PRODUCT MONOGRAPH

Pr **ZERIT®**

stavudine capsules USP, 15, 20, 30 and 40 mg

Antiretroviral Agent

Bristol-Myers Squibb Canada
Montreal, Canada

Date of Preparation
March 14, 1996

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Control No.: 212105

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients*
Oral	Capsules 15, 20, 30 and 40 mg	Lactose

** For a complete listing, see Dosage Forms, Composition and Packaging section*

INDICATIONS AND CLINICAL USE

ZERIT (stavudine), in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection (See CLINICAL TRIALS).

CONTRAINDICATIONS

ZERIT (stavudine) is contraindicated in patients with clinically significant hypersensitivity to stavudine or to any of the components contained in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

Co-administration of ZERIT with didanosine is contraindicated due to the potential for serious and/or life-threatening events notably lactic acidosis, liver function abnormalities, pancreatitis, and peripheral neuropathy.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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 antiretroviral agents (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Lactic Acidosis and Severe Hepatomegaly with Steatosis). 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 is contraindicated (see CONTRAINDICATIONS).

Treatment with ZERIT should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). Permanent discontinuation of ZERIT should be considered for patients with confirmed lactic acidosis.

Pancreatitis

Fatal and nonfatal pancreatitis have occurred during therapy (in controlled clinical studies and in postmarketing reports) when ZERIT was part of a combination regimen that included didanosine or didanosine and hydroxyurea, in both treatment-naive and treatment-experienced patients, regardless of degree of immunosuppression (See WARNING AND PRECAUTIONS, Hepatic / Biliary / Pancreatic, Pancreatic).

General

Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with ZERIT, didanosine and zidovudine. ZERIT therapy is associated with several severe side effects, such as lactic acidosis, lipoatrophy and polyneuropathy, for which a potential underlying mechanism is mitochondrial toxicity.

Patients receiving ZERIT (stavudine) or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection and, therefore, should remain under close clinical observation by physicians experienced in the treatment of patients with HIV disease and associated complications.

Carcinogenesis and Mutagenesis

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 μg/mL, without metabolic activation) and increased the frequency of transformed foci in mouse fibroblast cells (concentrations of 25 to 2500 μg/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.

Impairment of Fertility

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

Endocrine and Metabolism

Lipoatrophy

On the basis of mitochondrial toxicity, ZERIT has been shown to cause loss of subcutaneous fat, which is most evident in the face, limbs, and buttocks. The incidence and severity of lipoatrophy are related to cumulative exposure, and is often not reversible when ZERIT treatment is stopped. Patients receiving ZERIT should be frequently examined and questioned for signs of lipoatrophy. When such development is found, treatment with ZERIT should be discontinued.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. In some cases, for lipids, there is evidence of a treatment effect. While for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Hepatic/Biliary/Pancreatic

Hepatic

Hepatitis or liver failure, which was fatal in some cases, have been reported with ZERIT. Hepatotoxicity and hepatic failure resulting in death were reported during postmarketing surveillance in HIV-infected patients treated with antiretroviral agents in combination with hydroxyurea. Fatal hepatic events were reported most often in patients treated with the combination of hydroxyurea, didanosine, and stavudine. The combination of stavudine and didanosine is contraindicated (see **CONTRAINDICATIONS**). Patients treated with ZERIT and hydroxyurea should be closely monitored for signs of liver toxicity.

The safety and efficacy of ZERIT have not been established in patients with significant underlying liver disorders. 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.

Hepatic decompensation has been reported with ZERIT in combination with interferon or with interferon and ribavirin in HIV/HCV cirrhotic patients. Some of the cases had a fatal outcome. During treatment, patients' clinical status and hepatic function should be closely monitored for signs and symptoms of hepatic decompensation. Treatment with interferon/ribavirin should be discontinued immediately when hepatic decompensation is noted.

Lactic Acidosis and 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 antiretroviral agents. 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 is contraindicated (see CONTRAINDICATIONS).

Particular caution should be exercised when administering ZERIT 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, see **Neurologic Symptoms**) might be indicative of the development of symptomatic hyperlactatemia or lactic acidosis syndrome. Symptoms associated with hyperlactatemia may continue or worsen following discontinuation of antiretroviral therapy.

Treatment with ZERIT should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). Permanent discontinuation of ZERIT should be considered for patients with confirmed lactic acidosis.

Pancreatic

Fatal and nonfatal pancreatitis have occurred during therapy (in controlled clinical studies and in postmarketing reports) when ZERIT was part of a combination regimen that included didanosine or didanosine and hydroxyurea, in both treatment-naive and treatment-experienced patients, regardless of degree of immunosuppression. This combination of ZERIT and didanosine and any other agents that are toxic to the pancreas should be suspended in patients with suspected pancreatitis. Reinstitution of ZERIT after a confirmed diagnosis of pancreatitis should be

undertaken with particular caution and close patient monitoring. The new regimen should contain neither didanosine nor hydroxyurea.

Pancreatitis was generally attributed to advanced disease or to prior or concurrent treatment with medications known to be associated with pancreatitis. The occurrences were not dose-related, and were occasionally fatal. Patients with a history of pancreatitis appear to be at increased risk for recurrence.

Immune

Immune Reconstitution Inflammatory Syndrome: During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP, and TB), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Neurologic

Motor weakness (which was fatal in some cases) has been reported rarely in patients receiving combination antiretroviral therapy including ZERIT. Most of these cases occurred in the setting of symptomatic hyperlactatemia or lactic acidosis syndrome. The evolution of motor weakness may mimic the clinical presentation of Guillain-Barré syndrome (including respiratory failure). If motor weakness develops in a patient receiving ZERIT, the drug should be discontinued. Symptoms may continue or worsen following discontinuation of therapy.

ZERIT therapy has been associated with peripheral neuropathy which is manifested by weakness, atrophy, numbness, tingling, or pain in the hands or feet, and some symptoms can be severe. Peripheral motor and sensory neuropathy, which is dose related, has occurred more frequently in patients with advanced HIV disease, a history of neuropathy, or concurrent neurotoxic drug therapy, including didanosine (see ADVERSE REACTIONS).

Peripheral neuropathy, which was severe in some cases, has been reported in HIV-infected patients receiving hydroxyurea in combination with antiretroviral agents, including didanosine with or without stavudine.

Patients should be monitored for the development of neuropathy. 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 the dose (see DOSAGE AND ADMINISTRATION). If neuropathy recurs after resumption of ZERIT, permanent discontinuation of ZERIT should be considered

Peripheral neuropathy can be difficult to notice in children who take ZERIT. Caregivers of young children receiving ZERIT therapy should be instructed regarding detection and reporting of peripheral neuropathy.

