100.6%)	↑12% (100.3-126.1%)
Nelfinavir, 750 mg q8h for 56 days	30-40 mg q12h for 56 days	8	↔	↔

↑ indicates increase.
↔ indicates no change, or mean increase or decrease of <10%.
^a HIV-infected patients.

Drug	Stavudine Dosage	n ^a	AUC of Coadministered Drug (95% CI)	C _{max} of Coadministered Drug (95% CI)
Didanosine, 100mg q12h for 4 days	40 mg q12h for 4 days	10	↔	↔
Lamivudine, 150mg single dose	40 mg single dose	18	↔ (90.5-107.6%)	↔ (87.1-110.6%)
Nelfinavir, 750 mg q8h for 56 days	30-40 mg q12h for 56 days	8	↔	↔

↔ indicates no change, or mean increase or decrease of <10%.
^a HIV-infected patients.

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/HCV co-infected patients (see WARNINGS).

INDICATIONS AND USAGE

Lamivudine/Stavudine tablets in combination with other antiretroviral agents is indicated for the treatment of HIV infection as a component of combination antiretroviral therapy.

CONTRAINDICATIONS

Lamivudine/Stavudine Tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the products.

WARNINGS

Lamivudine and Stavudine:

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine and other antiretrovirals. Obesity and prolonged nucleoside exposure may be risk factors. A majority of the cases of lactic acidosis and severe hepatomegaly with steatosis have been in women. Particular caution should be exercised when administering lamivudine and stavudine 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/stavudine tablets should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Generalized fatigue, digestive symptoms (nausea, vomiting, abdominal pain, and unexplained weight loss); respiratory symptoms (tachypnea and dyspnea); or neurologic symptoms associated with stavudine use (including motor weakness, see **Neurologic Symptoms**) might be indicative of the development of symptomatic hyperlactatemia or lactic acidosis syndrome.

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 stavudine. Although no evidence of a pharmacokinetic or pharmacodynamic (eg, loss of HIV/HCV Virologic suppression) interaction was seen when ribavirin was coadministered with lamivudine and stavudine in HIV/HCV co-infected patients (see **CLINICAL PHARMACOLOGY: Drug Interactions**), **hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon and ribavirin.** Patients receiving interferon with or without ribavirin, lamivudine and stavudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of lamivudine/stavudine tablets should be considered as medically appropriate. Dose reduction or discontinuation of interferon, ribavirin,

or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (eg, Child Pugh >6) (see **the complete prescribing information for interferon and ribavirin**).

Lamivudine:

Posttreatment Exacerbations of Hepatitis: In clinical trials in non-HIV-infected patients treated with lamivudine for chronic hepatitis B, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from postmarketing experience after changes from lamivudine-containing HIV treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory followup 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.

Lamivudine

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine should be used with caution. Treatment with Lamivudine/Stavudine Tablets should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see ADVERSE REACTIONS).

Important differences among Lamivudine-containing products:

Lamivudine/Stavudine Tablets contain a higher dose of the same active ingredient (lamivudine) than in EPIVIR-HBV Tablets and Oral Solution. EPIVIR-HBV was developed for patients with chronic hepatitis B. Lamivudine/Stavudine Tablets should not be administered concomitantly with lamivudine, EPIVIR-HBV, EPZICOM[®], or TRIZIVIR[®].

Stavudine:

Hepatic Impairment and Toxicity:

The safety and efficacy of stavudine have not been established in HIV-infected patients with significant underlying liver disease. During combination antiretroviral therapy, patients with preexisting liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities, including severe and potentially fatal hepatic adverse events, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Use with Didanosine and Hydroxyurea-Based Regimens:

An increased risk of hepatotoxicity may occur in patients treated with stavudine in combination with didanosine and hydroxyurea compared to when stavudine is used alone. Deaths attributed to hepatotoxicity have occurred in patients receiving this combination. This combination should be avoided.

Neurologic Symptoms:

Motor weakness has been reported rarely in patients receiving combination antiretroviral therapy including stavudine. Most of these cases occurred in the setting of lactic acidosis. The evolution of motor weakness may mimic the clinical presentation of Guillain-Barré syndrome (including respiratory failure). Symptoms may continue or worsen following discontinuation of therapy.

Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been reported in patients receiving stavudine therapy. Peripheral neuropathy has occurred more frequently in patients with advanced HIV disease, with a history of neuropathy, or in patients receiving other drugs that have been associated with neuropathy, including didanosine (see **ADVERSE REACTIONS**).

