

Lamivir-S

Lamivudine and stavudine tablets

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 STAVUDINE (SEE “WARNINGS AND PRECAUTIONS” SECTION).

SEVERE AND ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HBV AND HIV AND HAVE DISCONTINUED LAMIVUDINE, WHICH IS ONE OF THE COMPONENTS OF THE COMBINATION. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE LAMIVIR-S AND ARE COINFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS AND PRECAUTIONS).

COMPOSITION

LAMIVIR-S – 30

Each tablet contains

Stavudine 30 mg

Lamivudine 150 mg

DESCRIPTION

LAMIVIR-S is a combination of two drugs commonly used in the management of Human Immunodeficiency Virus (HIV) infection. Both stavudine and lamivudine belong to the nucleoside analogue class of antiretroviral drugs. Both drugs act by inhibiting the reverse transcriptase of HIV, and by terminating the growth of the DNA chain. Stavudine in combination with lamivudine has been shown to have synergistic antiretroviral activity.

Each tablet of **LAMIVIR-S** contains half of the commonly prescribed daily doses of both stavudine and lamivudine. With the availability of this combination tablet patients may be better able to adhere to complex drug treatment regimens, thereby enhancing compliance.

PHARMACOLOGY

Pharmacodynamics:

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 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 alpha and beta, and mitochondrial DNA polymerase-gamma.

Stavudine: Stavudine, a nucleoside analogue of thymidine, inhibits the replication of HIV in human cells *in vitro*. Stavudine 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 its incorporation into viral DNA causing a termination of DNA chain elongation because stavudine lacks the essential 3`-OH group. Stavudine triphosphate inhibits cellular DNA polymerase beta and gamma, and markedly reduces the synthesis of mitochondrial DNA.

Pharmacokinetics

Lamivudine

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

The pharmacokinetic properties of lamivudine have also been studied as single and multiple oral doses ranging from 5 to 600 mg/day, administered to HBV -infected patients. The steady-state pharmacokinetic properties of the lamivudine 300 mg tablet once daily for 7 days compared with the lamivudine 150 mg tablet twice daily for 7 days were assessed in a crossover study in 60 healthy volunteers. Lamivudine 300 mg once daily resulted in lamivudine exposures that were similar to lamivudine 150 mg twice daily with respect to the area under the plasma concentration versus time curve ($\text{AUC}_{24,ss}$); however, $C_{\text{max}24,ss}$ was 66% higher and the trough value was 53% lower compared with the 150 mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to $\text{AUC}_{24,ss}$ and $C_{\text{max}24,ss}$; however, trough values were lower compared with the 150 mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations. The clinical significance of observed differences for both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations is not known.

(mean \pm SD) for the 150-mg tablet. 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 \pm SD). The plasma AUC and C_{max} increased in proportion to the oral dosing range of 0.25 to 10 mg/kg.

The accumulation ratio of lamivudine in HIV - 1 -positive asymptomatic adults with normal renal function was 1.50 following 15 days of oral administration of 2 mg/kg twice daily.

Effects of Food on Oral Absorption:

An investigational 25-mg dosage form of lamivudine administered orally to 12 asymptomatic, HIV - 1 -infected patients on two occasions, once in the fasted state and once with food (1,099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrates). 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 $40\% \pm 23\%$ (mean \pm 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.

Distribution: The apparent volume of distribution after IV administration of lamivudine to 20 patients was 1.3 ± 0.4 L/kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight. Binding of lamivudine to human plasma proteins is low (<36%). In vitro studies showed that over the concentration range of 0.1 to 100 mcg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

Metabolism: Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose of lamivudine in 6 HIV-infected adults, $5.2\% \pm 1.4\%$ (mean \pm 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 \pm 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 \pm SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range from 0.25 to 10 mg/kg.

Special Populations

Renal Impairment: The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-infected adults with impaired renal function (Table 1).