Renal

In HIV-infected patients with renal impairment, renal clearance and apparent oral clearance of stavudine was decreased. The terminal elimination half-life (t½) was prolonged up to 8 hours. C_{max} and T_{max} were not significantly affected by reduced renal function. Based on these preliminary observations, it is recommended that stavudine dosage be modified in patients with reduced creatinine clearance (≤ 50 mL/min) (see DOSAGE AND ADMINISTRATION).

Special Populations

Pregnant Women

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 (see CONTRAINDICATIONS). It is not known if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in nonpregnant individuals receiving nucleoside analogues (see WARNINGS AND PRECAUTIONS - Lactic Acidosis / Severe Hepatomegaly with Steatosis / Hepatic Failure). Health care providers caring for HIV-infected pregnant women receiving stavudine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

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 or impaired fertility. A slight post-implantation loss was noted at 216 times the human exposure with no effect noted at approximately 135 times the human exposure. 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. 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. Stavudine has been shown to cross the human placenta in an *ex vivo* term model. Animal reproduction studies are not always predictive of human response.

Nursing Women

Studies in which lactating rats were administered a single dose (5 or 100 mg/kg) of stavudine demonstrated that stavudine is readily excreted into breast milk.

Although it is not known whether ZERIT 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 breast-feed if they are receiving ZERIT.**

Pediatrics

The safety and effectiveness of ZERIT have been established in pediatric patients supported by evidence from adequate and well-controlled studies of stavudine in adults with additional data concerning safety and pharmacokinetics in pediatric patients.

Patients should be monitored for clinically significant elevations of hepatic transaminases. If these elevations develop on treatment, ZERIT therapy should be interrupted. If the hepatic transaminase values return to pretherapy levels, resumption of treatment may be considered using a dosage schedule of 1 mg/kg/day, not to exceed the recommended adult dose of 20 mg twice daily.

One open-label, phase I trial enrolled 38 subjects aged 5 weeks to 15 years; 9 had received no prior antiretroviral therapy and 29 had received zidovudine for a median duration of 104 weeks. Patients in this trial received ZERIT in initial doses ranging from 0.125 to 4.0 mg/kg/day with an average dose of 1.7 mg/kg/day for a median duration of 84 weeks (range 8 - 140 weeks). A second open-label trial, initiated to provide stavudine for children who had failed or were intolerant of alternative antiretroviral therapy, enrolled 51 subjects aged 8 months to 18 years who had received prolonged zidovudine and didanosine. These patients were treated with ZERIT at a dose of 2 mg/kg/day, for a median duration of 33 weeks (range 2 days - 82 weeks).

A multi-centre, randomized, double-blind trial (Study ACTG 240) evaluated ZERIT [d4t] (2 mg/kg/day) versus zidovudine [ZDV] (200 mg QID) in the treatment of HIV-infected pediatric patients who had received <6 weeks of prior antiretroviral therapy. Two hundred and sixteen subjects, with a median baseline CD4 cell count of 1000 cells/mm^3, were enrolled. CD4 cell counts were better maintained on ZERIT treatment as compared with ZDV ($p<0.05$). Patients on ZDV experienced more neutropenia (19%) versus patients on ZERIT (7%) ($p<0.01$). No differences were observed in any other laboratory parameters, signs or symptoms.

Geriatrics

Clinical studies of ZERIT 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 ZERIT 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 b.i.d and 8 of 51 (16%) elderly patients receiving 20 mg b.i.d. 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 b.i.d and 25% of patients receiving 20 mg b.i.d. 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 - Dosage Adjustment).

Lactose Intolerance

Zerit capsules contain lactose (120 and 240 mg depending on capsule strength). This amount is probably insufficient to induce specific symptoms of intolerance.

Monitoring and Laboratory Tests

Complete blood counts and clinical laboratory tests should be performed prior to initiating ZERIT therapy and at appropriate intervals thereafter.

Moderate elevations of mean corpuscular volume may be observed in patients taking ZERIT and may provide an indication of treatment compliance.

ADVERSE REACTIONS

Adult Patients

Adverse Drug Event Overview

A total of 202 patients in two clinical studies were treated with combination therapy that included stavudine in the regimen. The most clinically relevant serious adverse events, regardless of relationship to study treatment in these two clinical studies, included lactic acidosis, pancreatitis, hepatic dysfunction and peripheral neuropathy.

The most common adverse events in the stavudine-containing regimens of the combination therapy clinical studies, regardless of grade or relationship to study treatment, included asthenia, diarrhea, dry skin, headache, increased cough, nausea, pharyngitis, rash and vomiting. In total, 31 out of the 202 patients in the stavudine-containing regimens from these two clinical studies, discontinued study medication due to adverse events.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Many of the serious clinical adverse events reported from patients receiving stavudine in clinical trials were consistent with the course of HIV infection. Concurrent therapy with other

medications was permitted in these trials. Therefore, it is difficult to distinguish which events were related to stavudine, the disease itself, or other therapies.

When ZERIT is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when ZERIT is used alone. Pancreatitis, peripheral neuropathy, and liver function abnormalities occur more frequently in patients treated with the combination of ZERIT and didanosine (see CONTRAINDICATIONS).

Table 1: Clinical Adverse Events[a] in START 1[b]Studies with a Frequency of > 5% in at Least One Treatment group (Combination Therapy)

Adverse Events	Percent of Patients	
	START 1	
	ZERIT + lamivudine + indinavir n = 100[c]	zidovudine + lamivudine + indinavir n = 102
Digestive System		
Nausea	43	63
Diarrhea	34	16
Vomiting	18	33
Pain Abdomen	21	14
Dyspepsia	5	8
Anorexia	12	9
Disorder Gastrointestinal	3	9
Body as a Whole		
Asthenia	25	26
Headache	25	26
Pain Back	23	20
Infection	17	16
Fever	14	11
Pain	15	9
Flu Syndrome	8	6
Accidental Injury	6	6
Infection Fungal	7	5
Chills	7	1
Respiratory System		
Pharyngitis	28	24

Adverse Events	Percent of Patients	
	START 1	
	ZERIT + lamivudine + indinavir n = 100[c]	zidovudine + lamivudine + indinavir n = 102
Cough Increased	21	16
Rhinitis	18	6
Sinusitis	13	7
Bronchitis	6	7
Skin/Appendages		
Rash	18	13
Dry Skin	11	12
Acne	5	6
Nervous System		
Peripheral Neurologic Symptoms/Neuropathy	8	7
Depression	8	12
Insomnia	6	9
Dizziness	5	7
Metabolic/Nutritional System		
Bilirubinemia	9	4
Weight Decreased	4	8
Urogenital System		
Dysuria	9	6
Hematuria	10	4
Calculus Kidney	7	5
Special Senses		
Taste Perversion	6	10
Conjunctivitis	6	4
Musculoskeletal System		
Arthralgia	7	5
Myalgia	7	2

[a] Any severity, regardless of relationship to study regimen.