Pancreatitis:

Fatal and nonfatal pancreatitis have occurred during therapy when stavudine was part of a combination regimen that included didanosine, with or without hydroxyurea, in both treatment-naïve and treatment-experienced patients, regardless of degree of immunosuppression. The combination of stavudine and didanosine (with or without hydroxyurea) and any other agents that are toxic to the pancreas should be suspended in patients with suspected pancreatitis. Reinstitution of stavudine after a confirmed diagnosis of pancreatitis should be undertaken with particular caution and close patient monitoring. The new regimen should contain neither didanosine nor hydroxyurea.

PRECAUTIONS

Lamivudine and Stavudine:

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.

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection,

cytomegalovirus, Pneumocystis jirovecii pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Lamivudine:

Patients With HIV and Hepatitis B Virus Co-infection: Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and 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-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus. Posttreatment exacerbations of hepatitis have also been reported (see WARNINGS).

Information For patients:

Lamivudine and Stavudine:

Lamivudine/stavudine tablets are not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using lamivudine/stavudine tablets. Patients should be advised that the use of lamivudine/stavudine tablets has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Patients should be advised of the importance of taking lamivudine/stavudine tablets with combination therapy on a regular dosing schedule and to avoid missing doses.

Patients should be informed that the Centers for Disease Control and Prevention (CDC) recommend that HIV infected mothers not nurse newborn infants to reduce the risk of postnatal transmission of HIV infection.

Patients should be informed that redistribution or accumulation of body fat may occur in individuals receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Patients should be advised of the importance of adherence to any antiretroviral regimen, including those that contain stavudine.

Lamivudine/Stavudine tablets are for oral administration only.

Lamivudine:

Patients co-infected with HIV 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.

Stavudine: Patients should be informed of the importance of early recognition of symptoms of symptomatic hyperlactatemia or lactic acidosis syndrome, which include unexplained weight loss, abdominal discomfort, nausea, vomiting, fatigue, dyspnea, and motor weakness. Patients in whom these symptoms develop should seek medical attention immediately. Discontinuation of stavudine therapy may be required.

Patients should be informed that an important toxicity of stavudine is peripheral neuropathy. Patients should be aware that peripheral neuropathy is manifested by numbness, tingling, or pain in hands or feet, and that these symptoms should be reported to their physicians. Patients should be counseled that peripheral neuropathy occurs with greatest frequency in patients who have advanced HIV disease or a history of peripheral neuropathy, and that dose modification and/or discontinuation of stavudine may be required if toxicity develops.

Patients should be informed that when stavudine is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when stavudine is used alone. An increased risk of pancreatitis, which may be fatal, may occur in patients treated with the combination of stavudine and didanosine, with or without hydroxyurea. This combination should be avoided.

Drug Interactions:

Lamivudine:

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim)..

TMP 160 mg/SMX 800 mg once daily has been shown to increase lamivudine exposure (AUC) by 43% (see CLINICAL PHARMACOLOGY). 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. No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Lamivudine:

Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV infection. Lamivudine was not active in a microbial mutagenicity screen or an in vitro cell transformation assay, but showed weak in vitro mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of in vivo genotoxic activity in the rat at oral doses of up to 2,000 mg/kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV infection. In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

Stavudine:

In 2-year carcinogenicity studies in mice and rats, stavudine was noncarcinogenic at doses which produced exposures (AUC) 39 and 168 times, respectively, human exposure at the recommended clinical dose. Benign and malignant liver tumors in mice and rats and malignant urinary bladder tumors in male rats occurred at levels of exposure 250 (mice) and 732 (rats) times human exposure at the recommended clinical dose.

Stavudine was not mutagenic in the Ames, E. coli reverse mutation, or the CHO/HGPRT mammalian cell forward gene mutation assays, with and without metabolic activation. Stavudine produced positive results in the in vitro human lymphocyte clastogenesis and mouse fibroblast assays, and in the in vivo mouse micronucleus test. In the in vitro assays, stavudine elevated the frequency of chromosome aberrations in human lymphocytes (concentrations of 25 to 250 µg/mL, without metabolic activation) and increased the frequency of transformed foci in mouse fibroblast cells (concentrations of 25 to 2500 µg/mL, with and without metabolic activation). In the in vivo micro-nucleus assay, stavudine was clastogenic in bone marrow cells following oral stavudine administration to mice at dosages of 600 to 2000 mg/kg/day for 3 days.

