HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use stavudine safely and effectively. See full prescribing information for stavudine capsules, USP.
Stavudine Capsules, USP
Initial U.S. Approval: 1994

WARNING: LACTIC ACIDOSIS and HEPATOMEGALY with STEATOSIS; PANCREATITIS

See full prescribing information for complete boxed warning.

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases. Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine. (5.1)**
- **Fatal and nonfatal pancreatitis have occurred when stavudine was part of a combination regimen that included didanosine. (5.4)**

RECENT MAJOR CHANGES

Dosage and Administration, Dosage Adjustment (Peripheral Neuropathy) (2.3) – removal 12/2010
Warnings and Precautions
Fat Redistribution (5.5) 12/2010
Immune Reconstitution Syndrome (5.6) 11/2011

INDICATIONS AND USAGE

Stavudine is a nucleoside reverse transcriptase inhibitor for use in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV)-1 infection. (1)

DOSAGE AND ADMINISTRATION

- *Recommended Dosage for Adults:*
- less than 60 kg: 30 mg every 12 hours (2.1)
- at least 60 kg: 40 mg every 12 hours (2.1)
- *Recommended Dosage for Pediatric Patients:*
- newborns from birth to 13 days old: 0.5 mg/kg every 12 hours (2.2)
- at least 14 days old and weighing less than 30 kg: 1 mg/kg every 12 hours (2.2)
- weighing at least 30 kg: adult dose (2.2)
- *Renal Impairment:* Dose adjustment is recommended for CrCl ≤50 mL/min. (2.3)

DOSAGE FORMS AND STRENGTHS

- Capsules: 15 mg, 20 mg, 30 mg, 40 mg (3, 16.1)

CONTRAINDICATIONS

Stavudine capsules are contraindicated in patients with clinically significant hypersensitivity to stavudine or to any of the components of this product. (4)

WARNINGS AND PRECAUTIONS

- *Lactic Acidosis/Severe Hepatomegaly with Steatosis:* Suspend treatment with stavudine in patients who develop clinical symptoms or signs with or without laboratory findings. (5.1)
- *Hepatic Toxicity:* May be severe, fatal. Consider interruption or discontinuation. Avoid use in combination with didanosine and hydroxyurea. Risk of hepatic decompensation exists when used in combination with interferon and ribavirin; closely monitor and consider discontinuation of stavudine. (5.2)
- *Neurologic Symptoms:* Motor weakness, most often seen in the setting of lactic acidosis, may mimic Guillain-Barré syndrome; discontinue treatment. Monitor for peripheral neuropathy, which can be severe; treatment discontinuation should be considered. (5.3)
- *Pancreatitis:* Suspend treatment, resume with particular caution and close monitoring and avoid use in combination with didanosine. (5.4)
- Patients may develop redistribution/accumulation of body fat, monitor for signs and symptoms of lipoatrophy/lipodystrophy. Alternative antiretrovirals should be considered. (5.5)
- Patients may develop immune reconstitution syndrome. (5.6)

ADVERSE REACTIONS

- In adults, the most common adverse reactions are headache, diarrhea, neuropathy, rash, nausea, and vomiting. (6.1)
- Adverse reactions in pediatric patients were consistent with those seen in adults. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Aurobindo Pharma USA, Inc. at 1-866-850-2876 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Coadministration of stavudine with zidovudine should be avoided. (7)
- Coadministration of stavudine and doxorubicin or ribavirin should be undertaken with caution. (7)

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Fatal lactic acidosis has been reported in pregnant women who received both didanosine and stavudine with other agents. This combination should be used with caution during pregnancy and only if the potential benefit clearly outweighs the potential risk to the fetus. Pregnancy registry available. (8.1)
- *Nursing mothers* should be instructed not to breastfeed due to the potential for postnatal HIV transmission. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

Revised: 11/2012

FULL PRESCRIBING INFORMATION: CONTENTS *

WARNING: LACTIC ACIDOSIS AND HEPATOMEGALY WITH STEATOSIS; PANCREATITIS
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Adult Dosage
2.2 Recommended Pediatric Dosage
2.3 Dosage Adjustment
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Lactic Acidosis/Severe Hepatomegaly with Steatosis
5.2 Hepatic Toxicity
5.3 Neurologic Symptoms
5.4 Pancreatitis
5.5 Fat Redistribution
5.6 Immune Reconstitution Syndrome
6 ADVERSE REACTIONS
6.1 Clinical Trial Experience in Adults
6.2 Clinical Trial Experience in Pediatric Patients
6.3 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
12.4 Microbiology
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 Capsules
16.3 Storage
17 PATIENT COUNSELING INFORMATION
17.1 General
17.2 Lactic Acidosis
17.3 Hepatic Toxicity
17.4 Peripheral Neuropathy
17.5 Pancreatitis
17.6 Fat Redistribution
MEDICATION GUIDE
PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 15 MG (60 CAPSULE BOTTLE)
PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 20 MG (60 CAPSULE BOTTLE)
PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 30 MG (60 CAPSULE BOTTLE)
PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 40 MG (60 CAPSULE BOTTLE)

*** Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS AND HEPATOMEGALY WITH STEATOSIS; PANCREATITIS

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 (5.1)]*.
Fatal and nonfatal 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 degree of immunosuppression *[see Warnings and Precautions (5.4)]*.

