Stavudine and Lamivudine Tablets
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 STAVUDINE, LAMIVUDINE AND OTHER ANTIRETROVIRALS (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 OCCURED DURING THERAPY WHEN STAVUDINE WAS PART OF A COMBINATION REGIMEN THAT INCLUDED DIDANOSINE, WITH OR WITHOUT HYDROXYUREA, IN BOTH TREATMENT–NAIVE AND TREATMENT EXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF 1 IMMUNOSUPPRESSION (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. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE LAMIVUDINE AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

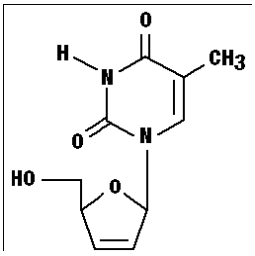
DESCRIPTION

Stavudine and lamivudine tablets are for oral administration. Each uncoated tablet contains the active ingredients 40mg of stavudine and 150mg of lamivudine, and the inactive ingredients microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium, ferric oxide red, povidone, magnesium stearate and purified water.

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

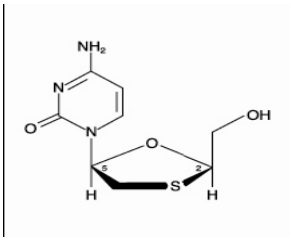
Lamivudine (3TC) is a synthetic nucleoside analogue with activity against HIV-1 and HBV.

Stavudine: The chemical name for stavudine is 2', 3'-didehydro-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 224.22. 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: 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 $C_8H_{11}N_3O_3S$ 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.

MICROBIOLOGY

MECHANISM OF ACTION

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 μM) 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.

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 mitochondrial DNA polymerase γ.

IN VITRO HIV SUSCEPTIBILITY

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 0.0009 to 4μM 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 μM concentrations tested, reduced the antiHIV-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 bas not been established

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 μM (1 μM = 0.23 mcg/mL). HIV from therapy-naive subjects with no mutations associated with resistance gave median EC_{50} values of 0.426 μM (range: 0.200 to 2.007 μM) from Virco (n = 93 baseline samples from COLA40263) and 2.35 μM (1.44 to 4.08 μM) 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 μM, and against HIV-2 isolates from 0.003 to 0.120 μM in peripheral blood mononuclear cells. Ribavirin (50 μM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells. In HIV– 1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity.

RESISTANCE

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 IC_{50} 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.

Lamivudine: Lamivudine-resistant variants of HIV-1 have been selected 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 residue to either isoleucine or valine (M 184 V/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 mono therapy 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 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).

CROSS-RESISTANCE

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

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.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults:

Stavudine and Lamivudine Tablets:

The rate and extent of absorption of Stavudine and Lamivudine from the combination tablets was similar to that from Zerit® capsules and Epivir® tablets, respectively, when administered to healthy volunteers in the fasted state. The effect of food on Stavudine and Lamivudine Tablets has not been evaluated.

Stavudine: The pharmacokinetics of stavudine have been evaluated in HIV-infected adult and pediatric patients (Tables 1-3). Peak plasma concentrations (Cmax) and area under the plasma concentration-time curve (AUC) increased in proportion to dose after both single and multiple doses ranging from 0.03 to 4mg/kg. There was no significant accumulation of stavudine with repeated administration every 6, 8, or 12 hours.

ABSORPTION AND BIOAVAILABILITY

Stavudine: 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 tablet or capsules or solution. Steady-state pharmacokinetic parameters of stavudine in HIV infected adults are shown in Table 1.

Table 1: Steady-State Pharmacokinetic Parameters of Stavudine in HIV Infected Adults

Parameter	Stavudine 40 mg BID Mean ± SD (n=8)
AUC (ng•h/mL)[a]	2568 ± 454
C_{max} (ng/mL)	536 ± 146
C_{min} (ng/mL)	8 ± 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.

Lamivudine: 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. An investigational 25-mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-infected patients on 2 occasions, once in the fasted state and once with food (1,099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate). Absorption of lamivudine was slower in the fed state (T_{max}: 3.2 ± 1.3 hours) compared with the fasted state (T_{max}: 0.9 ± 0.3 hours); C_{max} in the fed state was 40% ± 23% (mean SD) lower than in the fasted state. There was no significant difference in systemic exposure (AUC∞) in the fed and fasted states; therefore, lamivudine tablets and oral solution may be administered with or without food.The accumulation ratio of lamivudine in HIV-positive asymptomatic adults with normal renal function was 1.50 following 15 days of oral administration of 2 mg/kg twice daily.