No evidence of impaired fertility was seen in rats with exposures (based on C_{max}) up to 216 times that observed following a clinical dosage of 1 mg/kg/day.

Pregnancy: Pregnancy Category C

Lamivudine and stavudine are both classified under category C. There are no adequate and well-controlled studies in pregnant women. Lamivudine and Stavudine Tablets should be used during pregnancy only if the potential benefits outweigh the potential risk.

Lamivudine: Pregnancy Category C. Reproduction studies have been performed in rats and rabbits at orally administered doses up to 4,000 mg/kg/day and 1,000 mg/kg/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 similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

In 2 clinical studies conducted in South Africa, pharmacokinetic measurements were performed on samples from pregnant women who received lamivudine beginning at Week 38 of gestation (10 women who received 150 mg twice daily in combination with zidovudine and 10 who received lamivudine 300 mg twice daily without other antiretrovirals) or beginning at Week 36 of gestation (16 women who received lamivudine 150 mg twice daily in combination with zidovudine). These studies were not designed or powered to provide efficacy information. Lamivudine pharmacokinetics in the pregnant women were similar to those obtained following birth and in non-pregnant adults. Lamivudine concentrations were generally similar in maternal, neonatal, and cord serum samples. In a subset of subjects from whom amniotic fluid specimens were obtained following natural rupture of membranes, amniotic fluid concentrations of lamivudine ranged from 1.2 to 2.5 mcg/mL (150 mg twice daily) and 2.1 to 5.2 mcg/mL (300 mg twice daily) and were typically greater than 2 times the maternal serum levels. See the ADVERSE REACTIONS section for the limited late-pregnancy safety information available from these studies. Lamivudine should be used during pregnancy only if the potential benefits outweigh the risks.

Stavudine:

Pregnancy Category C. Reproduction studies have been performed in rats and rabbits with exposures (based on C_{max}) up to 399 and 183 times, respectively, of that seen at a clinical dosage of 1 mg/kg/day and have revealed no evidence of teratogenicity. The incidence in fetuses of a common skeletal variation, unossified or incomplete ossification of sternebra, was increased in rats at 399 times human exposure, while no effect was observed at 216 times human exposure. A slight post-implantation loss was noted at 216 times the human exposure with no effect noted at approximately 135 times the human exposure. An increase in early rat neonatal mortality (birth to 4 days of age) occurred at 399 times the human exposure, while survival of neonates was unaffected at approximately 135 times the human exposure. A study in rats showed that stavudine is transferred to the fetus through the placenta. The concentration in fetal tissue was approximately one-half the concentration in maternal plasma. Animal reproduction studies are not always predictive of human response.

There are no adequate and well-controlled studies of stavudine in pregnant women. Stavudine should be used during pregnancy only if the potential benefit justifies the potential risk.

Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. It is unclear if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in nonpregnant individuals receiving nucleoside analogues (see **WARNINGS: Lactic Acidosis/Severe Hepatomegaly with Steatosis**). **The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk.** Health care providers caring for HIV-infected pregnant women receiving stavudine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

Nursing Mothers:

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection. Additionally, because of the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving Lamivudine/ Stavudine Tablets.

Lamivudine:

A study in lactating rats administered 45 mg/kg of lamivudine showed that lamivudine concentrations in milk were slightly greater than those in plasma. Lamivudine is also excreted in human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Stavudine:

Studies in lactating rats demonstrated that stavudine is excreted in milk. Although it is not known whether stavudine is excreted in human milk, there exists the potential for adverse effects from stavudine in nursing infants.

Pediatric Use:

The pharmacokinetics of Lamivudine and Stavudine Tablets have not been studied in pediatric patients. Because it is a fixed-dose combination that cannot be adjusted for this patient population, Lamivudine/Stavudine Tablets should not be administered to pediatric patients who weigh less than 30 kg or who are younger than 12 years of age.

Geriatric Use: Clinical studies of lamivudine 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. **Because Lamivudine/Stavudine Tablets are a fixed-dose combination, they should not be prescribed** for patients who require dose reduction or have renal impairment with CrCL <50 mL/min

Stavudine:

Clinical studies of stavudine did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently than younger patients. Greater sensitivity of some older individuals to the effects of stavudine cannot be ruled out.