[b] START 1 compared triple combination regimens in 202 treatment-naive patients. Patients received either ZERIT (40 mg b.i.d.) plus lamivudine plus indinavir or zidovudine plus lamivudine plus indinavir.

[c] Duration of stavudine therapy = 48 weeks.

Table 2: Clinical Adverse Events[a] in START 2[b] Studies with a Frequency of > 5% in at Least One Treatment Group (Combination Therapy)

Adverse Events	Percent of Patients	
	START 2	
	ZERIT + didanosine + indinavir n = 102[c]	zidovudine + lamivudine + indinavir n = 103
Digestive System		
Nausea	53	67
Diarrhea	45	39
Vomiting	30	35
Pain Abdomen	20	24
Flatulence	14	14
Dyspepsia	10	11
Anorexia	7	12
Dry Mouth	8	6
Eructation	4	8
Constipation	4	7
Ulcer Mouth	6	4
Body as a Whole		
Asthenia	32	38
Headache	46	37
Pain Back	11	13
Infection	23	18
Fever	20	8
Pain	17	24
Flu Syndrome	10	8
Accidental Injury	6	8
Infection Fungal	6	5
Chills	7	5
Lesion	3	6
Respiratory System		
Pharyngitis	37	28
Cough Increased	27	20
Rhinitis	22	16
Sinusitis	17	7
Respiratory System (con't)		

Adverse Events	Percent of Patients	
	START 2	
	ZERIT + didanosine + indinavir n = 102[c]	zidovudine + lamivudine + indinavir n = 103
Bronchitis	3	6
Disorder Lung	6	0
Skin/Appendages		
Rash	30	18
Dry Skin	33	23
Acne	6	2
Pruritus	13	11
Sweating	9	6
Nervous System		
Peripheral Neurologic Symptoms/Neuropathy	21	10
Depression	12	12
Insomnia	7	4
Dizziness	11	9
Metabolic/Nutritional System		
Bilirubinemia	7	3
Urogenital System		
Dysuria	2	6
Hematuria	7	8
Infection Urinary Tract	4	7
Special Senses		
Taste Perversion	12	21
Musculoskeletal System		
Arthralgia	9	12
Myalgia	10	6

[a] Any severity, regardless of relationship to study regimen.

[b] START 2 compared two triple-combination regimens in 205 treatment-naive patients. Patients received either ZERIT (40 mg b.i.d) plus didanosine plus indinavir or zidovudine plus lamivudine plus indinavir.

[c] Duration of stavudine therapy = 48 weeks.

Laboratory Abnormalities

Selected laboratory abnormalities reported in two controlled combination studies are provided in Table 3 and Table 4.

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

Parameter	Percent of Patients			
	START 1		START 2	
	ZERIT + lamivudine + indinavir n = 100	zidovudine + lamivudine + indinavir n = 102	ZERIT + 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 4: Selected Laboratory Abnormalities in START 1 and START 2 Studies (All Grades)

Parameter	Percent of Patients			
	START 1		START 2	
	ZERIT + lamivudine + indinavir n = 100	zidovudine + lamivudine + indinavir n = 102	ZERIT + 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

Post-Market Adverse Drug Reactions

The following events have been identified during post-approval use of ZERIT. 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 ZERIT, or a combination of these factors.

Body as a Whole:	abdominal pain, allergic reactions, chills/fever, redistribution/accumulation of body fat, lipoatrophy / lipodystrophy (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Lipoatrophy).
Digestive Disorders:	anorexia.
Exocrine Gland Disorders:	pancreatitis [including fatal cases (see WARNINGS AND PRECAUTIONS)].
Hematologic Disorders:	anemia, neutropenia, leukopenia, macrocytosis, and thrombocytopenia.
Liver	lactic acidosis and hepatic steatosis [including fatal cases (see WARNINGS AND PRECAUTIONS)], hepatitis and liver failure [including fatal cases (see WARNINGS AND PRECAUTIONS)].
Metabolic Disorders:	diabetes mellitus, hyperglycemia
Musculoskeletal:	myalgia.
Nervous system:	insomnia, severe motor weakness (most often reported in the setting of symptomatic hyperlactatemia or lactic acidosis, including fatal cases, see WARNINGS AND PRECAUTIONS).

Pediatric Patients

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

DRUG INTERACTIONS

Drug-Drug Interactions

Zidovudine may competitively inhibit the intracellular phosphorylation of stavudine (see ACTIONS and CLINICAL PHARMACOLOGY). Therefore, use of zidovudine in combination with ZERIT is not recommended. In vitro data indicate that the phosphorylation of stavudine is also inhibited at relevant concentrations by doxorubicin and ribavirin; therefore coadministration of stavudine with either doxorubicin or ribavirin should be undertaken with caution.

No pharmacokinetic interactions were observed between ZERIT (stavudine) and didanosine, lamivudine (3TC), or nelfinavir when co-administered in clinical trials.

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.

Drug-Food Interactions

ZERIT may be taken without regard to meals. Absorption of stavudine was assessed in a study of 16 asymptomatic HIV-infected patients. Each patient received a 70 mg oral dose of ZERIT in the fasting state, 1 hour before a standardized meal, and immediately after a standardized meal. The results indicate that systemic exposure to stavudine is not reduced when ZERIT is taken with food. Although the rate of absorption decreased, the extent of absorption was not significantly ($p = 0.27$) affected by the presence of food when ZERIT was taken immediately after a meal. Mean (± SD) C_{MAX} of stavudine was reduced from 1.44 (± 0.49) µg/mL in the fasting state to 0.75 (± 0.16) µg/mL after a meal, and the median time to achieve C_{MAX} was prolonged from 0.6 to 1.5 hours. However, mean (± SD) $AUC_{0\rightarrow\infty}$ values were 2.50 (± 0.71) µg·hr/mL and 2.31 (± 0.55) µg·hr/mL in the fasting state and after a meal, respectively, indicating that systemic exposure was similar with or without the presence of food.

Drug-Herb Interactions

Interactions with herbs have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Adults

The interval between oral doses should be 12 hours. ZERIT (stavudine) may be taken with or without food. The recommended doses are based on body weight, as outlined in Table 5

Table 5: Adult dosing

Patient weight	ZERIT Dosage
< 60 kg	30 mg bid
≥ 60 kg	40 mg bid

Dosage Adjustment

Renal Impairment

Adults

The following dose adjustments in Table 6 are recommended in adult patients with renal impairment.

Table 6: Recommended ZERIT Dosing Modifications for Subjects with Renal Impairment

Creatinine Clearance (mL/min)	Recommended ZERIT Dose by Patient Weight	
	≥ 60 kg	< 60 kg
> 50 [a]	40 mg every 12 hours[a]	30 mg every 12 hours [a]
26 - 50	20 mg every 12 hours	15 mg every 12 hours
<26 [b]	20 mg every 24 hours	15 mg every 24 hours

[a] Normal dose, no adjustment necessary.