1 INDICATIONS AND USAGE
Stavudine capsules, USP in combination with other antiretroviral agents, are indicated for the treatment of human immunodeficiency virus (HIV)-1 infection *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION
The interval between doses of stavudine capsules should be 12 hours. Stavudine capsules may be taken with or without food.

2.1 Recommended Adult Dosage
The recommended adult dosage is based on body weight as follows:
- For patients weighing less than 60 kg: 30 mg every 12 hours.
- For patients weighing at least 60 kg: 40 mg every 12 hours.

2.2 Recommended Pediatric Dosage
- For newborns from birth to 13 days old: 0.5 mg/kg given every 12 hours.
- For pediatric patients at least 14 days old and weighing less than 30 kg: 1 mg/kg given every 12 hours.
- For pediatric patients weighing at least 30 kg: use the recommended adult dosage.

2.3 Dosage Adjustment

Renal Impairment

Adult Patients: Stavudine capsules may be administered to adult patients with impaired renal function with an adjustment in dosage as shown in Table 1.

Table 1: Recommended Dosage Adjustment for Adult Patients with Renal Impairment

Creatinine Clearance (mL/min)	**Recommended Stavudine Capsules Dose by Patient Weight**	
	at least 60 kg	**less than 60 kg**
greater than 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
Hemodialysis	20 mg every 24 hours*	15 mg every 24 hours*

* Administered after the completion of hemodialysis on dialysis days and at the same time of day on non-dialysis days.

Pediatric Patients: 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. There are insufficient data to recommend a specific dose adjustment of stavudine capsules in this patient population.

3 DOSAGE FORMS AND STRENGTHS

- **Stavudine Capsules 15 mg** are dark red opaque/light yellow opaque size ‘4’ 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.
- **Stavudine Capsules 20 mg** are light brown opaque/light brown opaque size ‘3’ 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.
- **Stavudine Capsules 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.
- **Stavudine Capsules 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.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including stavudine and other antiretrovirals. Although relative rates of lactic acidosis have not been assessed in prospective well-controlled trials, longitudinal cohort and retrospective studies suggest that this infrequent event may be more often associated with antiretroviral combinations containing stavudine. Female gender, obesity, and prolonged nucleoside exposure may be risk factors. Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk *[see Use in Specific Populations (8.1)]*.

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 unexplained weight loss); respiratory symptoms (tachypnea and dyspnea); or neurologic symptoms, including motor weakness *[see Warnings and Precautions (5.3)]* 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). Permanent discontinuation of stavudine should be considered for patients with confirmed lactic acidosis.

5.2 Hepatic 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.

Hepatotoxicity and hepatic failure resulting in death were reported during postmarketing surveillance in HIV-infected patients treated with hydroxyurea and other antiretroviral agents. Fatal hepatic events were reported most often in patients treated with the combination of hydroxyurea, didanosine, and stavudine. This combination should be avoided. *[See Adverse Reactions (6).]*

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 (e.g., loss of HIV-1/HCV virologic suppression) interaction was seen when ribavirin was coadministered with stavudine in HIV-1/HCV co-infected patients *[see Drug Interactions (7)]*, **hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 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 (e.g., Child-Pugh >6) (see **the full prescribing information for interferon and ribavirin**).

5.3 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). If motor weakness develops, stavudine should be discontinued. Symptoms may continue or worsen following discontinuation of therapy.

Peripheral sensory neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been reported in patients receiving stavudine therapy. Peripheral neuropathy, which can be severe, is dose related and occurs more frequently in patients with advanced HIV-1 disease, a history of peripheral neuropathy, or in patients receiving other drugs that have been associated with neuropathy, including didanosine *[see Adverse Reactions (6)]*.

Patients should be monitored for the development of peripheral neuropathy. Stavudine-related peripheral neuropathy may resolve if therapy is withdrawn promptly. If peripheral neuropathy develops permanent discontinuation of stavudine should be considered. In some cases, symptoms may worsen temporarily following discontinuation of therapy.

5.4 Pancreatitis

Fatal and nonfatal 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 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; avoid use in combination with didanosine.

5.5 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.