In a monotherapy Expanded Access Program for patients with advanced HIV infection, peripheral neuropathy or peripheral neuropathic symptoms were observed in 15 of 40 (38%) elderly patients receiving 40 mg of stavudine twice daily and 8 of 51 (16%) elderly patients receiving 20 mg twice daily. Of the approximately 12,000 patients enrolled in the Expanded Access Program, peripheral neuropathy or peripheral neuropathic symptoms developed in 30% of patients receiving 40 mg twice daily and 25% of patients receiving 20 mg twice daily. Elderly patients should be closely monitored for signs and symptoms of peripheral neuropathy.

ADVERSE REACTIONS

Lamivudine:

Clinical Trials in HIV: Adults: Selected clinical adverse events with a ≥5% frequency during therapy with lamivudine 150 mg twice daily plus RETROVIR 200 mg 3 times daily compared with zidovudine are listed in Table 5.

Table 5. Selected Clinical Adverse Events (≥5% Frequency) in Four Controlled Clinical Trials (A3001, A3002, B3001, B3002)

Adverse Event	Lamivudine 150 mg Twice Daily plus RETROVIR (n = 251)	RETROVIR* (n = 230)
Body as a Whole		
Headache	35%	27%
Malaise & fatigue	27%	23%
Fever or chills	10%	12%
Digestive		
Nausea	33%	29%
Diarrhea	18%	22%
Nausea & vomiting	13%	12%
Anorexia and/or decreased appetite	10%	7%
Abdominal pain	9%	11%

Abdominal cramps	6%	3%
Dyspepsia	5%	5%
Nervous System		
Neuropathy	12%	10%
Insomnia & other sleep disorders	11%	7%
Dizziness	10%	4%
Depressive disorders	9%	4%
Respiratory		
Nasal signs & symptoms	20%	11%
Cough	18%	13%
Skin		
Skin rashes	9%	6%
Musculoskeletal		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

*Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who received lamivudine in the controlled clinical trials EPV20001, NUCA3001, NUCB3001, NUCA3002, NUCB3002, and B3007. Selected laboratory abnormalities observed during therapy are summarized in Table 6.

Table 6. Frequencies of Selected Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Studies (A3001, A3002, B3001, B3002) and a Clinical Endpoint Study (B3007)

Test (Threshold Level)	24-Week Surrogate Endpoint Studies*		Clinical Endpoint Study*	
	lamivudine plus RETROVIR	RETROVIR [†]	lamivudine plus Current Therapy	Placebo plus Current Therapy [†]
Absolute neutrophil count ($<750/\text{mm}^3$)	7.2%	5.4%	15%	13%
Hemoglobin ($<8.0 \text{ g/dL}$)	2.9%	1.8%	2.2%	3.4%
Platelets ($<50,000/\text{mm}^3$)	0.4%	1.3%	2.8%	3.8%
ALT($>5.0 \times \text{ULN}$)	3.7%	3.6%	3.8%	1.9%
AST($>5.0 \times \text{ULN}$)	1.7%	1.8%	4.0%	2.1%
Bilirubin($>2.5 \times \text{ULN}$)	0.8%	0.4%	ND	ND
Amylase ($>2.0 \times$ ULN)	4.2%	1.5%	2.2%	1.1%

* The median duration on study was 12 months.

† Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

‡ Current therapy was either zidovudine, zidovudine plus didanosine, or zidovudine plus zalcitabine.

ULN = Upper limit of normal.

ND = Not done.

In small, uncontrolled studies in which pregnant women were given lamivudine alone or in combination with zidovudine beginning in the last few weeks of pregnancy (see PRECAUTIONS: Pregnancy), reported adverse events included anemia, urinary tract infections, and complications of labor and delivery. In postmarketing experience, liver function abnormalities and pancreatitis have been reported in women who received lamivudine in combination with other antiretroviral drugs during pregnancy. It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared to other HIV-infected patients.

Lamivudine in Patients With Chronic Hepatitis B: Clinical trials in chronic hepatitis B used a lower dose of lamivudine (100 mg daily) than the dose used to treat HIV. The most frequent adverse events with lamivudine versus placebo were ear, nose, and throat infections (25% versus 21%); malaise and fatigue (24% versus 28%); and headache (21% versus 21%), respectively. The most frequent laboratory abnormalities reported with lamivudine were elevated ALT, elevated serum lipase, elevated CPK, and posttreatment elevations of liver function tests. Emergence of HBV viral mutants during lamivudine treatment, associated with reduced drug susceptibility and diminished treatment response, was also reported (also see WARNINGS and PRECAUTIONS).

