

## Stavudine and Lamivudine Dispersible Tablets

### LAMIVIR-S BABY / JUNIOR

#### WARNINGS

LAMIVIR-S BABY/JUNIOR IS INTENDED FOR USE IN CHILDREN WEIGHING <30KG WHO ARE JUST INITIATING THERAPY WITH TRIOMUNE BABY/JUNIOR. THE LAMIVIR-S BABY/JUNIOR FORMULATION IS INTENDED TO FACILITATE THE 14-DAY LEAD-IN DOSING OF NEVIRAPINE.

PATIENTS SHOULD RECEIVE LAMIVIR-S BABY/JUNIOR ONCE DAILY AND TRIOMUNE BABY/JUNIOR ONCE DAILY FOR 2 WEEKS. TRIOMUNE BABY/JUNIOR TWICE DAILY SHOULD BE ADMINISTERED ONCE THEY DEMONSTRATE ADEQUATE TOLERABILITY TO NEVIRAPINE, DURING THIS PERIOD (SEE INDICATIONS, DOSAGE AND ADMINISTRATION).

IT IS IMPORTANT FOR THE TREATING PHYSICIAN TO BE FAMILIAR WITH THE PRESCRIBING INFORMATION OF BOTH PRODUCTS – TRIOMUNE BABY/JUNIOR AND LAMIVIR-S BABY/JUNIOR, BEFORE USING EITHER PRODUCT. IN PARTICULAR, THE TOXICITIES ASSOCIATED WITH NEVIRAPINE ARE DESCRIBED IN THE TRIOMUNE BABY/JUNIOR FULL PRESCRIBING INFORMATION.

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 ).

#### COMPOSITION

##### LAMIVIR-S BABY

Each dispersible tablet contains  
Stavudine 6 mg  
Lamivudine 30 mg

##### LAMIVIR-S JUNIOR

Each dispersible tablet contains  
Stavudine 12 mg  
Lamivudine 60 mg

#### DOSAGE FORM

Oral dispersible tablet

## PHARMACOLOGY

### Stavudine

#### *Pharmacodynamics*

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

#### Pharmacokinetics

The pharmacokinetic properties of stavudine in pediatric patients is explained in Table 1

**Table 1: Pharmacokinetic properties of stavudine**

Parameter	Ages 5 weeks to 15 years	n	Ages 14 to 28 days	n	Day of Birth	n
Oral bioavailability (%)	76.9 ± 31.7	20	ND		ND	
Volume of distribution (L/kg) <sup>a</sup>	0.73 ± 0.32	21	ND		ND	
Ratio of CSF: plasma concentrations (as %) <sup>b</sup>	59 ± 35	8	ND		ND	
Total body clearance (mL/min/kg) <sup>a</sup>	9.75 ± 3.76	21	ND		ND	
Apparent oral clearance <sup>a</sup>	13.75 ± 4.29	20	11.52 ± 5.93	30	5.08 ± 2.80	17
Elimination half-life, I.V. dose <sup>a</sup> (h)	1.11 ± 0.28	21	ND		ND	
Elimination half-life oral dose <sup>c</sup> (h)	0.96 ± 0.26	20	1.59 ± 0.29	30	5.27 ± 2.01	17

Urinary recovery of stavudine of dose) <sup>c,d</sup>	34 ± 16	19	ND		ND	
a	following	1	hour		I.V.	infusion
b	at median time of 2.5 hours (range 2-3 hours)			following multiple oral doses		
c	following	single		oral		dose
d	over		8			hours
ND = not determined						

