

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 from two controlled combination studies are provided in Table 8.

 Table 8: Selected Clinical Adverse Events* in START 1 and START 2^b Studies (Combination Therapy)

Adverse Events	Percent (%)			
	START 1		START 2 ^b	
	Stavudine + lamivudine + indinavir (n=100 ^c)	Zidovudine + lamivudine + indinavir (n=102)	Stavudine + didanosine + indinavir (n=102 ^c)	Zidovudine + lamivudine + indinavir (n=103)
Nausea	43	63	53	67
Diarrhea	34	16	45	39
Headache	25	26	46	37
Rash	18	13	30	18
Vomiting	18	33	30	35
Peripheral Neurologic Symptoms/Neuropathy	8	7	21	10

^a Any severity, regardless of relationship to study regimen.

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

^c Duration of stavudine therapy = 48 weeks.

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

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

 Table 9: Selected Adult Laboratory Abnormalities in Study AI455-019^{a,b}

Parameter	Percent (%)	
	Stavudine (40 mg twice daily) (n=412)	Zidovudine (200 mg 3 times daily) (n=402)
	AST (SGOT) (>5 x ULN)	11
ALT (SGPT) (>5 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 10 and 11.

Table 10: Selected Laboratory Abnormalities in START 1 and START 2 Studies (Grades 3 to 4)

Parameter	Percent (%)			
	START 1		START 2	
	Stavudine + lamivudine + indinavir (n=100)	Zidovudine + lamivudine + indinavir (n=102)	Stavudine + didanosine + indinavir (n=102)	Zidovudine + lamivudine + indinavir (n=103)
Bilirubin (>2.6 x ULN)	7	6	16	8
AST (SGOT) (>5 x ULN)	5	2	7	7
ALT (SGPT) (>5 x ULN)	6	2	8	5
GGT (>5 x ULN)	2	2	5	2
Lipase (>2 x ULN)	6	3	5	5
Amylase (>2 x ULN)	4	<1	8	2

ULN = upper limit of normal.

Table 11: Selected Laboratory Abnormalities in START 1 and START 2 Studies (All Grades)

Parameter	Percent (%)			
	START 1		START 2	
	Stavudine + lamivudine + indinavir (n=100)	Zidovudine + lamivudine + indinavir (n=102)	Stavudine + didanosine + indinavir (n=102)	Zidovudine + lamivudine + indinavir (n=103)
Total Billirubin	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 **PRECAUTIONS: Fat Redistribution**).

Digestive Disorders—anorexia.

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

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

Liver—symptomatic hyperlactatemia/lactic acidosis and hepatic steatosis (see **WARNINGS**), 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**).

Pediatric Patients

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 (see **PRECAUTIONS: Pediatric Use**).

OVERDOSAGE

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

DO dosage AND ADMINISTRATION

The interval between doses of stavudine capsules should be 12 hours. Stavudine 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.

Pediatrics

The recommended dose for newborns from birth to 13 days old is 0.5 mg/kg/dose given every 12 hours (see **CLINICAL 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**). 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:

20 mg twice daily for patients ≥60 kg.

15 mg twice daily for patients <60 kg.

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

Renal Impairment

Stavudine capsules may be administered to adult patients with impaired renal function with adjustment in dose as shown in Table 12.

Table 12: Recommended Dosage Adjustment for Renal Impairment

Creatinine Clearance (mL/min)	Recommended Stavudine Capsules 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 capsules 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.

HOW SUPPLIED

Stavudine Capsules USP, 15 mg are dark red opaque/light yellow opaque size 4¹ hard gelatin capsule filled with white to off white granular powder and imprinted with "E" on dark red opaque cap and "76" on light yellow opaque body with black ink.

Bottle of 60 Capsules

NDC 65862-111-60

Stavudine Capsules USP, 20 mg are light brown opaque/light brown opaque size 3¹ hard gelatin capsule filled with white to off white granular powder and imprinted with "E" on light brown opaque cap and 77" on light brown opaque body with black ink.

Bottle of 60 Capsules

NDC 65862-112-60

Stavudine Capsules USP, 30 mg are dark orange opaque/light orange opaque size "2" hard gelatin capsule filled with white to off white granular powder and imprinted with "C" on dark orange opaque cap and "36" on light orange opaque body with black ink.