In randomized controlled trials of treatment-naive patients, clinical lipoatrophy or lipodystrophy developed in a higher proportion of patients treated with stavudine compared to other nucleosides (tenofovir or abacavir). Dual energy x-ray absorptiometry (DEXA) scans demonstrated overall limb fat loss in stavudine-treated patients compared to limb fat gain or no gain in patients treated with other nucleosides (abacavir, tenofovir, or zidovudine). The incidence and severity of lipoatrophy or lipodystrophy are cumulative over time with stavudine-containing regimens. In clinical trials, switching from stavudine to other nucleosides (tenofovir or abacavir) resulted in increases in limb fat with modest to no improvements in clinical lipoatrophy. Patients receiving stavudine should be monitored for symptoms or signs of lipoatrophy or lipodystrophy and questioned about body changes related to lipoatrophy or lipodystrophy. Given the potential risks of using stavudine including lipoatrophy or lipodystrophy, a benefit-risk assessment for each patient should be made and an alternative antiretroviral should be considered.

5.6 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 jiroveci* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment. Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- lactic acidosis and severe hepatomegaly with steatosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- hepatic toxicity *[see Warnings and Precautions (5.2)]*
- neurologic symptoms and motor weakness *[see Warnings and Precautions (5.3)]*
- pancreatitis *[see Boxed Warning and Warnings and Precautions (5.4)]*
- lipoatrophy/lipodystrophy *[see Warnings and Precautions (5.5)]*

When stavudine is used in combination with other agents with similar toxicities, the incidence of adverse reactions may be higher than when stavudine is used alone.

6.1 Clinical Trial Experience in Adults

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Selected adverse reactions that occurred in adult patients receiving stavudine in a controlled monotherapy study (Study AI455-019) are provided in Table 2.

Table 2: Selected Adverse Reactions in Study AI455-019[a] (Monotherapy)

Adverse Reaction	**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] The incidences reported included all severity grades and all reactions regardless of causality.

[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 study AI455-019.

Selected adverse reactions that occurred in antiretroviral-naive adult patients receiving stavudine from two controlled combination studies are provided in Table 3.

Table 3: Selected Adverse Reactions[a] in START 1 and START 2[b] Studies (Combination Therapy)

Adverse Reaction	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] The incidences reported included all severity grades and all reactions regardless of causality.

[b] START 2 compared two triple-combination regimens in 205 treatment-naive 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.

Selected laboratory abnormalities reported in a controlled monotherapy study (Study AI455-019) are provided in Table 4.

Table 4: Selected 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	10
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 5 and 6.

Table 5: 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 6: 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

6.2 Clinical Trial Experience in Pediatric Patients

Adverse reactions and serious laboratory abnormalities reported in pediatric patients from birth through adolescence during clinical trials were similar in type and frequency to those seen in adult patients. *[See Use in Specific Populations (8.4).]*

6.3 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of stavudine. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions 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 (5.5)]*.

Digestive Disorders: anorexia.

Exocrine Gland Disorders: pancreatitis, including fatal cases *[see Warnings and Precautions (5.4)]*.

Hematologic Disorders: anemia, leukopenia, thrombocytopenia, neutropenia, and macrocytosis.

Liver: symptomatic hyperlactatemia/lactic acidosis and hepatic steatosis *[see Warnings and Precautions (5.1)]*, hepatitis and liver failure.

Metabolic Disorders: lipoatrophy, lipodystrophy *[see Warnings and Precautions (5.5)]*, 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 (5.1, 5.3)]*.

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 *[see Warnings and Precautions (5)]*. The combination of stavudine and hydroxyurea, with or without didanosine, should be avoided.

7 DRUG INTERACTIONS

Stavudine is unlikely to interact with drugs metabolized by cytochrome P450 isoenzymes.

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 inhibited at relevant concentrations by doxorubicin. The clinical significance of this interaction is unknown; therefore, concomitant use of stavudine with doxorubicin should be undertaken with caution.
Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. The clinical significance of the interaction with stavudine is unknown; therefore, concomitant use of stavudine with ribavirin should be undertaken with caution. No pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n=18), stavudine (n=10), or zidovudine (n=6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected patients *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic Effects
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. Stavudine should be used during pregnancy only if the potential benefit justifies the potential risk.

Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. It is unclear if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in nonpregnant individuals receiving nucleoside analogues *[see Boxed Warning and Warnings and Precautions (5.1)]*. **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 early diagnosis of lactic acidosis/hepatic steatosis syndrome.
Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to stavudine and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

8.3 Nursing Mothers
The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Studies in lactating rats demonstrated that stavudine is excreted in milk. Although it is not known whether stavudine is excreted in human milk, there exists the potential for adverse effects from stavudine in nursing infants. 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 stavudine**.

8.4 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 *[see Dosage and Administration (2.2) and Adverse Reactions (6.2)]*.

Adverse reactions 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 ages 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-1-infected pediatric patients ranging in age from 5 weeks to 15 years and in weight from 2 to 43 kg after IV or oral administration of single doses and twice-daily regimens and in 30 HIV-1-exposed or -

infected newborns ranging in age from birth to 4 weeks after oral administration of twice-daily regimens *[see Clinical Pharmacology (12.3, Table 9)]*.

8.5 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 older individuals to the effects of stavudine cannot be ruled out.