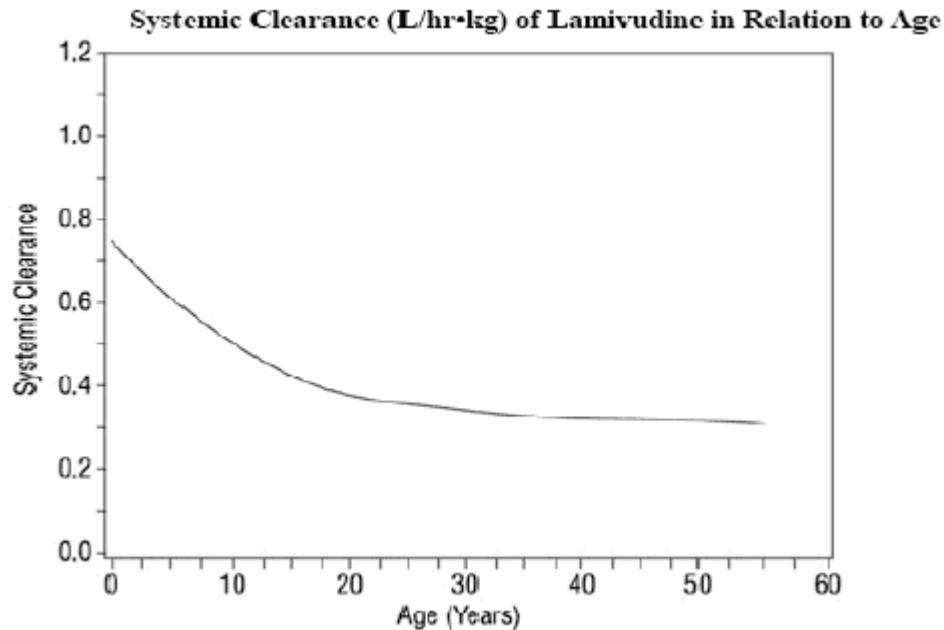
## Lamivudine

### *Pharmacodynamics*

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 alpha and beta, and mitochondrial DNA polymerase gamma.

***Pharmacokinetics*** In Study NUCA2002, the pharmacokinetic properties of lamivudine were assessed in a subset of 57 HIV-infected pediatric patients (age range: 4.8 months to 16 years, weight range: 5 to 66 kg) after oral and IV administration of 1, 2, 4, 8, 12, and 20 mg/kg/day. In the 9 infants and children (range: 5 months to 12 years of age) receiving oral solution 4 mg/kg twice daily (the usual recommended pediatric dose), absolute bioavailability was 66% ± 26% (mean ± SD), which was less than the 86% ± 16% (mean ± SD) observed in adults. The mechanism for the diminished absolute bioavailability of lamivudine in infants and children is unknown.

Systemic clearance decreased with increasing age in pediatric patients, as shown in the figure below.



After oral administration of lamivudine 4 mg/kg twice daily to 11 pediatric patients ranging from 4 months to 14 years of age,  $C_{max}$  was  $1.1 \pm 0.6$  mcg/mL and half-life was  $2.0 \pm 0.6$  hours. (In adults with similar blood sampling, the half-life was  $3.7 \pm 1$  hours) Total exposure to lamivudine, as reflected by mean AUC values, was comparable between pediatric patients receiving an 8-mg/kg/day dose and adults receiving a 4-mg/kg/day dose.

Distribution of lamivudine into cerebrospinal fluid (CSF) was assessed in 38 pediatric patients after multiple oral dosing with lamivudine. CSF samples were collected between 2 and 4 hours postdose. At the dose of 8 mg/kg/day, CSF lamivudine concentrations in 8 patients ranged from 5.6% to 30.9% (mean  $\pm$  SD of  $14.2\% \pm 7.9\%$ ) of the concentration in a simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to 0.3 mcg/mL.

Limited, uncontrolled pharmacokinetic and safety data are available from the administration of lamivudine (and zidovudine) to 36 infants, up to 1 week of age, in two studies in South Africa. In these studies, lamivudine clearance was substantially reduced in 1-week-old neonates relative to pediatric patients (>3 months of age) studied previously. There is insufficient information to establish the time course of changes in clearance between the immediate neonatal period and the age ranges of >3 months old.

The effect of renal impairment on lamivudine pharmacokinetics in pediatric patients is not known. The safety and pharmacokinetic properties of lamivudine in combination with antiretroviral agents other than zidovudine have not been established in pediatric patients.

## INDICATIONS

**LAMIVIR-S BABY/JUNIOR** is indicated for use during the 14-day lead-in dosing period of nevirapine, in children (weight < 30 kg) initiating therapy with **Triomune Baby/Junior** (see **DOSAGE AND ADMINISTRATION**).

## DOSAGE AND ADMINISTRATION

For children < 30 kg

**LAMIVIR-S BABY/JUNIOR** should be administered to patients who are initiating therapy with **Triomune Baby/Junior**, as per the schedule given in Table 2 below. This is to facilitate the 14-day lead-in dosing for nevirapine.