DISTRIBUTION

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

Table 2: Pharmacokinetic Parameters of Stavudine in HIV-Infected Adults: Bioavailability, Distribution, and Clearance

Parameter	Mean ± SD	n
Oral bioavailability (%)	86.4 ± 18.2	25
Volume of distribution (L)[a]	46 ± 21	44
Total body clearance (mL/min)[a]	594 ± 164	44
Apparent oral clearance (mL/min)[b]	560 ± 182 [c]	113
Renal clearance (mL/min)a	237 ± 98	39
Elimination half-life, IV dose (h)[a]	1.15 ± 0.35	44
Elimination half-life, oral dose (h)[b]	1.6 ± 0.23	8
Urinary recovery of stavudine (% of dose)[a,d]	42 ± 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.

Lamivudine: 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 extra vascular spaces. Volume of distribution was independent of dose and did not correlate with body weight. Binding of lamivudine to human plasma proteins is low (<36%). In vitro studies showed that, over the concentration range of 0.1 to 100 mcg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

METABOLISM / ELIMINATION

Stavudine: The metabolic fate of stavudine has not been elucidated in humans. Renal elimination accounted 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 persumably eliminated by endogenous pathways.

Lamivudine: 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.
The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300-mg oral dose of lamivudine, renal clearance was 199.7 ± 56.9 mL/min (mean ± SD). In 20 HIV-infected patients given a single IV dose, renal clearance was 280.4 ± 75.2 mL/min (mean ± SD), representing 71% ± 16% (mean ± SD) of total clearance of lamivudine. In most single-dose studies in HIV-infected patients, HBV-infected patients, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life (t½) ranged from 5 to 7 hours. In HIV-infected patients, total clearance was 398.5 ± 69.1 mL/min (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range from 0.25 to 10 mg/kg.

Effect of Food on Absorption of Lamivudine and Stavudine.

The effect of food on the rate and extent of absorption of Stavudine and Lamivudine combination tablets has not been evaluated in a clinical study. Therefore, Stavudine and Lamivudine combination tablets should be taken under fasting conditions.

PHARMACOKINETICS IN SPECIAL POPULATIONS

RENAL IMPAIRMENT:

Adjustment of the dose of stavudine or lamivudine is not possible with this fixed dose combination. Therefore, Stavudine and Lamivudine Tablets are not recommended for patients with creatinine clearance ≤ 50 mL.min.

HEPATIC IMPAIRMENT

Stavudine: Stavudine pharmacokinetics were not altered in 5 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.

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.

Pregnancy: See PRECAUTIONS: Pregnancy
No data are available on pharmacokinetics of Stavudine and Lamivudine during pregnancy.

Nursing Mothers: See PRECAUTIONS: Nursing Mothers

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

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.

Pediatric Patients:
The pharmacokinetics of Stavudine and Lamivudine Tablets have not been studied in pediatric patients. Because it is a fixed-dose combination that cannot be adjusted for this patient population, Stavudine and Lamivudine Tablets should not be administered to pediatric patients who weigh less than 60 kg or who are younger than 12 years of age.

Geriatric Patients:
The pharmacokinetics of Stavudine and Lamivudine Tablets have not been studied in patients over 65 years of age.

Gender
Stavudine and Lamivudine: There are no significant gender differences in lamivudine or stavudine pharmacokinetics.

Race
Stavudine and Lamivudine: There are no significant racial differences in lamivudine or stavudine pharmacokinetics.

DRUG INTERACTIONS

No drug interaction studies have been conducted with the Stavudine and Lamivudine Combination Tablets.

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

In vitro data indicate that the phosphorylation of stavudine is inhibited at relevant concentrations by doxorubicin and ribavirin.

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 co-administration of stavudine with didanosine, lamivudine, and nelfinavir. No clinically significant pharmacokinetic interactions were observed.

Table 3: Results of Drug Interaction Studies with stavudine: Effects of Co-administered Drug on Stavudine Plasma AUC and C_{max} Values

Drug	Stavudine Dosage	n[a]	AUC of Stavudine (95% CI)	C_{max} of Stavudine (95% CI)
Didanosine, 100 mg q12h for 4 days	40 mg q12h for 4 days	10	↔	↑17%
Lamivudine, 150 mg single dose	40 mg single dose	18	↔ (92.7-00.6%)	↑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.