In a monotherapy Expanded Access Program for patients with advanced HIV-1 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 kidney, 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 (2.3)]*.

8.6 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. Based on these observations, it is recommended that the stavudine dosage be modified in patients with reduced creatinine clearance and in patients receiving maintenance hemodialysis *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

10 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.

11 DESCRIPTION

Stavudine capsules, USP contain stavudine (d4T), which is a synthetic thymidine nucleoside analogue, active against the human immunodeficiency virus type 1 (HIV-1). The chemical name for stavudine is 2#,3#-didehydro-3#-deoxythymidine. Stavudine has the following structural formula:

Stavudine USP is a white to off-white crystalline solid with the molecular formula $C_{10}H_{12}N_2O_4$ and a molecular weight of 224.2. The solubility of stavudine at 23°C is approximately 83 mg/mL in water and 30 mg/mL in propylene glycol. The n-octanol/water partition coefficient of stavudine at 23°C is 0.144.

Stavudine is available as capsules for oral administration containing either 15 mg, 20 mg, 30 mg, or 40 mg of stavudine. Each capsule also contains 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. The capsules are printed with black ink containing black iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Stavudine is an antiviral drug *[see Clinical Pharmacology (12.4)]*.

12.3 Pharmacokinetics

The pharmacokinetics of stavudine have been evaluated in HIV-1-infected adult and pediatric patients (Tables 7, 8, and 9). 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-1-infected adults are shown in Table 7.

Table 7: Steady-State Pharmacokinetic Parameters of Stavudine in HIV-1-Infected Adults

Parameter	Stavudine 40 mg BID Mean ± SD (n=8)
AUC_{0-24} (ng•h/mL)	2568 ± 454
C_{max} (ng/mL)	536 ± 146
C_{min} (ng/mL)	8 ± 9

AUC_{0-24} = 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 mcg/mL. Stavudine distributes equally between red blood cells and plasma. Volume of distribution is shown in Table 8.

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 ^{14}C-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 ^{14}C-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%, 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-1-infected patients, renal elimination of unchanged drug accounts for about 40% of the overall clearance regardless of the route of administration (Table 8). The mean renal clearance was about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration.

Table 8: Pharmacokinetic Parameters of Stavudine in HIV-1-Infected Adults: Bioavailability, Distribution, and Clearance

Parameter	Mean ± SD	n
Oral bioavailability (%)	86.4 ± 18.2	25
Volume of distribution (L)[a]	46 ± 21	44
Total body clearance (mL/min)[a]	594 ± 164	44
Apparent oral clearance (mL/min)[b]	560 ± 182[c]	113
Renal clearance (mL/min)[a]	237 ± 98	39
Elimination half-life, IV dose (h)[a]	1.15 ± 0.35	44
Elimination half-life, oral dose (h)[b]	1.6 ± 0.23	8
Urinary recovery of stavudine (% of dose)[a,d]	42 ± 14	39

[a] Following 1-hour IV infusion.

[b] Following single oral dose.

[c] Assuming a body weight of 70 kg.

[d] Over 12 to 24 hours.

Special Populations

Pediatric

Pharmacokinetic parameters of stavudine in pediatric patients are presented in Table 9.

Table 9: Pharmacokinetic Parameters (Mean ± SD) of Stavudine in HIV-1-Exposed or -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 ± 2.8	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 to 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 10). 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 to 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 (2.3)]*.

Table 10: 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 to 50 mL/min (n=5)**	**9 to 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
$T_{½}$ (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.

$T_{½}$ = Terminal elimination half-life.

NA = Not applicable.

Hepatic Impairment

Stavudine pharmacokinetics were 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 have not been studied in patients >65 years of age. *[See Use in Specific Populations (8.5).]*

Gender

A population pharmacokinetic analysis of data collected during a controlled clinical study in HIV-1-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-1-infected patients showed no clinically important differences between races (n=233 Caucasian, 39 African-American, 41 Hispanic, 1 Asian, and 4 other).

Drug Interaction Studies

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 11 and 12 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 11: Results of Drug Interaction Studies with Stavudine: Effects of Coadministered 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 q 12 h for 4 days	40 mg q 12 h 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 q 8 h for 56 days	30 to 40 mg q 12 h for 56 days	8	↔	↔

↑ indicates increase.

↔ Indicates no change, or mean increase or decrease of <10%.

[a] HIV-1-infected patients.

Table 12: 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 q 12 h for 4 days	40 mg q 12 h 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 q 8 h for 56 days	30 to 40 mg q 12 h for 56 days	8	↔	↔

↔ Indicates no change, or mean increase or decrease of <10%.

[a] HIV-1-infected patients.