Table 1: Pharmacokinetic Parameters (Mean ± SD) After a Single 300 mg Oral Dose of Lamivudine in Three Groups of Adults with Varying Degrees of Renal Function

Parameter	Creatinine Clearance Criterion (Number of Subjects)		
	>60 mL/min (n = 6)	10-30 mL/min (n = 4)	<10 mL/min (n = 6)
Creatinine clearance (mL/min)	111 ± 14	28 ± 8	6 ± 2
C _{max} (mcg/mL)	2.6 ± 0.5	3.6 ± 0.8	5.8 ± 1.2
AUC _∞ (mcg·hr/mL)	11.0 ± 1.7	48.0 ± 19	157 ± 74
Cl/F (mL/min)	464 ± 76	114 ± 34	36 ± 11

Exposure (AUC_∞), C_{max}, and half-life increased with diminishing renal function (as

expressed by creatinine clearance). Apparent total oral clearance (Cl/F) of lamivudine decreased as creatinine clearance decreased. T_{max} was not significantly affected by renal function. Based on these observations, it is recommended that the dosage of lamivudine be modified in patients with renal impairment (see **DOSAGE AND ADMINISTRATION**).

Based on a study in otherwise healthy subjects with impaired renal function, hemodialysis increased lamivudine clearance from a mean of 64 to 88 mL/min; however, the length of time of hemodialysis (4 hours) was insufficient to significantly alter mean lamivudine exposure after a single-dose administration. Continuous ambulatory peritoneal dialysis and automated peritoneal dialysis have negligible effects on lamivudine clearance. Therefore, it is recommended that following correction of dose for creatinine clearance, no additional dose modification should be made after routine hemodialysis or peritoneal dialysis. It is not known whether lamivudine can be removed by continuous (24hours) hemodialysis.

Hepatic Impairment: 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.

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

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

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

Stavudine

The pharmacokinetics of stavudine has been evaluated in HIV-infected adult and pediatric patients. Peak plasma concentrations (C_{max}) 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 4 mg/kg. There was no significant accumulation of stavudine with repeated administration every 6, 8, or 12 hours. *Absorption* : Following oral administration, stavudine is rapidly absorbed, with peak plasma concentrations occurring within 1 hour after dosing. The oral bioavailability of stavudine is $86.4 \pm 18.2\%$. The systemic exposure to stavudine is the same following administration as capsules or solution.

Distribution: Binding of stavudine to serum proteins was negligible over the concentration range of 0.01 to 11.4 $\mu\text{g/mL}$. Stavudine distributes equally between red blood cells and plasma. The apparent oral volume of distribution is 46 ± 21 L.

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

Elimination: Renal elimination accounted for about 40% of the overall clearance regardless of the route of administration. The mean renal clearance was about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration. Elimination half-life for oral dose is 1.6 ± 0.23 h.

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

Parameter	Mean \pm 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, I.V. 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 I.V. infusion ^b following single oral dose ^c assuming a body weight of 70 kg ^d over 12–24 hours		

Renal impairment

Data from two studies in adults indicated that the apparent oral clearance of stavudine decreased and the terminal elimination half-life increased as creatinine clearance decreased (see Table 4). C_{max} and T_{max} were not significantly altered by renal impairment. The mean ± SD hemodialysis clearance value of stavudine was 120 ± 18 mL/min (n=12); the mean ± SD percentage of the stavudine dose recovered in the dialysate, timed to occur between 2–6 hours post-dose, was 31 ± 5%. Based on these observations, it is recommended that stavudine dosage be modified in patients with reduced creatinine clearance and in patients receiving maintenance hemodialysis (see **DOSAGE AND ADMINISTRATION**).

Table 3: Mean ± SD Pharmacokinetic Parameter Values of Stavudine^a in Adults with Varying Degrees of Renal Function

	Creatinine Clearance			Hemodialysis Patients ^b (n=11)
	>50 mL/min (n=10)	26-50 mL/min (n=5)	9-25 mL/min (n=5)	
Creatinine clearance (mL/min)	104 ± 28	41 ± 5	17 ± 3	NA
Apparent oral clearance (mL/min)	335 ± 57	191 ± 39	116 ± 25	105 ± 17
Renal clearance (mL/min)	167 ± 65	73 ± 18	17 ± 3	NA
T _{1/2} (h)	1.7 ± 0.4	3.5 ± 2.5	4.6 ± 0.9	5.4 ± 1.4

^a Single 40-mg oral dose.

^b Determined while patients were off dialysis.

T_{1/2} = terminal elimination half-life.

NA = not applicable.

Hepatic impairment

Stavudine pharmacokinetics was 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.

Geriatric

Stavudine pharmacokinetics has not been studied in patients >65 years of age (see **WARNINGS AND PRECAUTIONS, Geriatric Use**).

Gender

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).

Race

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).

INDICATIONS

LAMIVIR-S tablets are indicated for the treatment of HIV infection as a component of combination antiretroviral therapy.