Table 4: Results of Drug Interaction Studies with Stavudine: Effects of Stavudine on Co-administered Drug Plasma AUC and C_{max} Values

Drug	Stavudine Dosage	n[a]	AUC of Co-administered Drug (95% CI)	C_{max} of Co-administered Drug (95% CI)
Didanosine, 100 mg q12h for 4 days	40 mg q12h for 4 days	10	↔	↔
Lamivudine, 150 mg 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.

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 co-administered 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. Co-administration of TMP/SMX with lamivudine resulted in an increase of 43% ± 23% (mean ± SD) in lamivudine AUC, a decrease of 29% ± 13% in lamivudine oral clearance, and a decrease of 30% ± 36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by co-administration 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.

INDICATIONS AND USAGE

Stavudine and Lamivudine Tablets in combination with other antiretroviral agents are indicated for the treatment of HIV-1 infection in patients that weigh ≥60kg and are 12 years of age or older.

CONTRAINDICATIONS

Stavudine and lamivudine fixed dose combination tablet is contraindicated in patients with clinically significant hypersensitivity to any of the components contained in the tablet.

WARNINGS

Stavudine and Lamivudine Tablets should not be administered concomitantly with formulations containing either of the two drugs. The complete prescribing information for all agents being considered for use with Stavudine and Lamivudine Tablets should be consulted before combination therapy with Stavudine and Lamivudine Tablets is initiated.

Stavudine and Lamivudine:

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 stavudine and other antiretrovirals. Although relative rates of lactic acidosis have not been assessed in prospective well-controlled trials, longitudinal cohort and retrospective studies suggest that this infrequent event may be more often associated with antiretroviral combinations containing stavudine. Female gender, obesity, and prolonged nucleoside exposure may be risk factors. 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 PRECAUTIONS: Pregnancy).

Particular caution should be exercised when administering stavudine to any patient with known risk factors for liver disease; however, cases of lactic acidosis have also been reported in patients with no known risk factors. Generalized fatigue, digestive symptoms (nausea, vomiting, abdominal pain, and sudden unexplained weight loss); respiratory symptoms (tachypnea and dyspnea); or neurologic symptoms might be indicative of lactic acidosis syndrome development.

Treatment with stavudine should be suspended in any patient who develops clinical or laboratory findings suggestive of symptomatic hyperlactatemia, lactic acidosis, or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Use with Interferon and Ribavirin-Based Regimens
In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as stavudine. Although no evidence of a pharmacokinetic or pharmacodynamic (eg, loss of HIV/HCV virologic suppression) interaction was seen when ribavirin was coadministered with stavudine in HIV/HCV co-infected patients., 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 and stavudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of stavudine 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).

Stavudine
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-Barre 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, a history of neuropathy, or concurrent neurotoxic drug therapy, including didanosine (see ADVERSE REACTIONS).

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 pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities, including severe and potentially fatal hepatic advese 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.

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. Patients treated with this combination should be closely monitored for signs of liver toxicity.

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-naive 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.

Lamivudine
Post treatment 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 alanine transaminase (ALT) elevations in addition to re-emergence of hepatitis B virus (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 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of post treatment exacerbations of hepatitis.

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

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

PRECAUTIONS

Stavudine and Lamivudine

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including stavudine. 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 jirovecipneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

Fat Redistribution: 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.

Patients with Impaired Renal Function*:* Stavudine and Lamivudine Tablets are not recommended for patients with CrCL ≤ 50 mL/min or for patients on hemodialysis.

If dose adjustment is required, Stavudine and Lamivudine Tablets should not be administered because the tablet contains a fixed-dose combination of lamivudine and stavudine.

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 (see EPIVIR-HBV package insert for additional information).

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. Post-treatment exacerbations of hepatitis have also been reported (see WARNINGS).

INFORMATION FOR PATIENTS

Stavudine and Lamivudine Tablets:
Stavudine and Lamivudine Tablets are for oral ingestion only.
Patients should be advised of the importance of taking Stavudine and Lamivudine Tablets on a regular dosing schedule and to avoid missing doses.

Patients should be advised Stavudine and Lamivudine Tablets should be taken under fasting conditions.