[b] For patients undergoing hemodialysis, the daily dose of ZERIT should be administered after the completion of a scheduled hemodialysis session. On nondialysis days, ZERIT should be administered at the same time of day as it is on dialysis days.

Hepatic Impairment

Adults

Dosing adjustment is not necessary in subjects with stable hepatic impairment. In the event of rapidly elevating aminotransferase levels, treatment with ZERIT should be suspended.

Peripheral Neuropathy

Clinical symptoms of peripheral neuropathy which is usually characterized by numbness, tingling or pain in the feet or hands should prompt interruption of ZERIT treatment and evaluation of the patient. These symptoms may be difficult to detect in children. Caregivers of young children receiving ZERIT therapy should be instructed regarding detection and reporting of peripheral neuropathy (see WARNINGS AND PRECAUTIONS). If symptoms develop, ZERIT should be interrupted. Symptoms may resolve if therapy is withdrawn promptly. Some patients may experience a temporary worsening of symptoms following discontinuation of therapy. If symptoms resolve completely, resumption of treatment may be considered. If a reduced dose is warranted, use one-half the recommended dose.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There is no known antidote for ZERIT (stavudine) overdosage. Experience with adults treated with 12 to 24 times the recommended daily dosage revealed no acute toxicity. Patients may benefit from administration of activated charcoal. Stavudine can be removed by hemodialysis, the mean ±SD hemodialysis clearance of stavudine is 120 ±18 mL/min. It is not known whether stavudine is eliminated by peritoneal dialysis.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ZERIT (stavudine), also known as d4T, is a synthetic thymidine nucleoside analogue active against the Human Immunodeficiency Virus (HIV).

In vitro studies demonstrate that stavudine is converted to the triphosphate by cellular kinases. The 5'-triphosphate is the active form of the drug. In cell culture studies with two different cell lines, stavudine triphosphate had an intracellular half-life of 3.5 hours. Stavudine triphosphate has been shown to be a potent competitive inhibitor of HIV reverse transcriptase (ki = 0.0083 to 0.032 μM). In addition, both stavudine triphosphate and the natural substrate, thymidine triphosphate, are used by HIV reverse transcriptase *in vitro* for incorporation into the nascent DNA chain. Stavudine lacks the 3'-hydroxyl group necessary for DNA elongation and once incorporated into DNA, functions as a DNA chain terminator *in vitro*. Both the inhibition of binding of thymidine triphosphate to reverse transcriptase and DNA chain termination may be partially responsible for inhibition of HIV replication *in vitro*. In addition to the inhibitory effect on HIV reverse transcriptase, stavudine triphosphate exhibits some inhibitory effect on DNA polymerase beta and gamma, and markedly reduces the syntheses of mitochondrial DNA.

Clinically, ZERIT has been studied in various combinations with other classes of anti-retroviral drugs, including didanosine, lamivudine (3TC), ritonavir, nelfinavir, saquinavir, indinavir, and hydroxyurea (see PHARMACOLOGY - Clinical Studies). However, zidovudine in combination with ZERIT is not recommended (see WARNINGS AND PRECAUTIONS - Drug Interactions). Both drugs are phosphorylated by the same cellular enzyme (thymidine kinase), which may preferentially phosphorylate zidovudine, thereby decreasing the phosphorylation of stavudine to its active triphosphate form.

Based on *in vitro* testing, the activation of stavudine has also been shown to be inhibited by other drugs. Among the several drugs tested, the only ones that may interfere with stavudine phosphorylation at relevent concentrations are doxorubicin and ribavirin, but not other drugs used in the therapy of HIV infection which are similarly phosphorylated. The clinical significance of this is unknown.

Clinical trials supporting the use of ZERIT in appropriate antiretroviral regimens for the treatment of HIV-infected patients, demonstrated, overall, greatest inhibition of HIV RNA levels and greatest increase in CD4 cell counts with triple-combination regimens (see PHARMACOLOGY - Clinical Studies).

Drug Resistance

HIV isolates with reduced susceptibility to stavudine have been selected in vitro and were also obtained from patients treated with stavudine. Phenotypic analysis of HIV-1 isolates from 61 patients receiving prolonged (6-29 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 mutation T215Y and K219E, and isolates from another patient contained the multiple-nucleoside- resistance-associated mutation 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. Five of 11 stavudine post-treatment isolates developed moderate resistance to zidovudine (9- to 176-fold) and 3 of those 11 isolates developed moderate resistance to didanosine (7- to 29-fold). Several studies have demonstrated that prolonged stavudine treatment can select and /or maintain thymidine analogue mutations (TAMs) associated with zidovudine resistance. The decrease of susceptibility in cell culture is subtle requiring two or more TAMs (generally M41L and T215Y) before stavudine susceptibility is decreased (> 1.5 fold). 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, especially M41L and T215Y .

Pharmacokinetics in Adults

The pharmacokinetics of stavudine have been evaluated in HIV-infected adult and pediatric patients (refer to Table 7). Peak plasma concentrations (Cmax) 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.

Table 7: Mean ± SD Pharmacokinetic Parameters of Stavudine in Adult and Pediatric HIV-Infected Patient

Parameter	Adult Patients	n	Pediatric Patients	n
Oral bioavailability (F)	86.4 ± 18.2%	25	76.9 ± 31.7%	20
Volume of distribution [a] (VD)	58 ± 21 L	44	18.5 ± 9.2 L/m^2	21
Apparent oral volume of distribution [b] (VD/F)	66 ± 22 L	71	not determined	–
Ratio of CSF: plasma concentrations (as %) [c]	not determined	–	59 ± 35%	8
Total body clearance [a] (CL)	8.2 ± 2.3 mL/min/kg	44	247 ± 94 mL/min/m^2	21
Apparent oral clearance [b] (CL/F)	8.0 ± 2.6 mL/min/kg	113	333 ± 87 mL/min/m^2	20
Elimination half-life ($T_{1/2}$), IV dose [a]	1.15 ± 0.35 h	44	1.11 ± 0.28 h	21
Elimination half-life ($T_{1/2}$), oral dose [b]	1.44 ± 0.30 h	115	0.96 ± 0.26 h	20

Urinary recovery of stavudine (% of dose)	39 ± 23%	88	34 ± 16%	19

a following 1 hour i.v. infusion

b following single oral dose

c following multiple oral doses

Absorption

Following oral administration, stavudine is rapidly absorbed, with peak plasma concentrations occurring within 1 hour after dosing.

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.

Metabolism

The metabolic fate of stavudine has not been elucidated in humans.

Excretion

Renal elimination accounted for about 40% of the overall clearance regardless of the route of administration. The mean renal clearance was about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration.