12.4 Microbiology

Mechanism of Action

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

Antiviral Activity in Cell Culture

The cell culture antiviral activity of stavudine was measured in peripheral blood mononuclear cells, monocytic cells, and lymphoblastoid cell lines. The concentration of drug necessary to inhibit HIV-1 replication by 50% (EC_{50}) ranged from 0.009 to 4 μM against laboratory and clinical isolates of HIV-1. In cell culture, stavudine exhibited additive to antagonistic activity in combination with zidovudine. Stavudine in combination with either abacavir, didanosine, tenofovir, or zalcitabine exhibited additive to synergistic anti-HIV-1 activity. Ribavirin, at the 9 to 45 μM concentrations tested, reduced the anti-HIV-1 activity of stavudine by 2.5- to 5-fold.

The relationship between cell culture susceptibility of HIV-1 to stavudine and the inhibition of HIV-1 replication in humans has not been established.

Resistance

HIV-1 isolates with reduced susceptibility to stavudine have been selected in cell culture (strain-specific) and were also obtained from patients treated with stavudine. Phenotypic analysis of HIV-1 isolates from 61 patients receiving prolonged (6 to 29 months) stavudine monotherapy showed that post-therapy isolates from four patients exhibited EC_{50} values more than 4-fold (range 7- to 16-fold) higher than the average pretreatment susceptibility of baseline isolates. Of these, HIV-1 isolates from one patient contained the zidovudine-resistance-associated substitutions T215Y and K219E, and isolates from another patient contained the multiple-nucleoside-resistance-associated substitution Q151M. Mutations in the RT gene of HIV-1 isolates from the other two patients were not detected. The genetic basis for stavudine susceptibility changes has not been identified.

Cross-resistance

Cross-resistance among HIV-1 reverse transcriptase inhibitors has been observed. Several studies have demonstrated that prolonged stavudine treatment can select and/or maintain thymidine analogue mutations (TAMs; M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) associated with zidovudine resistance. HIV-1 isolates with one or more TAMs exhibited reduced susceptibility to stavudine in cell culture. These TAMs are seen at a similar frequency with stavudine and zidovudine in virological treatment. The clinical relevance of these findings suggests that stavudine should be avoided in the presence of thymidine analogue mutations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In 2-year carcinogenicity studies in mice and rats, stavudine was noncarcinogenic at doses which produced exposures (AUC) 39 and 168 times, respectively, human exposure at the recommended clinical dose. Benign and malignant liver tumors in mice and rats and malignant urinary bladder tumors in male rats occurred at levels of exposure 250 (mice) and 732 (rats) times human exposure at the recommended clinical dose.

Stavudine was not mutagenic in the Ames, *E. coli* reverse mutation, or the CHO/HGPRT mammalian cell forward gene mutation assays, with and without metabolic activation. Stavudine produced positive results in the *in vitro* human lymphocyte clastogenesis and mouse fibroblast assays, and in the *in vivo* mouse micronucleus test. In the *in vitro* assays, stavudine elevated the frequency of chromosome aberrations in human lymphocytes (concentrations of 25 to 250 mcg/mL, without metabolic activation) and increased the frequency of transformed foci in mouse fibroblast cells (concentrations of 25 to 2500 mcg/mL, with and without metabolic activation). In the *in vivo* micronucleus assay, stavudine was clastogenic in bone marrow cells following oral stavudine administration to mice at dosages of 600 to 2000 mg/kg/day for 3 days.

No evidence of impaired fertility was seen in rats with exposures (based on C_{max}) up to 216 times that observed following a clinical dosage of 1 mg/kg/day.

14 CLINICAL STUDIES

Combination Therapy

The combination use of stavudine is based on the results of clinical studies in HIV-1-infected patients in double- and triple-combination regimens with other antiretroviral agents.

One of these studies (START 1) was a multicenter, randomized, open-label study comparing stavudine (40 mg twice daily) plus lamivudine plus indinavir to zidovudine plus lamivudine plus indinavir in 202 treatment-naive patients. Both regimens resulted in a similar magnitude of inhibition of HIV-1 RNA levels and increases in $CD4^+$cell counts through 48 weeks.

Monotherapy

The efficacy of stavudine was demonstrated in a randomized, double-blind study (AI455-019, conducted 1992 to 1994) comparing stavudine with zidovudine in 822 patients with a spectrum of HIV-1-related symptoms. The outcome in terms of progression of HIV-1 disease and death was similar for both drugs.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Capsules

Stavudine Capsules USP, 15 mg are dark red opaque/light yellow opaque size ‘4’ 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 ‘3’ 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

16.3 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].

17 PATIENT COUNSELING INFORMATION

See MEDICATION GUIDE.

17.1 General

Patients should be advised that stavudine is not a cure for HIV-1 infection, and that they may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should be advised to remain under the care of a physician when using stavudine and the importance of adherence to any antiretroviral regimen including those that contain stavudine.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** It is not known if stavudine can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in breast milk.

Patients should be informed that when stavudine is used in combination with other agents with similar toxicities, the incidence of adverse reactions may be higher than when stavudine is used alone.
Patients should be instructed that if they miss a dose, to take it as soon as possible. If it is almost time for the next dose, skip the missed dose and continue the regular dosing schedule.