DOSAGE AND ADMINISTRATION

The interval between doses of **Lamivir S** should be 12 hours. **Lamivir S** may be taken with or without food.

Adults

LAMIVIR-S – 30

1 tablet twice daily for patients weighing <60 kg

Dose adjustment: Because it is a fixed-dose combination, **LAMIVIR-S** should not be prescribed for patients requiring dosage adjustment, such as those with reduced renal function (creatinine clearance \leq 50 ml/min), or those experiencing dose-limiting adverse events.

CONTRAINDICATIONS

LAMIVIR-S is contraindicated in patients with clinically significant hypersensitivity (anaphylaxis) to any of the components contained in the formulation.

WARNINGS AND PRECAUTIONS

Lactic Acidosis/Severe Hepatomegaly with Steatosis/Hepatic Failure

Lactic acidosis/severe hepatomegaly with steatosis, including fatal cases, has been reported with the use of antiretroviral nucleoside analogues alone or in combination, including stavudine, lamivudine 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.

Particular caution should be exercised when administering stavudine and lamivudine to any patient, and particularly to those with known risk factors for liver disease. 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 (including motor weakness), might be indicative of the development of

symptomatic hyperlactatemia or lactic acidosis syndrome.

Treatment should be discontinued 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 aminotransferase elevations).

. Patients with HIV and HBV Co-infection

Post treatment Exacerbations of Hepatitis

In clinical trials in non-HIV-infected patients treated with lamivudine for chronic hepatitis B, clinical and laboratory evidence 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 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 posttreatment exacerbations of hepatitis.

Important Differences Among Lamivudine-Containing Products **LAMIVIR-S** Tablets contain a higher dose of the same active ingredient (lamivudine) than in **Lamivir-HBV** Tablets. **Lamivir-HBV** was developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine in **Lamivir-HBV** are not appropriate for patients dually infected with HIV and HBV. Lamivudine has not been adequately studied for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. If treatment with **Lamivir-HBV** is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV infection, rapid emergence of HIV resistance is likely to result because of the subtherapeutic dose and the inappropriateness of monotherapy HIV treatment. If a decision is made to administer lamivudine to patients dually infected with HIV and HBV, **Lamivir** Tablets, **LAMIVIR-S** Tablets, or **Duovir** tablets should be used as part of an appropriate combination regimen. **Duovir** (a fixed-dose combination tablet of lamivudine and zidovudine) should not be administered concomitantly with **Lamivir**, **Lamivir-HBV** or **Zidovir**

Use with Interferon- and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine. Although no evidence of a pharmacokinetic or

pharmacodynamic interaction (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was co-administered with lamivudine 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 alfa with or without ribavirin.** Patients receiving interferon alfa with or without ribavirin and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of lamivudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Childs Pugh >6) (see the complete prescribing information for interferon and ribavirin).

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.

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 co-administered 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).

Neurological 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, a history of neuropathy, or concurrent neurotoxic drug therapy including didanosine (see **Undesirable Effects**).

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

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, including lamivudine and 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 jirovecii* pneumonia

[PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Drug Interactions

.Stavudine

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)

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 also inhibited at relevant concentrations by doxorubicin and ribavirin.

Ribavirin: *In vitro* data indicate that ribavirin reduces the phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (eg, plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (eg, loss of HIV/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n=18), or stavudine (n=10), or zidovudine (n=6) was coadministered as part of a multi-drug regimen to HIV/HCV co-infected patients (see **WARNINGS AND PRECAUTIONS**).

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 4 and 5 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.

Table 4: Results of Drug Interaction Studies with Stavudine: Effects of

Coadministered Drug on Stavudine Plasma AUC and Cmax 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	↔ (92.7-100.6%)	↑ 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.

Table 5: Results of Drug Interaction Studies with Stavudine: Effects of Stavudine on Coadministered Drug Plasma AUC and Cmax Values

Drug	Stavudine Dosage	n ^a	AUC of Coadministered Drug (95% CI)	C _{max} of Coadministered 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:

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

Interferon- and Ribavirin-Based Regimens

Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of

HIV -1 /HCV virologic suppression) was seen when ribavirin was co administered with lamivudine in HIV-I/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV –I/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin (see WARNINGS AND PRECAUTIONS)

Zalcitabine:

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

Trimethoprim/Sulfamethoxazole (TMP/SMX)

No change in the 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.

Drugs with No Observed Interactions with lamivudine

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

Renal Impairment

Reduction of the dosage of both stavudine and lamivudine is required in patients with a creatinine clearance of 50 ml/min or less. Hence, **LAMIVIR-S** cannot be used in this patient population.