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

Body as a Whole: Redistribution/accumulation of body fat (see PRECAUTIONS: Fat Redistribution).

Digestive: Stomatitis.

Endocrine and Metabolic: Hyperglycemia.

General: Weakness.

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

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment exacerbation of hepatitis B (see WARNINGS and PRECAUTIONS).

Hypersensitivity: Anaphylaxis, urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, rash, pruritus.

Stavudine:

Adults

Fatal lactic acidosis has occurred in patients treated with stavudine in combination with other antiretroviral agents. Patients with suspected lactic acidosis should immediately suspend therapy with stavudine. Permanent discontinuation of stavudine should be considered for patients with confirmed lactic acidosis.

Stavudine therapy has rarely been associated with motor weakness, occurring predominantly in the setting of lactic acidosis. If motor weakness develops, stavudine should be discontinued.

Stavudine therapy has also been associated with peripheral sensory neuropathy, which can be severe, is dose related, and occurs more frequently in patients being treated with other drugs that have been associated with neuropathy (including didanosine), in patients with advanced HIV infection, or in patients who have previously experienced peripheral neuropathy.

Patients should be monitored for the development of neuropathy, which is usually manifested by numbness, tingling, or pain in the feet or hands. Stavudine-related peripheral neuropathy may resolve if therapy is withdrawn promptly. In some cases, symptoms may worsen temporarily following discontinuation of therapy. If neuropathy recurs after resumption, permanent discontinuation of stavudine should be considered.

When stavudine is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when stavudine is used alone. Pancreatitis, peripheral neuropathy, and liver function abnormalities occur more frequently in patients treated with the combination of stavudine and didanosine, with or without hydroxyurea. Fatal pancreatitis and hepatotoxicity may occur more frequently in patients treated with stavudine in combination with didanosine and hydroxyurea (see **WARNINGS** and **PRECAUTIONS**).

Selected clinical adverse events that occurred in adult patients receiving stavudine in a controlled monotherapy study (Study AI455-019) are provided in Table 7

Table 7 : Selected Clinical Adverse Events in Study AI455-019^a (Monotherapy)		
Adverse Events	Percent (%)	
	stavudine ^b (40 mg twice daily) (n=412)	zidovudine (200 mg 3 times daily) (n=402)
Headache	54	49
Diarrhea	50	44
Peripheral Neurologic Symptoms/Neuropathy	52	39
Rash	40	35
Nausea and Vomiting	39	44

^a Any severity, regardless of relationship to study drug.
^b Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.

Pancreatitis was observed in 3 of the 412 adult patients who received stavudine in a controlled monotherapy study.

Selected clinical adverse events that occurred in antiretroviral-naive adult patients receiving stavudine from two controlled combination studies are provided in Table 8.

Table 8: Selected Clinical Adverse Events^a in START 1 and START 2^b Studies (Combination Therapy)				
Adverse Events	Percent (%)			
	START 1		START 2 ^b	
	stavudine + lamivudine+ indinavir (n=100 ^c)	zidovudine+ lamivudine+ indinavir (n=102)	stavudine + didanosine+ indinavir (n=102 ^c)	zidovudine+ lamivudine+ indinavir (n=103)
Nausea	43	63	53	67
Diarrhea	34	16	45	39
Headache	25	26	46	37
Rash	18	13	30	18
Vomiting	18	33	30	35
Peripheral Neurologic Symptoms/Neuropathy	8	7	21	10

^a Any severity, regardless of relationship to study regimen.
^b START 2 compared two triple-combination regimens in 205 treatment-naive patients. Patients received either lamivudine/stavudine tablets (40 mg twice daily) plus didanosine plus indinavir or zidovudine plus lamivudine plus indinavir.
^c Duration of stavudine therapy = 48 weeks.

Pancreatitis resulting in death was observed in patients treated with stavudine plus didanosine, with or without hydroxyurea, in controlled clinical studies and in postmarketing reports.

Selected laboratory abnormalities reported in a controlled monotherapy study (Study AI455-019) are provided in Table 9.

Table 9 : Selected Adult Laboratory Abnormalities in Study AI455-019^{a,b}		
Parameter	Percent (%)	
	stavudine (40 mg twice daily) (n=412)	zidovudine (200 mg 3 times daily) (n=402)
	AST (SGOT) (>5.0 x ULN)	11
ALT (SGPT) (>5.0 x ULN)	13	11
Amylase (≥ 1.4 x ULN)	14	13

^aData presented for patients for whom laboratory evaluations were performed.
^bMedian duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.
 ULN = upper limit of normal.