Patients should be instructed if they take too much stavudine, they should contact a poison control center or emergency room right away.

Patients should be informed that the Centers for Disease Control and Prevention (CDC) recommend that HIV-infected mothers not nurse newborn infants to reduce the risk of postnatal transmission of HIV infection.

17.2 Lactic Acidosis

Patients should be informed of the importance of early recognition of symptoms of symptomatic hyperlactatemia or lactic acidosis syndrome, which include unexplained weight loss, abdominal discomfort, nausea, vomiting, fatigue, dyspnea, and motor weakness. Patients in whom these symptoms develop should seek medical attention immediately. Discontinuation of stavudine therapy may be required.

17.3 Hepatic Toxicity

Patients should be informed that an increased risk of hepatotoxicity, which may be fatal, may occur in patients treated with stavudine in combination with didanosine and hydroxyurea. This combination should be avoided.

17.4 Peripheral Neuropathy

Patients should be informed that an important toxicity of stavudine is peripheral neuropathy. Patients should be aware that peripheral neuropathy is manifested by numbness, tingling, or pain in hands or feet, and that these symptoms should be reported to their physicians. Patients should be counseled that peripheral neuropathy occurs with greatest frequency in patients who have advanced HIV-1 disease or a history of peripheral neuropathy, and discontinuation of stavudine may be required if toxicity develops.

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

17.5 Pancreatitis
Patients should be informed that an increased risk of pancreatitis, which may be fatal, may occur in patients treated with the combination of stavudine and didanosine. This combination should be avoided. Patients should be closely monitored for symptoms of pancreatitis.

The patient should be instructed to avoid alcohol while taking stavudine. Alcohol may increase the patient's risk of pancreatitis or liver damage.

17.6 Fat Redistribution
Patients should be informed that redistribution or accumulation of body fat may occur in individuals receiving antiretroviral therapy including stavudine. Patients receiving stavudine should be monitored for clinical signs and symptoms of lipoatrophy/lipodystrophy. Patients should be routinely questioned about body changes related to lipoatrophy/lipodystrophy.

Manufactured for:
Aurobindo Pharma USA, Inc.
2400 Route 130 North
Dayton, NJ 08810

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

Revised: 10/2012

MEDICATION GUIDE
Stavudine Capsules, USP

Read this Medication Guide before you start taking stavudine capsules and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment. You and your healthcare provider should talk about your treatment with stavudine capsules before you start taking them and at regular check-ups. You should stay under your healthcare provider's care when taking stavudine capsules.
What is the most important information I should know about stavudine capsules?
Stavudine capsules can cause serious side effects, including:
1. **Build up of acid in your blood (lactic acidosis).** Lactic acidosis can cause death and must be treated in the hospital. The risk of lactic acidosis may be higher if you:
- have liver problems
- are pregnant. There have been deaths reported in pregnant women who get lactic acidosis after taking stavudine capsules and VIDEX, or stavudine capsules and VIDEX EC (didanosine).
- are female
- are overweight
- have been treated for a long time with other medicines used to treat HIV

It is important to call your healthcare provider right away if you:
- feel weak or tired
- have unusual (not normal) muscle pain
- have trouble breathing
- have stomach pain with nausea and vomiting
- feel cold, especially in your arms and legs
- feel dizzy or light-headed

- have a fast or irregular heartbeat

2. Liver problems. Some people (including pregnant women) who have taken stavudine capsules have had serious liver problems. These problems include liver enlargement (hepatomegaly), fat in the liver (steatosis), liver failure, and death due to liver problems. Your healthcare provider should check your liver function while you are taking stavudine capsules. You should be especially careful if you have a history of heavy alcohol use or liver problems. Use of stavudine capsules with VIDEX EC or VIDEX (didnosine) may increase your risk for liver damage.

It is important to call your healthcare provider right away if you have:

- yellowing of your skin or the white of your eyes (jaundice)
- dark urine
- pain on the right side of your stomach
- swelling of your stomach
- easy bruising or bleeding
- loss of appetite
- nausea or vomiting

3. Swelling of the pancreas (pancreatitis) that may cause death has occurred when stavudine capsules were used with VIDEX EC or VIDEX (didanosine). Pancreatitis can happen at any time during your treatment with stavudine capsules.

It is important to call your healthcare provider right away if you have:

- stomach pain
- swelling of your stomach
- nausea and vomiting
- fever

What are stavudine capsules?

Stavudine capsules are a prescription medicine used with other HIV medicines to treat human immunodeficiency virus (HIV) infection in children and adults. Stavudine belongs to a class of drugs called nucleoside analogues.

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

Who should not take stavudine capsules?

Do not take stavudine capsules if you:

- are allergic to stavudine or any of the ingredients in stavudine capsules. See the end of this Medication Guide for a complete list of the ingredients in stavudine capsules.