**Table 2: Lead-in dosage schedule for children weighing < 30 kg**

<b>Weight range</b>	<b>Schedule</b>
3-<6 kg	1 tablet <b>Triomune Baby</b> in the morning + 1 tablet <b>Lamivir-S Baby</b> in the evening
6-<10 kg	1 ½ tablets <b>Triomune Baby</b> in the morning + 1½ tablets <b>Lamivir-S Baby</b> in the evening
10-<15 kg	1 tablet <b>Triomune Junior</b> in the morning + 1 tablet <b>Lamivir-S Junior</b> in the evening
15-<20 kg	1 tablet <b>Triomune Junior</b> in the morning + 1½ tablets <b>Lamivir-S Junior</b> in the evening
20-<25 kg	1½ tablets <b>Triomune Junior</b> in the morning + 1½ tablets <b>Lamivir-S Junior</b> in the evening
25-<30 kg	2 tablets <b>Triomune Junior</b> in the morning + 2 tablets <b>Lamivir-S Junior</b> in the evening

	evening
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Following this 14-day lead-in dose, treatment with **Triomune Baby/Junior** twice daily may be carried out in the absence of any hypersensitivity reactions to nevirapine, such as rash, liver function test abnormalities, given as per **Table 3**.

**Table 3: Chronic dosage schedule for Triomune Baby/Junior**

Weight range	Schedule
3-<6 kg	1 tablet <b>Triomune Baby</b> bid
6-<10 kg	1½ tablets <b>Triomune Baby</b> bid
10-<15 kg	1 tablet <b>Triomune Junior</b> bid
15-<20 kg	1 tablet <b>Triomune Junior</b> in the morning and 1 ½ tablets <b>Triomune Junior</b> in the evening
20-<25 kg	1½ tablets <b>Triomune Junior</b> bid
25-<30 kg	2 tablets <b>Triomune Junior</b> bid

#### For children ≥ 30 kg

For children weighing ≥ 30 kg, **Lamivir-S 30** should be administered to patients who are initiating therapy with **Triomune-30**, as per the schedule given in **Table 4**. This is to be followed by **Triomune-30** twice daily in the absence of any hypersensitivity reactions as given in **Table 5**

**Table 4: Lead-in dosage schedule for children weighing ≥ 30 kg**

Weight range	Schedule
≥30kg	1 tablet <b>Lamivir-S 30</b> in the morning + 1 tablet <b>Triomune -30</b> in the evening

**Table 5: Chronic dosage schedule for Triomune-30**

Weight range	Schedule
≥ 30 kg	1 tablet <b>Triomune-30</b> bid

#### Monitoring of patients

##### **Stavudine**

Patients should be monitored for the development of peripheral neuropathy, which is usually manifested by numbness, tingling or pain in the feet or hands. These symptoms may be difficult to detect in young children. If these symptoms develop during treatment, stavudine therapy should be interrupted. Symptoms 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 recommended dose.

## **CONTRAINDICATIONS**

**Lamivir-S Baby/Junior** is contraindicated in patients with clinically significant hypersensitivity 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 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).

### **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 BABY/JUNIOR** Tablet is developed for children with HIV/AIDS. **LAMIVIR-HBV** was developed for adult patients with chronic hepatitis B, whereas **LAMIVIR** Oral Solution is for children and **LAMIVIR** tablets is for adults with HIV/AIDS.

**Lamivudine Tablets and Oral Solution** contain a higher dose of the same active ingredient (lamivudine) than in **Lamivir-HBV Tablet**.

Lamivudine has not been adequately studied for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. If treatment with lamivudine is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV-1 infection, rapid emergence of HIV-1 resistance is likely to result because of the sub-therapeutic dose and the inappropriateness of monotherapy HIV-1 treatment. If a decision is made to administer lamivudine to patients dually infected with HIV-1 and HBV, lamivudine should be used as part of an appropriate combination regimen.

### ***Emergence of Lamivudine-Resistant HBV:***

In non-HIV-1-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response. Emergence of HBV variants associated with resistance to lamivudine has also been reported in HIV -1-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with HBV.

### **Use with Other Lamivudine- and Emtricitabine-Containing Products**

Lamivudine should not be administered concomitantly with other lamivudine- and containing products.