Selected laboratory abnormalities reported in two controlled combination studies are provided in Tables 10 and 11.

Table 10: Selected Laboratory Abnormalities in START 1 and START 2 Studies (Grades 3-4)				
Parameter	Percent (%)			
	START 1		START 2	
	stavudine + lamivudine+ indinavir (n=100)	zidovudine+ lamivudine+ indinavir (n=102)	stavudine + didanosine+ indinavir (n=102)	zidovudine+ lamivudine+ indinavir (n=103)
Bilirubin (>2.6 x ULN)	7	6	16	8
AST (SGOT) (>5 x ULN)	5	2	7	7
ALT (SGPT) (>5 x ULN)	6	2	8	5
GGT (>5 x ULN)	2	2	5	2
Lipase (>2 x ULN)	6	3	5	5
Amylase (>2 x ULN)	4	<1	8	2

ULN = upper limit of normal.

Table -11: Selected Laboratory Abnormalities in START 1 and START 2 Studies (All Grades)				
Parameter	Percent (%)			
	START 1		START 2	
	stavudine + lamivudine+ indinavir (n=100)	zidovudine+ lamivudine+ indinavir (n=102)	stavudine + didanosine+ indinavir (n=102)	zidovudine+ lamivudine+ indinavir (n=103)
Total Bilirubin	65	60	68	55
AST (SGOT)	42	20	53	20
ALT (SGPT)	40	20	50	18
GGT	18	8	28	12
Lipase	27	12	26	19
Amylase	21	19	31	17

Observed During Clinical Practice

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

Body as a Whole — abdominal pain, allergic reaction, chills/fever, and redistribution/accumulation of body fat (see **PRECAUTIONS: Fat Redistribution**).

Digestive Disorders — anorexia and Stomatitis

Exocrine Gland Disorders — hyperglycemia, pancreatitis [including fatal cases (see **WARNINGS**)].

Hematologic Disorders — anemia, leukopenia, thrombocytopenia, macrocytosis, lymphadenopathy and splenomegaly.

Liver — symptomatic hyperlactatemia/lactic acidosis and hepatic steatosis (see **WARNINGS**), hepatitis and liver failure and post treatment exacerbation of hepatitis B.

Musculoskeletal — myalgia, CPK elevations, rhabdomyolysis

Nervous System — insomnia, severe motor weakness, paresthesia, peripheral neuropathy (most often reported in the setting of lactic acidosis, see **WARNINGS**).

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, rash, pruritus

OVERDOSAGE

Lamivudine:

There is no known antidote for lamivudine. One case of an adult ingesting 6 g 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. There were no clinical signs or symptoms noted in either case. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

Stavudine: Experience with adults treated with 12 to 24 times the recommended daily dosage revealed no acute toxicity. Complications of chronic overdosage include peripheral neuropathy and hepatic toxicity. Stavudine can be removed by hemodialysis; the mean \pm SD hemodialysis clearance of stavudine is 120 ± 18 mL/min. Whether Stavudine is eliminated by peritoneal dialysis has not been studied.

DOSAGE AND ADMINISTRATION

The interval between doses of lamivudine/stavudine tablets should be 12 hours. Lamivudine/Stavudine tablets may be taken with or without food.

Adults: The recommended dose based on body weight is as follows:

150/40 mg twice daily for patients ≥ 60 kg.

150/30 mg twice daily for patients < 60 kg.

Pediatrics:

150 mg/ 30 mg twice daily for children weighing ≥ 30 kg and < 60 kg and > 12 years of age

150 mg/ 40 mg twice daily for children weighing ≥ 60 kg and > 12 years of age

Dose Adjustment:

Because it is a fixed-dose combination, Lamivudine/Stavudine Tablets should not be prescribed for patients requiring dosage adjustment, such as those with reduced renal function (creatinine clearance ≤ 50 ml/min) and those experiencing dose-limiting adverse events. If peripheral neuropathy recurs after resumption of lamivudine/stavudine tablets, permanent discontinuation should be considered.

HOW SUPPLIED

Lamivudine/Stavudine Tablets, 150 mg/30 mg are pink colored, mottled capsule shaped biconvex uncoated tablet, debossed with "M113" on one side and plain on the other side.