What should I tell my healthcare provider before taking stavudine capsules?

Before you take stavudine capsules, tell your healthcare provider if you:

- have or had liver problems (such as hepatitis)
- have or had problems with your pancreas (pancreatitis)
- have or had kidney problems
- have or had persistent numbness, tingling, or pain in the hands or feet (neuropathy)
- have gallstones
- drink alcoholic beverages
- have any other medical conditions

- are pregnant or plan to become pregnant. It is not known if stavudine capsules will harm your unborn baby. Tell your healthcare provider right away if you become pregnant while taking stavudine capsules. You and your healthcare provider will decide if you should take stavudine capsules while you are pregnant.

Pregnancy Registry: There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of the registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.

- **are breastfeeding or plan to breastfeed. Do not breastfeed.** It is not known if stavudine can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Tell your healthcare provider about all the medicines that you take, including prescription and non-prescription medicines, vitamins, or herbal supplements. Stavudine capsules may affect the way other medicines work, and other medicines may affect how stavudine capsules work.

Especially tell your healthcare provider if you take:

- COMBIVIR®, RETROVIR®, TRIZIVIR® (zidovudine or AZT)
- VIDEX® or VIDEX EC® (didanosine)
- ADRIAMYCIN®, RUBEX® (doxorubicin)
- COPEGUS®, REBETOL®, RIBASPHERE®, RIBAVIRIN®, VIRAZOLE® (ribavirin)
- ROFERON-A®, INTRON-A®, and others (interferon)
- HYDREA®, DROXIA® (hydroxyurea)

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

Ask your healthcare provider if you are not sure if you take one of the medicines listed above.

How should I take stavudine capsules?

- Take stavudine capsules exactly as your healthcare provider tells you to take them.
- Your healthcare provider will tell you how much stavudine to take and when to take it.
- If your child will be taking stavudine capsules, your child's healthcare provider should give you instructions on how to give this medicine.
- Your healthcare provider may change your dose. Do not change your dose of stavudine capsules without talking to your healthcare provider.
- Stavudine capsules may be taken with or without food.
- 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.
- Some medicines may require your healthcare provider to monitor your therapy or change your therapy. Check with your healthcare provider.
- If your kidneys are not working well, your healthcare provider will need to do regular blood and urine tests to check how they are working while you take stavudine capsules. Your healthcare provider may also lower your dosage of stavudine capsules if your kidneys are not working well.
- **If you take too much stavudine**, contact a poison control center or emergency room right away.

What should I avoid while taking stavudine capsules?

- **Alcohol. You should avoid drinking alcohol while taking stavudine capsules.** Alcohol may increase your risk of getting pain and swelling of your pancreas (pancreatitis) or may damage your liver.

What are the possible side effects of stavudine capsules?

Stavudine capsules can cause serious side effects including:

- Stavudine capsules can cause lactic acidosis, liver problems, and pancreatitis. See "**What is the most important information I should know about stavudine capsules?**"

- **Neurologic symptoms. Symptoms include: weakness of your legs, feet, arms, or hands (motor weakness) and numbness or tingling in your hands or feet (neuropathy).** These problems can happen more often in people who have advanced HIV disease, have a history of peripheral neuropathy, or in people who take other medicines that also are associated with neuropathy including didanosine. In some cases, neuropathy may temporarily worsen after you stop taking stavudine capsules. Neuropathy can be difficult to notice in children who take stavudine capsules. Ask your child's healthcare provider for the signs and symptoms of peripheral neuropathy in children.

It is important to call your healthcare provider right away if you have:

- numbness in your hands or feet

- tingling in your hands or feet

- weakness in your legs, feet, arms, or hands

- **Changes in body fat (fat redistribution).** Changes in body fat (lipoatrophy or lipodystrophy) have been seen in some people taking HIV medicines including stavudine capsules. Loss of body fat (lipoatrophy) happens more often in people who take stavudine capsules than in people who take other similar HIV medicines.

These changes may include:

- more fat in or around your
  - trunk
  - upper back and neck (buffalo hump)
  - breast or chest
- loss of fat in your
  - legs
  - arms
  - face

Your healthcare provider will monitor you for changes in your body fat. It is important to tell your healthcare provider if you notice any of these changes.

- **Changes in your immune system (immune reconstitution syndrome).** Your immune system may begin to fight infections that have been in your body for a long time. Tell your healthcare provider if you start having new or worse symptoms of infection after you start taking HIV medicine.

The most common side effects of stavudine capsules include:

- headache

- diarrhea

- rash

- nausea

- vomiting

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of stavudine capsules. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store stavudine capsules?

Store stavudine capsules in a tightly closed container at room temperature at 15° to 30°C (59° to 86°F).

Keep stavudine capsules and all medicines out of the reach of children and pets.