Patients should be informed that Stavudine and Lamivudine Tablets are not a cure for HIV-1 infection, and that they may continue to acquire illnesses associated with HIV-1 infection, including opportunistic infections. They should be advised that this combination therapy has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination.

Patients should be advised to remain under the care of a physician when using Stavudine and Lamivudine Tablets.

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.

Patients should be informed to take Stavudine and Lamivudine Tablets every day as prescribed. Patients should not alter the dose without consulting their doctor. If a dose is missed, patients should take the next dose as soon as possible. However, if a dose is skipped, the patient should not double the next dose. Patients should be advised to report to their doctor the use of any other medications.

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 therapy may be required.

Caregivers of young children receiving stavudine therapy should be instructed regarding detection and reporting of peripheral neuropathy.

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 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. Patients treated with this combination should be closely monitored for

symptoms of pancreatitis. An increased risk of hepatotoxicity, which may be fatal, may occur in patients treated with stavudine in combination with didanosine and hydroxyurea. This combination should be avoided.

Patients should be informed that stavudine is not a cure for HIV infection, and that they may continue to acquire illnesses associated with HIV infection, including opportunistic infections. Patients should be advised to remain under the care of a physician when using stavudine. They should be advised that stavudine therapy has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination. Patients should be informed that the long-term effects of stavudine are unknown at this time.
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.
Patients should be advised of the importance of adherence to any antiretroviral regimen, including those that contain stavudine.

Lamivudine:
Patients should be advised that Stavudine and Lamivudine Tablets contain a higher dose of the same active ingredient (lamivudine) as EPIVIR-HBV tablets and oral solution. If a decision is made to include lamivudine in the HIV treatment regimen of a patient dually infected with HIV and HBV, the formulation and dosage of lamivudine in Stavudine and Lamivudine Tablets (not EPIVIR-HBV) should be used.

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. Patients should be advised that the long-term effects of lamivudine are unknown at this time.

Parents or guardians should be advised to monitor pediatric patients for signs and symptoms of pancreatitis.

DRUG INTERACTIONS

Stavudine® See CLINICAL PHARMACOLOGY: DRUG INTERACTIONS) Zidovudine may competitively inhibit the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with stavudine should be avoided.
In vitro data indicate that the phosphorylation of stavudine is also inhibited at relevant concentrations by doxorubicin and ribavirin. The clinical significance of these in vitro interactions is unknown; therefore, concomitant use of stavudine with either of these drugs should be undertaken with caution. (See WARNINGS.)

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 Pneumocystis carinii pneumonia. 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, IMPAIRMENT OF FERTILITY

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 micronucleus 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.

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.

PREGNANCY

Pregnancy Category C

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

Stavudine: 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 non pregnant 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.

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 embryo lethality 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 that 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

NURSING MOTHERS

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

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.

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.

PEDIATRIC USE

The pharmacokinetics of Stavudine and Lamivudine Tablets have not been studied in pediatric patients. Because it is a fixed-dose combination that cannot be adjusted for this patient population, Stavudine and Lamivudine Tablets should not be administered to pediatric patients who weigh less than 60 kg or who are younger than 12 years of age.

GERIATRIC USE:
Clinical studies of Stavudine and Lamivudine did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. 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. Since Stavudine and Lamivudine Tablets are a fixed-dose combination, it should not be prescribed for patients who require dose reduction or have renal impairment with CrCL <50 mL/min.

Stavudine
Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

In a monotherapy Expanded Access Program for patients with advanced HIV infection, peripheral neuropathy or peripheral neuropathic symptoms were observed in 15/40 (38%) elderly patients receiving 40 mg twice daily and 8/51 (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

Adverse events reported with Stavudine and Lamivudine may be expected with the use of Stavudine and Lamivudine Tablets. The adverse events reported with Stavudine and Lamivudine are presented below.

Stavudine:
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 stavudien 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 neurotoxic drug therapy, 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 symptoms resolve completely, patients may tolerate resumption of treatment at one-half the dose (see DOSAGE AND ADMINISTRATION). 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 (stavudine) in a controlled monotherapy study are provided in Table 5.

Table 5: Selected Clinical Adverse Events in a Monotherapy Study

	Percent (%)	
Adverse Events	**Stavudine[b] (40 mg twice daily) (n=412)**	**Zidovudine (200 mg 3 times daily) (n=402)**

[a] Any severity, regardless of relationship to study drug.