Bottle of 60 tablets NDC-65015-028-17.

Unit dose packages of 20 NDC-65015-028-06

Lamivudine/Stavudine Tablets 150 mg/40 mg are yellow colored, mottled capsule shaped biconvex uncoated tablet, debossed with "M114" on one side and plain on the other side.

Bottle of 60 tablets NDC-65015-029-17.

Unit dose packages of 20 NDC-65015-029-06

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

Manufactured by:



Secunderabad, INDIA.
October 2007

PATIENT INFORMATION

Lamivudine/Stavudine Tablets

Rx Only

What are lamivudine/stavudine tablets?

Lamivudine (lah MIH vue deen) and stavudine (STA vue deen) is a prescription medicine used in combination with other drugs to treat adults and children who are infected with HIV (the human immunodeficiency virus), the virus that causes AIDS. Lamivudine and stavudine belongs to a class of drugs called nucleoside reverse transcriptase inhibitors (NRTIs). By reducing the growth of HIV, lamivudine and stavudine helps your body maintain its supply of CD4 cells, which are important for fighting HIV and other infections.

Lamivudine and stavudine tablets will not cure your HIV infection. At present there is no cure for HIV infection. Even while taking Lamivudine and stavudine tablets, you may continue to have HIV-related illnesses, including infections caused by other disease-producing organisms. Continue to see your doctor regularly and report any medical problems that occur.

Lamivudine and stavudine tablets does not prevent a person infected with HIV from passing the virus to other people. To protect others, you must continue to practice safe sex and take precautions to prevent others from coming in contact with your blood and other body fluids.

There is limited information on the long-term use of stavudine in lamivudine/stavudine tablets.

Who should not take lamivudine/stavudine tablets?

People weighing less than 30 kg or children under the age of 12 should not take lamivudine/stavudine tablets.

- Do not take lamivudine/stavudine tablets if you are allergic to any of its ingredients, including its active ingredients, lamivudine or stavudine, and the inactive ingredients. (See **Inactive Ingredients** at the end of this leaflet.) Tell your doctor if you think you have had an allergic reaction to any of these ingredients.
- Do not restart the medication after you recover from side effects of this medication such as serious blood problems, lactic acidosis, serious liver reactions, until your doctor advises.
- Do not take these medications if you take certain other medicines. (See “other medications to be avoided” for a list of medicines.)

How should I take lamivudine/stavudine tablets? How should I store it?

Your doctor will determine your dose based on your body weight, kidney and liver function, and any side effects that you may have had with other medicines. Take lamivudine/stavudine tablets exactly as instructed. Try not to miss a dose, but if you do, take it as soon as possible. If it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. Lamivudine/stavudine tablets may be taken with food or on an empty stomach.

- Lamivudine/stavudine tablets are usually taken twice a day (every 12 hours). Store lamivudine/stavudine tablets in a tightly closed container at room temperature away from heat and out of the reach of children and pets. Do NOT store this medicine in a damp place such as a bathroom medicine cabinet or near the kitchen sink.

If you have a kidney problem: If your kidneys are not working properly, your doctor may monitor your kidney function while you take lamivudine/stavudine tablets and may even consider discontinuation of therapy.

What should I do if someone takes an overdose of lamivudine/stavudine tablets?

If you suspect that you or someone else has taken an overdose of lamivudine/stavudine tablets, get medical help right away. Contact a doctor or a poison control center.

What important information should I know about taking lamivudine/stavudine tablets with other medicines?

- Do not take zidovudine (AZT) while taking lamivudine/stavudine tablets, because AZT may interfere with the actions of lamivudine/stavudine tablets. Products containing AZT include Combivir[®], Retrovir[®], Epzicom[®] and Trizivir[®].
- If you are taking ribavirin or interferon, your doctor may need to monitor your therapy more closely or may consider a change in your therapy.

Tell your doctor or pharmacist about any other medicine, vitamin, supplement, or herbal preparation you are taking.

What about pregnancy and nursing (breast-feeding)?

- It is not known if lamivudine/stavudine tablets can harm a human fetus. Pregnant women have experienced serious side effects when taking stavudine (one of the active ingredient in lamivudine/stavudine tablets) in combination with didanosine and other HIV medicines. Lamivudine/stavudine tablets should be used during pregnancy only after discussion with your

doctor. **Tell your doctor if you become pregnant or plan to become pregnant while taking lamivudine/stavudine tablets.**

- Because studies have shown stavudine (one of the active ingredient in lamivudine/stavudine tablets) is in the breast milk of animals receiving the drug, it may be present in human breast milk. The Centers for Disease Control and Prevention (CDC) recommend that HIV-infected mothers **not** breast-feed to reduce the risk of passing HIV infection to their babies and the potential for serious adverse reactions in nursing infants. Therefore, do not nurse a baby while taking lamivudine/stavudine tablets.