### **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.

### **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 (see **UNDESIRABLE EFFECTS Fat Redistribution**)

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo lump), 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. 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:

*Zidovudine:* Zidovudine may competitively inhibit the intracellular phosphorylation of stavudine. Therefore, the use of zidovudine in combination with stavudine is not recommended. *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 ribavirin reduces 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), 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 6 and 7 summarize the effects on AUC and C<sub>max</sub>, 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 6: Results of Drug Interaction Studies with Stavudine: Effects of Coadministered Drug on Stavudine Plasma AUC and C<sub>max</sub> Values**

Drug	Stavudine Dosage	n <sup>a</sup>	AUC of Stavudine (95% CI)	C <sub>max</sub> 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%.

<sup>a</sup> HIV-infected patients.

**Table 7: Results of Drug Interaction Studies with Stavudine: Effects of Stavudine on Coadministered Drug Plasma AUC and C<sub>max</sub> Values**

Drug	Stavudine Dosage	n <sup>a</sup>	AUC of Coadministered Drug (95% CI)	C <sub>max</sub> 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%.

<sup>a</sup> 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/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV /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 BABY/JUNIOR** cannot be used in this patient population.

## **UNDESIRABLE EFFECTS**

### **Lamivudine**

Selected clinical adverse events and physical findings with a  $\geq 5\%$  frequency during therapy with lamivudine 4 mg/kg twice daily plus zidovudine 160 mg/m<sup>2</sup> three times

daily compared with didanosine in therapy-naïve ( ≤ 56 days of antiretroviral therapy) pediatric patients are listed in **Table 8**.

**Table 8: Selected Clinical Adverse Events and Physical Findings ( ≥ 5% Frequency) in Pediatric Patients in Study ACTG300**

<b>Adverse Event</b>	<b>Lamivudine plus Zidovudine (n = 236)</b>	<b>Didanosine (n = 235)</b>
<b>Body as a whole</b>		
Fever	25%	32%
<b>Digestive</b>		
Hepatomegaly	11%	11%
Nausea and vomiting	8%	7%
Diarrhoea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
<b>Respiratory</b>		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
<b>Ear, Nose and Throat</b>		
Signs or symptoms of ears*	7%	6%
Nasal discharge or congestion	8%	11%
<b>Other</b>		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

\* Includes pain, discharge, erythema or swelling of an ear

Pancreatitis: Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric patients receiving Lamivudine alone or in combination with other antiretroviral agents. In an open-label dose-escalation study (NUCA2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with Lamivudine. Three of these patients died of complications of pancreatitis. In a second open-label study (NUCA2005), 12 patients (18%) developed pancreatitis. In Study ACTG300, pancreatitis was not observed in 236 patients randomized to Lamivudine plus zidovudine. Pancreatitis was observed in 1 patient in this study who received open-label Lamivudine in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy (see **WARNINGS AND PRECAUTIONS**)

Paresthesias and Peripheral Neuropathies: Paresthesias and peripheral neuropathies were reported in 15 patients (15%) in Study A2002, 6 patients (9%) in Study A2005, and 2 patients (1%) in Study ACTG300.

Selected laboratory abnormalities experienced by therapy-naïve ( $\leq 56$  days of antiretroviral therapy) pediatric patients are listed in **Table 9**.

**Table 9: Frequencies of Selected Grade 3-4 Laboratory Abnormalities in Pediatric Patients in Study ACTG300**

Test (Threshold Level)	Lamivudine plus Zidovudine	Didanosine
Absolute neutrophil count ( $< 400/\text{mm}^3$ )	8%	3%
Haemoglobin ( $< 7.0$ g/dL)	4%	2%
Platelets ( $< 50,000/\text{mm}^3$ )	1%	3%
ALT ( $> 10$ x ULN)	1%	3%
AST ( $> 10$ x ULN)	2%	4%
Lipase ( $> 2.5$ x ULN)	3%	3%
Total Amylase ( $> 2.5$ x ULN)	3%	3%

ULN = Upper limit of normal

Limited short-term safety information is available from 2 small, uncontrolled studies in South Africa in neonates receiving lamivudine with or without zidovudine for the first week of life following maternal treatment starting at week 38 or 36 of gestation. Adverse events reported in these neonates included increased liver function tests, anemia, diarrhea, electrolyte disturbances, hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, sepsis and syphilis; 3 neonates died (1 from gastroenteritis with acidosis and convulsions, 1 from traumatic injury, and 1 from unknown causes). Two other nonfatal gastroenteritis or diarrhea cases were reported, including 1 with convulsions; 1 infant had transient renal impairment associated with dehydration. The absence of control groups further limits assessments of causality, but it should be assumed that perinatally-exposed infants may be at risk for adverse events comparable to those reported in pediatric and adult HIV-infected patients treated with lamivudine-containing combination regimens. Long-term effects of *in utero* and infant lamivudine exposure are not known.