[b] Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.

Headache	54	49
Diarrhea	50	44
Peripheral Neurologic Symptoms/Neuropathy	52	39
Rash	40	35
Nausea and Vomiting	39	44

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 6.

Table 6: Selected Clinical Adverse Events in START 1 and START 2[b] Studies (Combination Therapy)

	Percent (%)			
	START 1		START 2b	
Adverse Events	**Stavudine + lamivudine + indinavir (n=100[c])**	**zidovudine + lamivudine + indinavir (n=102)**	**Stavudine + didanosine + indinavir (n= 102[c])**	**zidovudine + lamivudine + indinavir (n=103)**

[a] Any severity, regardless of relationship to study regimen.

[b] START 2 compared two triple-combination regimens in 205 treatment-naive patients. Patients received stavudine (40 mg twice daily) plus didanosine plus indinavir or zidovudine plus lamivudine plus indinavir.

[c] Duration of stavudine therapy = 48 weeks.

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

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 10.

Table 7: Selected Adult Laboratory Abnormalities in a Monotherapy Study [a,b]

	Percent (%)	
Parameter	**Stavudine (40 mg twice daily) (n=412)**	**zidovudine (200 mg 3 times daily) (n=402)**

[a] Data presented for patients for whom laboratory evaluations were performed.

[b] Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.

ULN = upper limit of normal.

AST (SGOT) (>5.0 x ULN)	11	10
ALT (SGPT) (>5.0 x ULN)	13	11
Amylase (≥1.4 x ULN)	14	13

Observed During Clinical Practice
The following events have been identified during post-approval use of stavudine. 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, 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.
Exocrine Gland Disorders – pancreatitis including fatal cases (see WARNINGS)].
Hematologic Disorders - anemia, leukopenia, thrombocytopenia and macrocytosis.
Liver - lactic acidosis and hepatic steatosis and hepatic steatosis (see WARNINGS), hepatitis and liver failure.
Musculoskeletal - myalgia.
Nervous System- insomnia, severe motor weakness (most often reported in the setting of lactic acidosis, see WARNINGS).

Lamivudine: Clinical Trials in HIV:

Adults: Selected clinical adverse events with a ≥5% frequency during therapy with lamivudine 150 mg twice daily plus zidovudine 200 mg 3 times daily compared with zidovudine are listed in Table 8.

Table 8: Selected Clinical Adverse Events (≥5% Frequency) in Four Controlled Clinical Trials (A3001, A3002, B3001, B3002)

Adverse Event	**Lamivudine 150 mg Twice Daily Plus zidovudine (n = 251)**	**zidovudine * (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.

The types and frequencies of clinical adverse events reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV 20001 and EPV 40001) were similar. The most common adverse events in both treatment groups were nausea, dizziness, fatigue and/or malaise, headache, dreams, insomnia and other sleep disorders, and skin rash.
Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who received lamivudine in the controlled clinical trials EPV20001, NUCA3001, NUCA3002, NUC3002, and B3007.

Selected laboratory abnormalities observed during therapy are summarized in Table 9.

Table 9: Frequencies of Selected Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Studies (A3001, A3002, B3001, B3002) and a Clinical Endpoint Study (B3007)

	24-Week Surrogate Endpoint Studies*		**Clinical Endpoint Study***	
Test (Threshold Level)	**Lamivudine plus Zidovudine**	**Zidovudine †**	**Lamivudine plus Current Therapy**	**Placebo plus Current Therapy ‡**
Absolute neutrophil count (<750/mm^3)	7.2%	5.4%	15%	13%
Hemoglobin (<8.0 g/dL)	2.9%	1.8%	2.2%	3.4%
Platelets (>5.0 x ULN)	0.4%	1.3%	2.8%	3.8%
ALT (>5.0 x ULN)	3.7%	3.6%	3.8%	1.9%
AST(>5.0 x ULN)	1.7%	1.8%	4.0%	2.1%
Bilirubin (2.5 x ULN)	0.8%	0.4%	ND	ND
Amylase (<2.0 x ULN)	4.2%	1.5%	2.2%	1.1%

***** 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, reported adverse events included anemia, urinary tract infections, and complications of labor and delivery. In post marketing 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.

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 (A2002), 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 (A2005), 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.

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.

