

Stavudine Capsules

STAVIR

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 AND OTHER ANTIRETROVIRALS. 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 NON-FATAL PANCREATITIS HAVE OCCURRED DURING THERAPY WHEN STAVUDINE WAS PART OF A COMBINATION REGIMEN THAT INCLUDED DIDANOSINE IN BOTH TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF THE DEGREE OF IMMUNOSUPPRESSION (SEE WARNINGS AND PRECAUTIONS).

COMPOSITION

STAVIR-30 Capsules

Each capsule contains:

Stavudine 30 mg

STAVIR-40 Capsules

Each capsule contains:

Stavudine40 mg

DOSAGE FORM

Capsule

PHARMACOLOGY

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 β and γ and markedly reduces the synthesis of mitochondrial DNA.

Pharmacokinetics

The pharmacokinetics of stavudine has been evaluated in HIV-infected adult and pediatric patients (Tables 1-3). 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 systemic exposure to stavudine is the same following administration as capsules or solution. Steady-state pharmacokinetic parameters of stavudine in HIV-infected adults are shown in Table 1.

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

Parameter	Stavudine 40 mg b.i.d. Mean + SD (n=8)
AUC (ng•h/mL) ^a	2568 ± 454
C_{max} (ng/mL)	536 ± 146
C_{min} (ng/mL)	8 ± 9

^afrom 0 to 24 hours

AUC = area under the curve over 24 hours

C_{max} = maximum plasma concentration

C_{min} = trough or minimum plasma concentration

Distribution

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

Metabolism

Metabolism plays a limited role in the clearance of stavudine. Unchanged stavudine was the major drug-related component circulating in plasma after an 80-mg dose of ¹⁴C-stavudine, while metabolites constituted minor components of the circulating radioactivity. Minor metabolites include oxidized stavudine, glucuronide conjugates of stavudine and its oxidized metabolite, and an *N*-acetylcysteine conjugate of the ribose after glycosidic cleavage, suggesting that thymine is also a metabolite of stavudine.

Elimination

Following an 80-mg dose of ¹⁴C-stavudine to healthy subjects, approximately 95% and 3% of the total radioactivity was recovered in urine and feces, respectively. Radioactivity due to parent drug in urine and feces was 73.7% and 62.0%, respectively. The mean terminal elimination half-life is approximately 2.3 hours

following single oral doses. Mean renal clearance of the parent compound is approximately 272 mL/min, accounting for approximately 67% of the apparent oral clearance.

In HIV-infected patients, renal elimination of unchanged drug accounts for about 40% of the overall clearance regardless of the route of administration (Table 2). The mean renal clearance was about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration.

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, 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

Special Populations

Pediatric

For pharmacokinetic properties of stavudine in pediatric patients, see Table 3.

Table 3: Pharmacokinetic Parameters (Mean ± SD) of Stavudine in HIV-Exposed or HIV-Infected Pediatric Patients

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) ^a	0.73 ± 0.32	21	ND		ND	
Ratio of CSF: plasma concentrations (as %) ^b	59 ± 35	8	ND		ND	
Total body clearance (mL/min/kg) ^a	9.75 ± 3.76	21	ND		ND	
Apparent oral clearance (mL/min/kg) ^c	13.75 ± 4.29	20	11.52 ± 5.93	30	5.08 ± 2.80	17
Elimination half-life, IV dose (h) ^a	1.11 ± 0.28	21	ND		ND	
Elimination half-life, oral dose (h) ^c	0.96 ± 0.26	20	1.59 ± 0.29	30	5.27 ± 2.01	17
Urinary recovery of stavudine (% of dose) ^{c,d}	34 ± 16	19	ND		ND	

^a following 1-hour IV 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.

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 4: 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 five non-HIV-infected patients with hepatic impairment secondary to cirrhosis (Child-Pugh classification B or C) following the administration of a single 40 mg dose.

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

STAVIR Capsules, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.

DOSAGE AND ADMINISTRATION

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

Adults

The recommended dose based on body weight is as follows:

40 mg twice daily for patients ≥ 60 kg

30 mg twice daily for patients < 60 kg

Pediatric Use

The recommended dose for newborns from birth to 13 days old is 0.5 mg/kg/dose given every 12 hours.(see **PHARMACOLOGY**).The recommended dose for pediatric patients at least 14 days old and weighing less than 30 kg is 1 mg/kg/dose, given every 12 hours. Pediatric patients weighing 30 kg or greater should receive the recommended adult dosage.

Dosage Adjustment

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 (see **WARNINGS AND PRECAUTIONS**). 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, as follows:

20 mg twice daily for patients ≥ 60 kg

15 mg twice daily for patients < 60 kg

If peripheral neuropathy recurs after resumption of stavudine, permanent discontinuation of stavudine should be considered.

Renal Impairment

STAVIR Capsules may be administered to adult patients with impaired renal function after an adjustment in dose, as shown in Table 5.

Table 5: Recommended Dosage Adjustment for Renal Impairment

Creatinine Clearance (mL/min)	Recommended Stavudine Dose by Patient Weight	
	≥ 60 kg	< 60 kg
>50	40 mg every 12 hours	30 mg every 12 hours
26–50	20 mg every 12 hours	15 mg every 12 hours
10–25	20 mg every 24 hours	15 mg every 24 hours

Since urinary excretion is also a major route of elimination of stavudine in pediatric patients, the clearance of stavudine may be altered in children with renal impairment. Although there are insufficient data to recommend a specific dose adjustment of stavudine in this patient population, a reduction in the dose and/or an increase in the interval between doses should be considered.