Bottle of 60 Capsules

NDC 65862-046-60

Stavudine Capsules USP, 40 mg are dark orange opaque/dark orange opaque size "1" hard gelatin capsule filled with white to off white granular powder and imprinted with "C" on dark orange opaque cap and "37" on dark orange opaque body with black ink.

Bottle of 60 Capsules

NDC 65862-047-60

Storage

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Manufactured for:

Aurobindo Pharma USA, Inc.
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Dayton, NJ 08810

Manufactured by:
Aurobindo Pharma Limited
Hyderabad–500 072, India

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PATIENT INFORMATION

Stavudine Capsules, USP

Rx only

(Stavudine is also known as d4T)

What is stavudine?

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

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

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

There is limited information on the long-term use of stavudine.

Who should not take stavudine?

Do not take stavudine capsules if you are allergic to any of their ingredients, including their active ingredient, stavudine, and the inactive ingredients. (See **Inactive Ingredients** at the end of this leaflet.) Tell your doctor if you think you have had an allergic reaction to any of these ingredients.

How should I take stavudine? How should I store it?

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

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

If you have a kidney problem: If your kidneys are not working properly, your doctor may monitor your kidney function while you take stavudine. Also, your dosage of stavudine may be adjusted.

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

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

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

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

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

What about pregnancy and nursing (breast-feeding)?

- It is not known if stavudine can harm a human fetus. Pregnant women have experienced serious side effects when taking stavudine (the active ingredient in stavudine capsules) in combination with didanosine and other HIV medicines. Stavudine should be used during pregnancy only after discussion with your doctor. **Tell your doctor if you become pregnant or plan to become pregnant while taking stavudine.**

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

What are the possible side effects of stavudine?

- Lactic acidosis**, severe increase of lactic acid in the blood, **severe liver enlargement**, including inflammation (pain and swelling) of the liver, and **liver failure**, which can cause death, have been reported among patients taking stavudine. ***Symptoms of lactic acidosis may include:***

- nausea, vomiting, or unusual or unexpected stomach discomfort;***

- feeling very weak and tired;***

- shortness of breath;***

- weakness in arms and legs.***

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

- Peripheral neuropathy** is a nerve disorder of the hands and feet. If not recognized promptly, this disorder may worsen. ***Tell your doctor right away if you or a child taking stavudine has continuing numbness, tingling, burning, or pain in the feet and/or hands.*** A child may not recognize these symptoms or know to tell you that his or her feet or hands are numb, burning, tingling, or painful. Ask your child's doctor for instructions on how to find out if your child develops peripheral neuropathy.

Let your doctor know if you or a child taking stavudine has ever had peripheral neuropathy, because this condition occurs more often in patients who have had it previously. Peripheral neuropathy is also more likely to occur in patients taking drugs that affect the nerves and in patients with advanced HIV disease, but it can occur at any disease stage. If you develop peripheral neuropathy, your doctor may tell you to stop taking stavudine. In some cases the symptoms worsen for a short time before getting better. Once symptoms of peripheral neuropathy go away completely, stavudine may be started again at a lower dose.

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



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

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

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

What else should I know about stavudine?

Inactive Ingredients

Microcrystalline cellulose, sodium starch glycolate, anhydrous lactose, and magnesium stearate. The hard gelatin shell consists of gelatin, sodium lauryl sulfate, titanium dioxide, yellow iron oxide, and red iron oxide. In addition the 15 mg and 20 mg also contains black iron oxide. Black iron oxide is used for printing on the capsules.

This medicine was prescribed for your particular condition. Do not use stavudine for another condition or give it to others. Keep stavudine and all other medicines out of the reach of children and pets at all times. Do not keep medicine that is out of date or that you no longer need. Dispose of unused stavudine through community take-back disposal programs when available or by placing it in an unrecognizable closed container in the household trash.

This summary does not include everything there is to know about stavudine. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you have questions or concerns, or want more information about stavudine, your physician and pharmacist have the complete prescribing information upon which this leaflet was based. You may want to read it and discuss it with your doctor or other healthcare professional. Remember, no written summary can replace careful discussion with your doctor.

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