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.

**Hemic and Lymphatic:** Anemia (including pure red cell aplasia and severe anemia progressing on therapy).

**Hepatic and Pancreatic:** Lactic acidosis and hepatic steatosis, pancreatitis, post-treatment exacerbation of hepatitis B (see **WARNINGS AND PRECAUTIONS**).

**Hypersensitivity:** Anaphylaxis, urticaria.

**Musculoskeletal:** Muscle weakness, CPK elevation, rhabdomyolysis.

**Skin:** Alopecia, pruritus.

## **Stavudine**

### **Pediatrics**

Adverse events and laboratory abnormalities reported to occur in pediatric patients in clinical studies were generally consistent with the safety profile of stavudine in adults. These studies include ACTG 240, where 105 pediatric patients aged 3 months to 6 years received stavudine 2 mg/kg/day for a median of 6.4 months; a controlled clinical trial where 185 newborns received stavudine 2 mg/kg/day either alone or in combination with didanosine from birth through 6 weeks of age; and a clinical trial where 8 newborns received stavudine 2 mg/kg/day in combination with didanosine and nelfinavir from birth through 4 weeks of age. Adverse reactions and serious laboratory abnormalities in pediatric patients from birth through adolescence were similar in type and frequency to those seen in adult patients

### **Adults**

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

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

Stavudine therapy has also been associated with peripheral sensory neuropathy, which can be severe, is dose related, and occurs more frequently in patients being treated with 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 (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.

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 the study.

### Laboratory Abnormalities

Selected laboratory abnormalities reported in a controlled monotherapy study (Study AI455- 019) are provided in **Table 10**.

**Table 10: Selected Adult Laboratory Abnormalities in Study AI455-019** <sup>a, b</sup>

Parameter	Percent (%)	
	stavudine (40 mg twice daily) (n=412)	zidovudine (200 mg 3 times daily) (n=402)
AST (SGOT) (>5.0 x ULN)	11	10
ALT (SGPT) (>5.0 x ULN)	13	11
Amylase (≥1.4 x ULN)	14	13

<sup>a</sup> Data presented for patients for whom laboratory evaluations were performed.

<sup>b</sup> Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.

ULN = upper limit of normal.

Selected laboratory abnormalities reported in two controlled combination studies are provided in **Tables 11 and 12**.

**Table 11: 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 ( $\geq 2.6$ x ULN)	7	6	16	8
SGOT (AST) ( $\geq 5$ x ULN)	5	2	7	7
SGPT (ALT) ( $\geq 5$ x ULN)	6	2	8	5
GGT ( $\geq 5$ x ULN)	2	2	5	2
Lipase ( $\geq 2$ x ULN)	6	3	5	5
Amylase ( $\geq 2$ x ULN)	4	<1	8	2

ULN = upper limit of normal.

**Table 12: 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 adverse 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 **WARNINGS AND PRECAUTIONS: Fat Redistribution**).

**Digestive Disorders:** Anorexia

**Exocrine Gland Disorders:** Pancreatitis [including fatal cases] (see **WARNINGS AND PRECAUTIONS**).

**Hematologic Disorders:** Anemia, leucopenia and thrombocytopenia and macrocytosis

**Liver:** Symptomatic hyperlactatemia/lactic acidosis and hepatic steatosis (see **WARNINGS AND PRECAUTIONS**), 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. Two cases of pediatric overdose have been reported. The first case was of a single dose of 7 mg/kg of lamivudine; the second case involved use of 5 mg/kg of lamivudine twice daily for 30 days. There were no clinical signs or symptoms noted in either case. Because a negligible amount of lamivudine was removed via 4-hour hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

### Stavudine

Experience with adults treated with 12 to 24 times the recommended daily dosage revealed no acute toxicity. Complications of chronic overdosage include peripheral neuropathy and hepatic toxicity. Stavudine can be removed by hemodialysis; the mean

+ SD hemodialysis clearance of stavudine is  $120 \pm 18$  mL/min. A study has not been made as to whether stavudine is eliminated by peritoneal dialysis.

## **PACKAGING INFORMATION**

**LAMIVIR-S BABY:** Strip of 10 tablets

**LAMIVIR-S JUNIOR:** Strip of 10 tablets

*Last updated: November 2009*