Pregnancy

Pregnancy category C. Both lamivudine and stavudine are classified under category C. There are no adequate and well-controlled studies in pregnant women. **LAMIVIR-S** should be used during pregnancy only if the potential benefits outweigh 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/Hepatic Failure**). **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.

Lactation

The Centres for Disease Control and Prevention recommend that HIV-infected mothers do not breast-feed their infants to avoid risking postnatal transmission of HIV infection. It is not known whether stavudine is excreted in human milk. Lamivudine is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving LAMIVIR-S.**

Pediatric Use

LAMIVIR-S is not intended for use in pediatric patients.

Geriatric Use

Clinical studies of lamivudine did not include a 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. In particular, because lamivudine is substantially excreted by the kidneys and elderly patients are more likely to have decreased renal function, renal function should be monitored and dosage adjustments should be made accordingly (see **DOSAGE AND ADMINISTRATION**)

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 elderly 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 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.

Stavudine is known to be substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function. Dose adjustment is recommended for patients with renal impairment (see **DOSAGE AND ADMINISTRATION, Dosage Adjustment**).

UNDESIRABLE EFFECTS

Lamivudine

Selected clinical adverse events with a $\geq 5\%$ frequency during therapy with lamivudine 150 mg twice daily plus zidovudine 200 mg three times daily for upto 24 weeks are listed below:

Table 6. Selected Clinical Adverse Events ($\geq 5\%$ 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 and 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 and	20%	11%

symptoms Cough	18%	13%
Skin Skin rashes	9%	6%
Musculoskeletal Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

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.

Laboratory Abnormalities: Selected laboratory abnormalities observed during therapy are summarized in Table 7.

Table 7. 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 zidovudine	Zidovudine†	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 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.

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

Endocrine and Metabolic: Hyperglycemia.

General: Weakness.

Haemic and Lymphatic: Anaemia (including pure red cell aplasia and severe anaemias progressing on therapy),.

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.

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Skin: Alopecia, , pruritus.

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 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 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 of the dose. 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 included headache, diarrhea, peripheral neurologic symptoms/neuropathy, rash, nausea and vomiting. Pancreatitis was observed in 3 of the 412 adult patients who received stavudine in a controlled monotherapy study.

Table 8: 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.

Selected clinical adverse events that occurred in antiretroviral-naive adult patients receiving stavudine in two controlled combination studies are provided in Table 9.

Table 9: Selected Clinical Adverse Events^a in START 1 and START 2^b Studies (Combination Therapy)

Adverse Events	Percent (%)			
	START 1 ^a		START 2 ^b	
	stavudine + lamivudine + indinavir (n=100 ^c)	stavudine + zidovudine + lamivudine + indinavir (n=102)	stavudine + didanosine + indinavir (n=102 ^c)	stavudine + 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 ZERIT (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 in controlled clinical studies and in postmarketing reports. **Laboratory Abnormalities:** Selected laboratory abnormalities reported in two controlled combination studies are provided in Table 10 .

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 ($\geq 2.6 \times$ ULN)	7	6	16	8
SGOT (AST) ($\geq 5 \times$ ULN)	5	2	7	7
SGPT (ALT) ($\geq 5 \times$ ULN)	6	2	8	5
GGT ($\geq 5 \times$ ULN)	2	2	5	2
Lipase ($\geq 2 \times$ ULN)	6	3	5	5
Amylase ($\geq 2 \times$ 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
SGOT (AST)	42	20	53	20
SGPT (ALT)	40	20	50	18
GGT	15	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. 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.

Digestive Disorders: Anorexia

Exocrine Gland Disorders: Pancreatitis (including fatal cases)

Haematologic Disorders: Anemia, leukopenia and thrombocytopenia and macrocytosis

Liver: Symptomatic hyperlactatemia/Lactic acidosis and hepatic steatosis, hepatitis and liver failure

Metabolic Disorders—diabetes mellitus and hyperglycemia

Musculoskeletal: Myalgia

Nervous System: Insomnia, severe motor weakness (most often reported in the setting of lactic acidosis). (see **WARNINGS AND PRECAUTIONS**)

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. 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 overdose 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. A study has not been made as to whether stavudine is eliminated by peritoneal dialysis has not been studied.

PACKAGING INFORMATION

LAMIVIR-S – 30 Container of 60 tablets

Last updated: May 2009