STORAGE AND STABILITY

ZERIT capsules should be stored at room temperature (15°to 30°C) and protected from excessive moisture. Keep bottles tightly closed.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Capsules

ZERIT (stavudine) is available as capsules containing:

15 mg of stavudine - light yellow and dark red capsule imprinted with "BMS 1964" and "15";

20 mg of stavudine - light brown capsule imprinted with "BMS 1965" and "20";

30 mg of stavudine - light orange and dark orange capsule imprinted with "BMS 1966" and "30"

40 mg of stavudine - dark orange capsule imprinted with "BMS 1967" and "40"

ZERIT capsules are available in bottles of 60, in packages of 100 individually foil-wrapped capsules and in unit dose blister strips of 4 X 14 capsules.

Composition

ZERIT (stavudine) capsules are available for oral administration in strengths of 15, 20, 30 and 40 mg of stavudine. Non medicinal ingredients: lactose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate. Capsule shell: gelatin, black iron oxide (20 mg only), printing ink, silicon dioxyde, sodium lauryl sulphate, titanium dioxide and yellow and red iron oxides.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

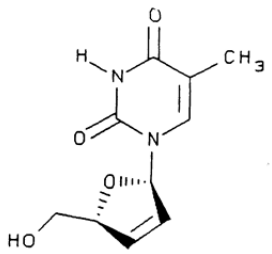
Proper name: Stavudine

Chemical name: 2',3'-didehydro-3'-deoxythymidine

Molecular formula: $C_{10}H_{12}N_2O_4$

Molecular mass: 224.2 daltons

Structural formula:



Physicochemical properties: Stavudine is a white to off-white crystalline solid.

The solubility of stavudine at 23^{o}C is approximately 87 mg/mL in water, 29 mg/mL in methanol, 30 mg/mL in propylene glycol, and 19 mg/mL in ethanol.

CLINICAL TRIALS

The following clinical trials support the use of ZERIT in appropriate antiretroviral regimens for the treatment of HIV-infected patients. Overall, greatest inhibition of HIV RNA levels and greatest increase in CD4 cell counts were observed with triple-combination regimens.

Combination Therapy

The START-1 study was a multi-center, randomized, open-label combination therapy trial of ZERIT [d4T] (40 mg b.i.d plus lamivudine [3TC] (150 mg b.i.d) plus indinavir [IDV] (800 mg TID) versus zidovudine [ZDV] (200 mg TID) plus 3TC (150 mg b.i.d) plus IDV (800 mg TID) for the treatment of HIV-infected adults with CD4 counts of >200 cells/mm3 and a plasma HIV-RNA baseline copy number of >5000 copies/mL who had received no prior antiretroviral treatment. The study enrolled a total of 200 subjects. The median baseline CD4 cell count was 400 cells/mm3 and the baseline median viral load was 4.6 log 10 copies/mL.

Table 9: Efficacy Endpoint Results: START 1

	Analysis Time Point (wks)	CD4 Mean Change from Baseline (cells/mm^3) (range), p value*	HIV-RNA Mean Change from Baseline (log_{10} copies/mL) (range), p value*
START 1			
ZERIT + lamivudine + indinavir	24	+ 161	-1.81
		(-124, +530), p=0.42	(-0.36, -3.06), p=0.35
	48	+ 237	-1.86
		(-142, +722), p=0.39	(-0.64, -3.06), p=0.28)
zidovudine + lamivudine + indinavir	24	+ 148	-1.63

* p values for comparison between treatments from Wilcoxon 2-sample test, stratified by investigational site.

DETAILED CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults

The pharmacokinetics of stavudine have been evaluated in 119 HIV-infected patients following the administration of oral doses ranging from 0.03 to 4 mg/kg administered as single doses and as multiple doses every 6, 8 or 12 hours. Stavudine pharmacokinetics have also been evaluated in 44 HIV-infected patients after single intravenous doses ranging from 0.0625 to 1 mg/kg administered as 1-hour infusions.

Absorption and Bioavailability in Adults

Following oral administration to HIV-infected patients, stavudine was rapidly absorbed with peak plasma concentrations occurring within 1 hour after dosing and a mean absolute bioavailability of 90.7% (n = 25). Peak plasma concentrations (C_{MAX}) increased in a dose-related manner for doses (n = 4 to 10 per dose level) ranging from 0.03 to 4 mg/kg. Mean (±SD) C_{MAX} values ranged from0.03 (± 0.01) to 4.19 (±1.73) µg/mL, respectively, occurring ≤ 1 hour after dosing. Plasma concentrations declined to ≤ 10% of mean C_{MAX} values by 5 to 8 hours postdose. Mean values for the area under the plasma concentration-time curve (AUC) were proportional to dose, both after single doses and at steady state. Mean (±SD) AUC values ranged from 0.05 (±0.02) to 7.08(±1.12) µg.hr/mL, respectively. There was no significant accumulation of stavudine with repeated administration every 6, 8 or 12 hours.

Effect of Food on Oral Absorption in Adults

ZERIT (stavudine) may be taken without regard to meals. Absorption of stavudine was assesesed in a study of 16 asymptomatic HIV-infected patients. Each patient received a 70 mg oral dose of ZERIT in the fasting state, 1 hour before a standardized meal, and immediately after a standardized meal. The results indicate that systemic exposure to stavudine is not reduced when

ZERIT is taken with food. Although the rate of absorption decreased, the extent of absorption was not significantly (p = 0.27) affected by the presence of food when ZERIT was taken immediately after a meal. Mean

(± SD) C_{MAX} of stavudine was reduced from 1.44 (± 0.49) µg/mL in the fasting state to 0.75 (± 0.16) µg/mL after a meal, and the median time to achieve C_{MAX} was prolonged from 0.6 to 1.5 hours. However, mean (± SD) $AUC_{0\rightarrow\infty}$ values were 2.50 (± 0.71) µg.hr/mL and 2.31 (± 0.55) µg.hr/mL in the fasting state and after a meal, respectively, indicating that systemic exposure was similar with or without the presence of food.

Distribution in Adults

Following intravenous infusions (n = 44) of stavudine at doses ranging from 0.0625 to 1 mg/kg, mean (±SD) values for volume of distribution were independent of dose and ranged from 28.4 (±5.9) to 81.2 (±41.7) L, suggesting that stavudine distributes into extravascular spaces. Mean (±SD) values for apparent volume of distribution following oral administration of doses (n = 110) ranging from 0.03 to 4 mg/kg were also independent of dose, and ranged from 42.2 (±8.3) to 81.0 (±21.7) L. Volume of distribution did not correlate with body weight.

Binding of stavudine to serum proteins was negligible over the concentration range of 0.01 - 11.4 µg/mL. Stavudine distributes equally between red blood cells and plasma.

Cerebrospinal fluid concentrations were determined in three subjects. Following oral doses of 1.33, 3.00 and 4.00 mg/kg, stavudine concentration in cerebrospinal fluid was 0.08, 0.20 and 0.48 µg/mL at 0.5, 1.75 and 5.0 hours after dosing.