What are the possible side effects of lamivudine/stavudine tablets?

- **Lactic acidosis**, severe increase of lactic acid in the blood, **severe liver enlargement**, including inflammation (pain and swelling) of the liver, and **liver failure**, which can cause death, have been reported among patients taking stavudine (one of the active ingredient in lamivudine/stavudine tablets). **Symptoms of lactic acidosis may include:**
 - **nausea, vomiting, or unusual or unexpected stomach discomfort;**
 - **feeling very weak and tired;**
 - **shortness of breath;**
 - **weakness in arms and legs.**

If you notice these symptoms or if your medical condition has suddenly changed, stop taking lamivudine/stavudine tablets and call your doctor right away. Lactic acidosis is a medical emergency that must be treated in a hospital. Women (including pregnant women), overweight patients, and those who have had lengthy treatment with nucleoside medicines are more likely to develop lactic acidosis. The combination of stavudine (one of the active ingredient in lamivudine/stavudine tablets), didanosine, and hydroxyurea may increase your risk for liver damage, which may cause death. Your doctor should closely monitor your liver function if you are taking this combination or if you are taking lamivudine/stavudine tablets and have a history of heavy alcohol use or a liver condition.

- **Peripheral neuropathy** is a nerve disorder of the hands and feet. If not recognized promptly, this disorder may worsen. **Tell your doctor right away** if you taking lamivudine/stavudine tablets has continuing numbness, tingling, burning, or pain in the feet and/or hands. Let your doctor know if you have ever had peripheral neuropathy, because this condition occurs more often with lamivudine/stavudine in patients who have had neuropathy previously. Peripheral neuropathy is also more likely to occur in patients taking drugs that affect the nerves and in patients with advanced HIV disease, but it can occur at any disease stage. If you develop peripheral neuropathy, your doctor may

tell you to stop taking lamivudine/stavudine tablets. In some cases the symptoms worsen for a short time before getting better.

- **Pancreatitis** is a dangerous inflammation of the pancreas. It may cause death. **Tell your doctor right away if you develop stomach pain, nausea, or vomiting. These can be signs of pancreatitis.** Let your doctor know if you have ever had pancreatitis, regularly drink alcoholic beverages, or have gallstones. Pancreatitis occurs more often in patients with these conditions. It is also more likely in people with advanced HIV disease, but can occur at any disease stage. The combination of stavudine (one of the active ingredient in lamivudine/stavudine tablets) and didanosine, with or without hydroxyurea, may increase your risk for pancreatitis.

People who take lamivudine/stavudine tablets along with other medicines that may cause similar side effects may have a higher chance of developing these side effects than if they took lamivudine/stavudine tablets alone.

Other side effects: In addition to peripheral neuropathy, the most frequent side effects observed in studies of adults taking the recommended dose of lamivudine/stavudine tablets were headache, diarrhea, rash, nausea, and vomiting. Other side effects may include abdominal pain, muscle pain, insomnia, loss of appetite, chills or fever, allergic reactions, and blood disorders.

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck (“buffalo hump”), breast, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

Inactive Ingredients:

Lamivudine/stavudine tablets: Colloidal silicon dioxide, ferric oxide red (in 150 mg/30 mg strength tablets) or ferric oxide yellow (in 150 mg/40 mg strength tablets), microcrystalline cellulose, sodium starch glycolate, and magnesium stearate.

This medicine was prescribed for your particular condition. Do not use lamivudine/stavudine tablets for another condition or give it to others. Keep lamivudine/stavudine tablets and all other medicines out of the reach of children. Throw away lamivudine/stavudine tablets when it is outdated or no longer needed by flushing it down the toilet or pouring it down the sink.

This summary does not include everything there is to know about lamivudine/stavudine tablets. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you have questions or concerns, or want more information about lamivudine/stavudine tablets, your physician and pharmacist have the complete prescribing information upon which this leaflet was based. You may want to read it and discuss it with your doctor or

other healthcare professional. Remember, no written summary can replace careful discussion with your doctor.

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