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.
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, post treatment exacerbation of hepatitis B.
Hypersensitivity: Anaphylaxis, urticaria.
Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.
Nervous: Paresthesia, peripheral neuropathy.
Respiratory: Abnormal breath sounds/wheezing.
Skin: Alopecia, rash, pruritus.

OVERDOSAGE

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 ± SD hemodialysis clearance of stavudine is 120 ± 18 mL/min. Whether stavudine is eliminated by peritoneal dialysis has not been studied.

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.

DOSAGE AND ADMINISTRATION

Adults: The recommended oral dosage for adults weighing ≥60kg is one Stavudine 40mg and Lamivudine 150mg combination tablet twice daily under fasted conditions.

Pediatrics:

One Stavudine and Lamivudine Tablet (40 mg/ 150 mg**)** tablet twice daily under fasted conditions for patients weighing >60 kg and > 12 years of age.

Dose Adjustment:

Stavudine and Lamivudine 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. In addition, Stavudine and Lamivudine Tablets should not be prescribed for patients who require mg/kg dosing regimen.

HOW SUPPLIED

Stavudine 40mg and lamivudine 150mg fixed dose combination tablet, is a light pink to pink colored, circular, flat bevel edged tablets with LS40 engraved on one side and plain on other side. 60 tablets are packed in a 50ml HDPE container closed by a snap cap with a tear-off tamper-evident strip.

STORAGE:
Stavudine and Lamivudine:
Store below 30˚C. Protect from light. Keep all medicines away from children.

STRIDES ARCOLAB LIMITED, Bangalore- India.

Patient information leaflet
Stavudine and Lamivudine Tablets

Generic name: Stavudine and Lamivudine (STA vue deen and lah MIH vue deen).
Each Tablet contains 150mg of Lamivudine and 40mg of Stavudine

What are Stavudine and Lamivudine Tablets?
Stavudine and Lamivudine Tablets are used in combination with other drugs to treat Human Immunodeficiency Virus (HIV), the virus that causes AIDS (Acquired Immune Deficiency Syndrome).
Stavudine and Lamivudine Tablets are a type of Anti-HIV medications called Nuceloside Reverse Transcriptase Inhibitors (NRTI). They act by reducing the growth of HIV in the body. This combination of stavudine and lamivudine is not a cure for HIV or AIDS. At present there is no cure for HIV infection. Even while taking Stavudine and Lamivudine Tablets, you may continue to have HIV-related illnesses, including infections caused by other disease producing organisms. Continue to see your doctor regularly.

Stavudine and Lamivudine Tablets do not prevent a person infected with HIV from passing the virus to other people. To protect others you must continue to take precautions to prevent others from coming in contact with your blood and other body fluids.

Who Should not take Stavudine and Lamivudine Tablets?
People weighing less than 60 kg (132 pounds) should not take Stavudine and Lamivudine Combination Tablets because these tablets do not contain the correct strength of medicines for these people.

Do not take Stavudine and Lamivudine Tablets if you are allergic to any of its ingredients, including its active ingredients, stavudine and lamivudine. Your doctor or pharmacist can tell you about the inactive 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.)

Tell you doctor if you think you have had an allergic reaction.

How should I take Stavudine and Lamivudine Tablets? How should I store it?
This medication should be taken exactly as directed by your doctor based on body weight, kidney and liver function and any side effects that you may have had with other medicines. If you do not understand these directions, ask your pharmacist, nurse, or doctor to explain them to you.
Stavudine and Lamivudine Tablets should be taken with a full glass of water and without food. If you miss a dose, take it as soon as possible. If it is time for the next dose, skip the missed dose and continue your regularly scheduled dose. **Do not** take a double dose

Stavudine and Lamivudine Tablets are usually taken 1 two times daily (every 12 hours). Store Stavudine and Lamivudine Tablets in a tightly closed container at room temperature away from heat and out of reach of children. Do Not store this medicine in damp place and protect the medicine from light.

This medication should be taken regularly.

<u>What Should I do if someone takes an overdose of Stavudine and Lamivudine Tablets?</u>
If you suspect that you or someone else has taken an overdose of Stavudine and Lamivudine Tablets, get medical help right away. Contact a doctor or a poison control center.

Can I take other medicines while taking Stavudine and Lamivudine Tablets?

Other medications may interact with this medication resulting in decreased effectiveness and/or side effects. Talk to your doctor and pharmacist before taking any other prescription or over-the-counter medicines, including vitamins, minerals, and herbal products, during treatment.