Elimination in Adults

Values for plasma clearance and terminal elimination half-life were found to be independent of dose administered over an intravenous dosing range of 0.0625 to 1 mg/kg and an oral dosing range of 0.03 to 4 mg/kg. Following 1-hour infusions (n = 44), plasma concentration of stavudine declined in a biphasic manner with mean (±SD) terminal elimination half-life values ranging from 0.86 (±0.20) to 1.27 (± 0.59) hours. After oral doses (n = 110), mean (± SD) terminal half-life estimates ranged from 1.03 (± 0.16) to 1.59 (± 0.34) hours. Within studies intrapatient variability of terminal half-life was 12% to 17%, and interpatient variability was 15% to 27%. Mean (±SD) total body clearance values after intravenous infusion ranged from 417 (±78) to 764 (±261) mL/min, and were independent of dose administered and of body weight. Following oral administration, mean (±SD) apparent oral clearance values were independent of dose and ranged from 441 (±47) to 771 (±345) mL/min, with intrapatient variability of 10% to 11% and interpatient variability of 13% to 44% among studies. About 40% of total clearance was by renal elimination, regardless of the route of administration. The mean renal clearance of stavudine is about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration. Mean (± SD) cumulative urinary excretion of unchanged drug over 12 to 24 hours after administration of an oral dose ranged from 22.9% (±3.7%) to 58.7% (±22.2%) of the dose. Nonrenal clearance is presumed to be due to intracellular metabolism to

the mono-, di-, and triphosphates, or intracellular cleavage to thymine and uptake by pyrimidine salvage pathways. In studies of [5-^{3}H] stavudine and [4-^{14}C] stavudine in nonhuman primates, biliary excretion of stavudine appeared to be negligible, with radioactivity in feces accounting for < 1% of an administered dose after either oral or intravenous administration.

The protein binding of stavudine *in vitro* is negligible; therefore, drug interactions involving binding site displacement are not anticipated.

Metabolism in Adults

The metabolic fate of stavudine has not been elucidated in humans. When stavudine was incubated with human liver slices for six hours, 87 percent of radioactivity was accounted for by parent compound, 2 percent was metabolized to thymine and 7 percent was associated with unidentified polar compounds.

Comparative pharmacokinetic studies of stavudine in humans and nonhuman primates suggest that the latter represent an appropriate animal model for the *in vivo* disposition of stavudine in humans. When ^{14}C-radiolabeled stavudine was administered to monkeys as a single intravenous or oral dose, approximately 48% of the radioactivity was recovered in urine. The major component identified in monkey urine was unchanged stavudine, representing approximately 44% of the administered dose. Two putative metabolites identified in the urine were thymine (accounting for approximately 1% of the dose) and β-aminoisobutyric acid (accounting for approximately 2% of the dose). The metabolic fate of the deoxyribose moiety has not been investigated.

Special Populations and Conditions

Pediatrics

Pharmacokinetics in Children

Stavudine pharmacokinetics have been evaluated in a subset of 25 HIV-infected pediatric patients (age range: 5 weeks to 15 years; weight range: 2 to 43 kg) after IV and oral administration of 0.125, 0.5, 1, and 2 mg/kg as single doses and as BID regimens. The mean absolute bioavailability was 76.9 ± 31.7% (n = 20). Peak plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increased in proportion to dose after both single and multiple doses.

Absorption and Bioavailability in Children

Total exposure to stavudine, as reflected by mean steady-state AUC values, was comparable between pediatric patients receiving the usual recommended 2 mg/kg/day dose (1.439 μg•hr/mL) and adults receiving 1 mg/kg/day dose (1.173 μg•hr/mL).

Distribution in Children

Following intravenous infusions (n = 14) of stavudine at doses ranging from 0.125 to 1 mg/kg, mean apparent volume of distribution ranged from 5.62 to 18.0 L (0.47 to 0.72 L/kg), suggesting

that stavudine distributes into extravascular spaces. The distribution of stavudine into cerebrospinal fluid (CSF) was assessed in 8 pediatric patients after 12 weeks of multiple oral dosing. The concentration of stavudine in cerebrospinal fluid samples ranged from 0.008 to 0.105 µg/mL at times ranging from 2 to 3 hours post-dose (dose ranging from 0.125 to 2 mg/kg). The cerebrospinal fluid concentrations ranged from 16% to 125% (mean ±SD of 59% ±35%) of the concentration in simultaneous plasma samples.

Elimination in Children

In 20 pediatric patients the mean ±SD terminal elimination half-life was 0.96 ±0.26 hours after single oral doses (in adults with similar blood sampling, the half-life was 1.44 ± 0.30 hours).

Renal Insufficiency

Data are available from two studies involving patients with renal insufficiency. One study recruited 15 non-HIV-infected subjects with reduced renal function and 5 subjects with normal renal function. The second study recruited 12 subjects with end-stage renal disease receiving maintenance hemodialysis; the pharmacokinetics of stavudine were determined between hemodialysis and at the time of a hemodialysis. The results of the two studies indicated that the apparent oral clearance (CL/F) of stavudine decreased and the terminal elimination half-life (t½) increased as creatinine clearance (Cl_{cr}) decreased (refer to the table below). C_{max} and T_{max} were not significantly affected by reduced renal function. The mean ±SD hemodialysis clearance value of stavudine was 120 ±18 mL/min; the mean ±SD percentage of the stavudine dose recovered in the dialysate, timed to occur between 2-6 hours post-dose, was 31±5 percent. Based on these observations, it is recommended that ZERIT (stavudine) dosage be modified in patients with reduced creatinine clearance; in patients receiving maintenance hemodialysis it is recommended that stavudine be administered after the completion of a scheduled hemodialysis and at the same time of day on non-hemodialysis days (see DOSAGE and ADMINISTRATION).

Table 10: Mean ± SD Pharmacokinetic Values Single 40 mg Oral Dose of Zerit

	Creatinine Clearance			
	>50mL/min (n=10)	26-50 mL/min (n=5)	9-25 mL/min (n=5)	Dialysis Dependent†
Cl_{cr} (mL/min)	104 ± 28	41 ± 5	17 ± 3	NA
CL/F (mL/min)	335 ± 57	191 ± 39	116 ± 12	105± 17
CL_R (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

CL_R = renal clearance; † = Off dialysis; NA = Not Applicable

Hepatic Insufficiency

Stavudine pharmacokinetics were not altered in 5 non-HIV infected patients with hepatic impairment secondary to cirrhosis following the administration of a single 40 mg dose.