Hemodialysis Patients

The recommended dose is 20 mg every 24 hours (>60 kg) or 15 mg every 24 hours (<60 kg), administered after the completion of hemodialysis and at the same time of day on non-dialysis days.

CONTRAINDICATIONS

STAVIR Capsules are contraindicated in patients with clinically significant hypersensitivity to stavudine or to any of the components contained in the formulation.

WARNINGS AND PRECAUTIONS

Drug Interactions

Zidovudine

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

Doxorubicin

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

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 co-administered 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_{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 6: 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	↔ (92.7-100.6%)	↑ 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 7: Results of Drug Interaction Studies with Stavudine: Effects of Stavudine on Coadministered Drug Plasma AUC and C_{max} 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.

Lactic Acidosis/Severe Hepatomegaly with Steatosis/Hepatic Failure

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 **WARNINGS AND 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 (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).

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 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.

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.

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).

Neurologic Symptoms

Motor weakness has been reported rarely in patients receiving combination antiretroviral therapy, including stavudine. Most of these cases occurred in the setting of lactic acidosis. The evolution of motor weakness may mimic the clinical presentation of Guillain-Barré syndrome (including respiratory failure). Symptoms may continue or worsen following the 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 non-fatal pancreatitis have occurred during therapy when stavudine was part of a combination regimen that included didanosine in both treatment-naïve and treatment-experienced patients, regardless of the degree of immunosuppression. The combination of stavudine and didanosine 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.

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 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.

Pregnancy

Pregnancy Category C

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

There are no adequate and well-controlled studies of stavudine in pregnant women. **STAVIR Capsules** should be used during pregnancy only if the potential benefit justifies the 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 AND PRECAUTIONS, 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.** Healthcare providers caring for HIV-infected pregnant women receiving stavudine should be alert for any early diagnosis of lactic acidosis/hepatic steatosis syndrome.

Lactation

The Centers for Disease Control and Prevention recommend that HIV-infected mothers do not breastfeed their infants to avoid risking postnatal transmission of HIV infection. Studies in lactating rats demonstrated that stavudine is excreted in breast 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. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving STAVIR Capsules.**

Pediatric Use

Use of stavudine in pediatric patients from birth through adolescence is supported by evidence from adequate and well-controlled studies of stavudine in adults, with additional pharmacokinetic and safety data in pediatric patients.

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.

Stavudine pharmacokinetics have been evaluated in 25 HIV-infected pediatric patients, ranging in age from 5 weeks to 15 years and in weight from 2 to 43 kg, after I.V. or oral administration of single doses and twice-daily regimens, and in 30 HIV-exposed or -infected newborns, ranging in age from birth to 4 weeks, after oral

administration of twice-daily regimens (see **PHARMACOLOGY, Pharmacokinetics**).

Geriatric Use

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

Adults

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

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

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

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

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.

Selected clinical adverse events that occurred in adult patients receiving stavudine in a controlled monotherapy study (Study AI455-019) are provided in Table 8.

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

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-naïve 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		START 2 ^b	
	Stavudine + lamivudine + indinavir (n = 100) ^c	Zidovudine + lamivudine + indinavir (n = 102)	Didanosine + indinavir (n=102) ^c	Zidovudine + lamivudine + indinavir (n = 103)
Nausea	43	63	53	67
Diarrhea	34	16	45	39

Headache	25	26	46	37
Rash	18	13	30	18
Vomiting	18	33	30	35
Peripheral Neurologic Symptoms/Neuropathy	8	7	21	10

^a Any severity, regardless of relationship to study regimen

^b START 2 compared two triple-combination regimens in 205 treatment-naïve patients. Patients receive either Stavudine (40 mg twice daily) plus didanosine plus indinavir or zidovudine plus lamivudine plus indinavir

^cDuration 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.

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 ^{a, b}

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

^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.

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 (>2.6 x ULN)	7	6	16	8
AST (SGOT) (>5 X ULN)	5	2	7	7

ALT (SGPT) (>5 X ULN)	6	2	8	5
GGT (>5 X ULN)	2	2	5	2
Lipase (>2 x ULN)	6	3	5	5
Amylase (>2 x ULN)	4	<1	8	2

ULN = upper limit of normal.

Table 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
AST (SGOT)	42	20	53	20
ALT (SGPT)	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 (see **WARNINGS AND PRECAUTIONS, Fat Redistribution**)

Digestive Disorders: Anorexia

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

Hematologic Disorders: Anemia, leukopenia, 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**)

Use with Didanosine- and Hydroxyurea-Based Regimens

When stavudine is used in combination with other agents with similar toxicities, the incidence of these toxicities may be higher than when stavudine is used alone. Thus, patients treated with stavudine in combination with didanosine, with or without hydroxyurea, may be at increased risk for pancreatitis and hepatotoxicity, which may be fatal, and severe peripheral neuropathy. The combination of stavudine and hydroxyurea, with or without didanosine, should be avoided (see **WARNINGS** and **PRECAUTIONS**).

Pediatric Patients

Adverse reactions and serious laboratory abnormalities in pediatric patients from birth to adolescence were similar in type and frequency to those seen in adult patients.

OVERDOSAGE

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.

PACKAGING INFORMATION

STAVIR-30 Capsules.....Blister strip of 10 capsules
STAVIR-40 CapsulesBlister strip of 10 capsules

Last updated: October 2010