What about pregnancy and nursing (breast-feeding)?

Stavudine and Lamivudine Tablets should be used in pregnancy only after talking with your doctor. Tell your doctor if you become pregnant or plan to become pregnant while taking Stavudine and Lamivudine Tablets.

The Centers for Disease Control and Prevention (CDC) recommends 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, no not breast-feed a baby while taking Stavudine and Lamivudine Tablets.

What are the possible side effects of Stavudine and Lamivudine Tablets?

The undesirable effects of stavudine and lamivudine tablets are:

- Lactic acidosis, severe increase of lactic acid in the blood, severe liver enlargement, sometimes including inflammation (pain and swelling) of the liver and liver failure, which can cause death. 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 Stavudine and Lamivudine Tablets and call you doctor right away. Women (including pregnant women), overweight patients, and those who have taken nucleoside medicines for a long time are more likely to develop lactic acidosis. The combination of Stavudine and Lamivudine Tablets, didanosine and hydroxyurea my increase your risk of liver damage, which may cause death. Your doctor should closely monitor your liver function if you are taking this combination of if you are taking Stavudine and Lamivudine Tablets and have a history of heavy alcohol use or a liver condition.

- Peripheral Neuropathy is a nerve disorder of the hands and feet. Tell your doctor right away if you feel numbness, tingling, burning, or pain in the feet and/or hands.

- 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 and/or fever.

- If you experience any of the following serious side effects, stop taking this combination of stavudine and lamivudine and seek emergency medical attention or notify your doctor immediately:
  - an allergic reaction (difficulty breathing; closing of the throat; swelling of the lips, tongue, or face; or hives);
  - muscle pain or weakness; or
  - peripheral neuropathy (nerve damage), which may cause numbness, tingling, or pain.

Other, less serious side effects may be more likely to occur. Continue taking this medication and talk to your doctor if you experience:

- mild nausea, vomiting, diarrhea, or decreased appetite;
- headache;
- dizziness;
- insomnia;
- redistribution of body fat (loss of fat from the arms, legs, and face and increased fat around the neck, breast, and trunk).
- rash
- fever or chill

Changes in body fat have also been seen in some patients taking antiretroviral therapy. The 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

If your doctor asks you to stop the use of stavudine and lamivudine tablets for any side effect, do not restart stavudine and lamivudine without the advice of your doctor after you have recovered from these side effects.

Inform your doctor

Before taking the combination of stavudine and lamivudine, tell your doctor if you

- have kidney disease;
- have liver disease;
- have or had hepatitis;
- weigh less than 132 pounds (60 kg).
- pancreatitis
- history of peripheral neuropathy (numbness and tingling sensation)

• if you are pregnant. Stavudine and lamivudine combination tablets is FDA pregnancy category C. This means that it is not known whether the combination of lamivudine and stavudine will be harmful to an unborn baby. It is very important to treat HIV/AIDS during pregnancy to reduce the risk of infecting the baby. Talk to your doctor about your treatment options.

• if you are breast feeding.. It is not known whether stavudine and lamivudine passes into breast milk and what affect it may have on a nursing baby. To prevent transmission of the virus to uninfected babies, it is recommended that HIV-positive mothers not breast-feed.

- Do not miss a dose. If you forget a dose , take the missed dose as soon as you remember. However, if it is almost time for the next dose, skip the missed dose and take only the next regularly scheduled dose.
- **Do not** take a double dose of this medication unless your doctor directs otherwise.
- If you miss too many doses, then contact your doctor.
- If you suspect that you have taken too much of this medication, contact your local poison control center or emergency room right away.

Take the following precautions

Follow your doctor's instructions with respect to high-risk activities such as unprotected sex and the sharing of needles. This medication does not cure HIV or AIDS and you can still transmit the virus to others during therapy with this medication.

Avoid alcohol. Alcohol may increase the risk of damage to the pancreas and/or liver.

The Centers for Disease Control and Prevention advises mothers with HIV not to breast feed so they will not pass HIV to the infant through their milk. Ask your doctor about the best way to feed your infant.

General information

Medicines are sometimes prescribed for purposes other than those listed in patient information leaflet. Do not use this medication for a condition for which it was not prescribed. Do not give

these medications to other people, even if they have the same condition you have. It may harm them.
This patient information leaflet summarizes the most important information about stavudine and lamivudine combination tablet. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about these medications.

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