MICROBIOLOGY

Stavudine has shown *in vitro* antiviral activity in HIV-infected T cell and monocyte/macrophage cultures. The drug concentration necessary to inhibit the cytopathic effects of HIV-1 infection by 50% (ED_{50}) in T cell cultures varied between 0.01 and 4.1 µM (0.002 to 0.91 µg/mL); the ED_{50} in monocyte/macrophage cultures was 0.04 to 0.3 µM (0.009 to 0.07 µg/mL) as measured by p24 antigen production. Stavudine also inhibits HIV-2 replication in T cells *in vitro* as measured by plaque reduction with an ED_{50} of 0.09 µM (0.02 µg/mL). *In vitro* sensitivity of HIV replication to stavudine varied over a 500-fold range depending on the assay conditions.

Table 11: Activities of Stavudine Against HIV-1, HIV-2 and Cells

Cell type	Stavudine		
	ED_{50}(µM)	CC_{50}(µM)	TI
HIV-1			
MT-4[1]	0.01	1.2	120
MT-4[2]	0.041	100	2400
MT-4[9]	0.05	19	380
ATH8[3]	4.1	110	27
CEM[4]	0.15	90	600
Tall 1[5]	0.4		
PBMC[6]	0.009 - 0.04	70	≥ 1750
M/M[7]	0.04		
M/M[8]	0.3		
HIV-2			
MT-4[9]	0.09		

ED_{50} = Dose required for 50 percent inhibitory effect.
CC_{50} = Concentration required for 50 percent cytotoxicity.
TI = Therapeutic Index = cell inhibition/ED_{50} for virus
µM x 0.224 = µg/mL.

As with other antiretroviral agents, a direct relationship has not been established between the *in vitro* inhibition of HIV replication and inhibition of HIV infection in humans or the clinical response to therapy.

Drug resistance

Preclinical studies: The potential for development of resistance to stavudine has been investigated *in vitro*. Selection studies performed with HIV 1 strains HXB2 and, IIIb have produced virus isolates with reduced (7- to 30-fold) sensitivity to stavudine.

Clinical studies: Limited phenotypic and genotypic resistance studies (20 paired HIV isolates) have shown that 4- to 12-fold decreases (3/20 isolates) in stavudine susceptibility are possible, however, the genetic bases for the observed susceptibility changes have not been identified. The clinical relevance of stavudine susceptibility changes has not been established.

Five of 11 stavudine post-treatment isolates (9 of which were from patients who had previously received zidovudine) developed moderate resistance (9- to 176-fold) to zidovudine and 3 of those 11 isolates developed moderate resistance (7- to 29-fold) to didanosine. The clinical relevance of these findings has not been established.

In three studies with human granulocyte/monocyte progenitor cells, stavudine was 20 to 100-fold less inhibitory than zidovudine. In one study using murine-derived granulocyte/monocyte progenitor cells, stavudine was 3 to 5-fold less inhibitory than zidovudine. Stavudine has no significant antibacterial activity when tested against a panel of common pathogenic bacteria.

TOXICOLOGY

Extensive toxicity studies in laboratory animals have been conducted with stavudine, including evaluations for reproductive and genetic toxicities, at multiples of exposure up to approximately 400 times the human dose. No life-threatening toxicity was observed in pivotal safety studies of up to one year duration. Slight decreases in red blood cell indices, and hepatic alteration were the principal findings in rats and monkeys. Stavudine was not teratogenic and had no effect on mating or fertility. As with other nucleoside analogs and naturally occurring nucleosides, stavudine produced positive responses in one in vivo and two in vitro genetic toxicity assays. These positive findings occurred at relatively high concentrations and doses that resulted in high levels of exposure and probably reflect nucleotide metabolic disturbances rather than true genotoxic effects.

Carcinogenicity and Mutagenicity

In 2-year carcinogenicity studies in mice and rats, stavudine was noncarcinogenic at doses which produced exposures (AUC) 39 and 168 times, respectively, the recommended clinical dose for humans. Benign and malignant liver tumors in mice and rats and malignant urinary bladder tumors in male rats occurred only at higher levels of exposure, 250 (mice) and 732-1785 (rats) times human exposure at the recommended clinical dose.

In the rat doses of 100, 600 and 4000 mg/kg/day were selected for the carcinogenicity study based on hepatic changes at 4000 mg/kg/day in the range-finding study. The high dose of 4000 mg/kg/day was reduced to 2000 mg/kg/day after 16 weeks of dosing due to mortality and hepatocellular injury. Interim data from the ongoing study indicate that possible drug-related finding of cholangio-carcinomas in the liver and transitional cell carcinomas of the urinary bladder at the high dose have been observed up through 18 months of dosing, while these neoplasms have not been seen at the lower doses. Exposures to stavudine in rats at the high dose are 718 - 1750 times the exposure observed in humans at the recommended dose.

Results from the genetic toxicity studies suggest that stavudine is genotoxic only at exposures greatly exceeding those occurring in clinical trials and are comparable to results seen with other nucleoside analogues and with the naturally-occurring DNA nucleoside thymidine. 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 25 to 250 µg/mL, without metabolic activation) and increased the frequency of transformed foci in mouse fibroblast cells (concentrations of 25 to 2500 µg/mL, with and without metabolic activation). In the *in vivo* micronucleus assay, stavudine was clastogenic in bone marrow cells following oral administration to mice at dosages of 600 to 2000 mg/kg/day for 3 days. The lowest concentration (25 µg/mL) producing positive responses in the *in vitro* assays was approximately 38 times higher than the C_{MAX} and 250 times higher than the average stavudine plasma concentration over 12 hours in humans receiving one-half the total daily clinical dose of 1 mg/kg. The positive response in the mouse micronucleus test occurred at dosages which produced mortalities and resulted in exposures estimated to be at least 110 times greater than those seen clinically at 1 mg/kg. Zidovudine and zalcitabine produce similarly positive results in this assay.

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PART III: CONSUMER INFORMATION

Pr ZERIT®

Stavudine

This leaflet is Part III of a three-part "Product Monogaph" published when ZERIT was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ZERIT. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for

ZERIT (Pronounced ZER it) is a prescription medicine used with other medicines to treat HIV, or human immunodeficiency virus in adults. HIV is the virus that causes AIDS (Acquired Immunodeficiency Syndrome).

What it does

ZERIT belongs to a class of medicines called nucleoside analogues. It works by reducing the HIV amount in the blood. It also increases CD4 cells. CD4 cells are type of white blood cells which are important for fighting HIV and other infections.

ZERIT will not cure your HIV infection. At present there is no cure for HIV infection. Even while taking ZERIT, you may:

- Continue to have HIV-related illnesses, including infections caused by other germs (microorganisms). Continue to see your doctor regularly and report any medical problems that occur.
- Still give HIV. **Do not have any kind of sex without protection.** Discuss with your healthcare professional the precautions needed to avoid infecting other people.

When it should not be used

Do not take ZERIT if you:

- Are allergic to stavudine or any of the ingredients in ZERIT. (See "What the nonmedicinal ingredients are" in this leaflet). Tell your doctor if you think you have had an allergic reaction to any of these ingredients.
- Take didanosine (another HIV medicine) (see "interaction with this medication" section below).