General information about the safe and effective use of stavudine capsules

Avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**

- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**

- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use stavudine capsules for a condition for which they were not prescribed. Do not give stavudine capsules to other people, even if they have the same symptoms as you have. They may harm them. Do not keep medicine that is out of date or that you no longer need. Dispose of unused medicines through community take-back disposal programs when available or place stavudine capsules in an unrecognizable closed container in the household trash.

This Medication Guide summarizes the most important information about stavudine capsules. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about stavudine capsules that is written for health professionals. For more information, call 1-866-850-2876.

What are the ingredients in stavudine capsules?

Active Ingredient: 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. The capsules are printed with black ink containing black iron oxide.

All brands listed are the trademarks of their respective owners and are not trademarks of Aurobindo Pharma Limited.

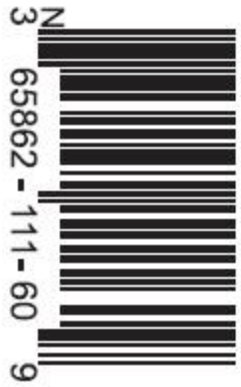
This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Aurobindo Pharma USA, Inc.
2400 Route 130 North
Dayton, NJ 08810

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

Revised: 10/2012

PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 15 MG (60 CAPSULE BOTTLE)
NDC 65862-111-60
Stavudine Capsules, USP
15 mg
PHARMACIST: Detach and dispense the enclosed Medication Guide to each patient.
Rx only **60 Capsules**
AUROBINDO



Each capsule contains:
15 mg of stavudine USP.

Usual Dosage: See package insert for Dosage and Administration.

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].

Replace cap securely after each opening.

Warning: As with all medications, keep out of the reach of children.

NDC 65862-111-60

Stavudine Capsules, USP
15 mg

PHARMACIST: Detach and dispense the enclosed Medication Guide to each patient.
Rx only **60 Capsules**

Manufactured for:
Aurobindo Pharma USA, Inc.
2400 Route 130 North
Dayton, NJ 08810

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

M.L.No.: 19/HD/AP/95/F/R

Batch :

Expiry :

P1408157

PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 20 MG (60 CAPSULE BOTTLE)
NDC 65862-112-60
Stavudine Capsules, USP
20 mg
PHARMACIST: Detach and dispense the enclosed Medication Guide to each patient.
Rx only **60 Capsules**
AUROBINDO

N 3 65862 - 112- 60 6

Each capsule contains:
20 mg of stavudine USP.

Usual Dosage: See package insert for Dosage and Administration.

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].

Replace cap securely after each opening.

Warning: As with all medications, keep out of the reach of children.

NDC 65862-112-60

Stavudine Capsules, USP
20 mg

PHARMACIST: Detach and dispense the enclosed Medication Guide to each patient.
Rx only **60 Capsules**

AUROBINDO

Manufactured for:
Aurobindo Pharma USA, Inc.
2400 Route 130 North
Dayton, NJ 08810

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

M.L.No.: 19/HD/AP/95/F/R

Batch :

Expiry :

P1408158

PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 30 MG (60 CAPSULE BOTTLE)
NDC 65862-046-60
Stavudine Capsules, USP
30 mg
PHARMACIST: Detach and dispense the enclosed Medication Guide to each patient.
Rx only **60 Capsules**
AUROBINDO

N 3 65862 - 046 - 60 4

Each capsule contains:
30 mg of stavudine USP.

Usual Dosage: See package insert for Dosage and Administration.

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].

Replace cap securely after each opening.

Warning: As with all medications, keep out of the reach of children.

NDC 65862-046-60

Stavudine Capsules, USP
30 mg

PHARMACIST: Detach and dispense the enclosed Medication Guide to each patient.
Rx only **60 Capsules**

AUROBINDO

Manufactured for:
Aurobindo Pharma USA, Inc.
2400 Route 130 North
Dayton, NJ 08810

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

M.L.No.: 19/HD/AP/95/F/R

Batch :

Expiry :

P1408159

PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 40 MG (60 CAPSULE BOTTLE)
NDC 65862-047-60
Stavudine Capsules, USP
40 mg
PHARMACIST: Detach and dispense the enclosed Medication Guide to each patient.
Rx only **60 Capsules**
AUROBINDO

N 3 65862 - 047 - 60 1

Each capsule contains:
40 mg of stavudine USP.

Usual Dosage: See package insert for Dosage and Administration.

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].

Replace cap securely after each opening.

Warning: As with all medications, keep out of the reach of children.

NDC 65862-047-60

Stavudine Capsules, USP

40 mg

PHARMACIST: Detach and dispense the enclosed Medication Guide to each patient.

Rx only **60 Capsules**

AUROBINDO

Manufactured for:
Aurobindo Pharma USA, Inc.
2400 Route 130 North
Dayton, NJ 08810

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

M.L.No.: 19/HD/AP/95/F/R

Batch :

Expiry :

P1408160

Revised: 11/2012

Distributed by: Aurobindo Pharma Limited