What the medicinal ingredient is:

Stavudine

What the nonmedicinal ingredients are:

ZERIT Capsules: lactose (milk sugar), magnesium stearate, microcrystalline cellulose, sodium starch glycolate.

Capsule shell: gelatin, black iron oxide (20 mg only), printing ink, silicon dioxyde, sodium lauryl sulphate, titanium dioxide and yellow and red iron oxides.

What dosage forms it comes in:

Capsules: 15, 20, 30 and 40 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ZERIT can cause serious side effects, including :

- **Buildup of acid in your blood (lactic acidosis) that can be life-threatening.** Lactic acidosis can cause death. It is a medical emergency that 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 had lactic acidosis after taking ZERIT and didanosine.
  - are female
  - are overweight
  - have been treated for a long time with other medicines used to treat HIV.
- **Liver problems:** Some people who have taken ZERIT have had serious liver problems. These problems include liver enlargement (hepatomegaly), liver failure, fat in the liver (steatosis) and death due to liver problems.
- **Swelling of the pancreas (pancreatitis)** that may cause death. Pancreatitis may happen any time during your treatment with ZERIT.

For further information and symptoms see "SIDE EFFECTS AND WHAT TO DO ABOUT THEM".

Talk to your healthcare professional before using ZERIT if:

- You have kidney, liver problems or history of heavy alcohol use.
- You have had problems with you pancreas (pancreatitis).
- You have had gallstones.
- You have had nerves problems that causes tingling, numbness, and pain in the hands and feet (peripheral neuropathy).
- **You are pregnant or planning on becoming pregnant**. It is not known if ZERIT can harm an unborn baby. In addition, pregnant women have experienced serious side effects when taking ZERIT in combination with didanosine and other HIV medicines (see Serious Warnings and Precautions box above). ZERIT should be used during pregnancy only after discussion with your doctor.
- **You are breastfeeding or planned to breastfeed**. It is not known if ZERIT can be passed to your baby in your breast milk and if it could harm your baby. In addition HIV-infected mothers should not breast-feed because HIV infection can be passed to the baby in the breast milk. **Do not breastfeed while taking ZERIT**.

While you are taking ZERIT:

- Your healthcare professional may check your liver regularly while you are taking ZERIT. Be careful if you have a history of heavy alcohol use or a liver problem.
- If your kidneys are not working properly, your healthcare professional may :
  - check your kidneys
  - lower your dosage of ZERIT.
- **Alcohol. You should avoid drinking alcohol while taking ZERIT.** Alcohol may increase your risk of getting pain and swelling of your pancreas (pancreatitis) or may damage your liver.
- **Changes in your immune system (Immune reconstitution inflammatory syndrome)** - Your immune system may get stronger when you start taking HIV medicines. It may begin to fight infections that have been in your body for a long time or your immune system could react against your own body (autoimmune disease). Autoimmune disease may develop at any time, sometimes months after the start of the HIV therapy. Call your healthcare professional right away if you start having high temperature (fever), joint or muscle pain, redness, rash, swelling or fatigue or any new symptoms after starting this ZERIT.

INTERACTIONS WITH THIS MEDICATION

Always keep a list of all the medicines, including prescription and non-prescription medicines, vitamins, herbals or other health products and show it to your healthcare professional when you get a new medicine. ZERIT may affect the way other medicines work, and other medicines may affect how ZERIT works.

Especially tell your healthcare professional if you are taking:

- Other HIV medications such as:

    - didanosine. The following serious side effects which may cause death may occur when ZERIT is used with didanosine (see Serious Warnings box above).
        - liver problems,
        - swelling of the pancreas (pancreatitis)
        - lactic acidosis (a condition where lactic acid buildup in the blood)
        - nerve problems (peripheral neuropathy)
    - zidovudine (AZT)
- doxorubicin, used to treat cancer
- ribavarin, used to treat hepatitis C infection
- hydroxyurea, used to treat cancer

PROPER USE OF THIS MEDICATION

Usual dose

- Your healthcare professional will tell you how much ZERIT to take and when to take it.
- Do not stop taking ZERIT or change your dosage unless directed to do so by your healthcare professional.
- You may take ZERIT with food or on an empty stomach.

Overdose

If you take too much ZERIT, contact a healthcare professional (e.g. your doctor), hospital emergency department or regional poison control centre, even if there are no symptoms

Missed Dose

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. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

ZERIT may cause side effects that must be treated right away before they become serious (see "Serious Warnings and Precautions" box above and "Serious and side effects" table below). Always tell your health care professional about any symptoms that you are having even symptoms that may not seem serious.

The most common side effects of ZERIT are:

- Headache,
- Diarrhea,
- Rash,
- Nausea and vomiting.

Other side effects may include:

- Abdominal pain,
- Muscle pain,
- Difficulty sleeping,
- Loss of appetite,
- Chills or fever,
- Allergic reactions,
- Blood disorders.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	Talk with your doctor right away		Stop taking drug and call your doctor
	Only if severe	In all cases	
Lactic acidosis : • stomach pain • nausea and vomiting • feeling very weak and tired • unusual muscle pain • shortness of breath • feeling cold, especially in your arms and legs • felling dizzy or light-headed • fast or irregular heart beat • weigh loss			✓
Liver problems • Yellowing of your skin or eyes • Dark urine or light-colored bowel movements • Stomach pain or stomach swelling • Nausea and vomiting • Loss of appetite			✓
Swelling of the pancreas (pancreatitis) • Severe stomach pain, swelling of your stomach • Fever • Nausea, or vomiting.			✓
Nerve problems (peripheral neuropathy): numbness, tingling, burning or pain in the feet and/or hands **Children**: Neuropathy can be difficult to notice in children who take ZERIT. Ask your child's healthcare professional for the signs of peripheral neuropathy in children.		✓ ✓	
Changes in body fat (Fat redistribution): Changes may include • More fat in or around your: o upper back and neck ("buffalo hump"), o breasts o trunk. • Loss of fat in your legs, arms, and face		✓	

This is not a complete list of side effects. For any unexpected effects while taking ZERIT, contact your doctor or pharmacist

HOW TO STORE IT

ZERIT capsules:

- store at room temperature (15° to 30°C)
- protect from excessive moisture.
- keep the bottle tightly closed

Keep ZERIT and all other medicines out of the reach of children.

Do NOT store ZERIT in a damp place such as a bathroom medicine cabinet or near the kitchen sink.

To help protect the environment, please return all unused medication to the pharmacist for proper disposal.

This medicine was prescribed for your particular condition. Do not use ZERIT for another condition or give it to others.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information or for the full Product Monograph on ZERIT, contact the sponsor, Bristol-Myers Squibb, at: 1-866-463-6267.

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