ZERIT® XR

Rx only

(stavudine)

Extended-Release Capsules

(Patient Information Leaflet Included)

WARNING

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING STAVUDINE AND OTHER ANTIRETROVIRALS. FATAL LACTIC ACIDOSIS HAS BEEN REPORTED IN PREGNANT WOMEN WHO RECEIVED THE COMBINATION OF STAVUDINE AND DIDANOSINE WITH OTHER ANTIRETROVIRAL AGENTS. THE COMBINATION OF STAVUDINE AND DIDANOSINE SHOULD BE USED WITH CAUTION DURING PREGNANCY AND IS RECOMMENDED ONLY IF THE POTENTIAL BENEFIT CLEARLY OUTWEIGHS THE POTENTIAL RISK (SEE WARNINGS AND PRECAUTIONS: PREGNANCY).

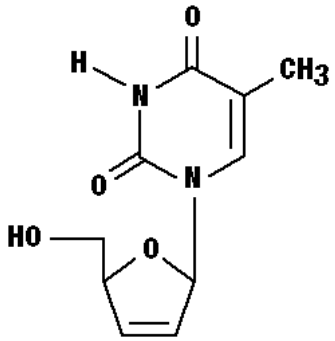
FATAL AND NONFATAL PANCREATITIS HAVE OCCURRED DURING THERAPY WHEN STAVUDINE WAS PART OF A COMBINATION REGIMEN THAT INCLUDED DIDANOSINE, WITH OR WITHOUT HYDROXYUREA, IN BOTH TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION (SEE WARNINGS).

DESCRIPTION

ZERIT® XR is the brand name for an extended-release formulation of stavudine (d4T), a synthetic thymidine nucleoside analogue, active against the human immunodeficiency virus (HIV).

ZERIT XR (stavudine) Capsules, containing extended-release beads, are supplied for oral administration in strengths of 37.5 mg, 50 mg, 75 mg, and 100 mg of stavudine. The beads contain stavudine and the following inactive ingredients: distilled acetylated monoglycerides, ethylcellulose aqueous dispersion, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and talc. The capsule shells contain gelatin, iron oxide colorant, silicon dioxide, sodium lauryl sulfate, and titanium dioxide. The capsules are printed with edible inks.

The chemical name for stavudine is 2',3'-didehydro-3'-deoxythymidine. Stavudine has the following structural formula:



Stavudine 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.

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

The *in vitro* 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% (IC_{50}) ranged from 0.009 to 4 μM against laboratory and clinical isolates of HIV-1. Stavudine had additive and synergistic activity in combination with didanosine and zalcitabine, respectively, *in vitro*. Stavudine combined with zidovudine had additive or antagonistic activity *in vitro* depending upon the molar ratios of the agents tested. The relationship between *in vitro* susceptibility of HIV-1 to stavudine and the inhibition of HIV-1 replication in humans has not been established.

Drug Resistance

HIV-1 isolates with reduced susceptibility to stavudine have been selected *in vitro* (strain-specific) 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 IC_{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 mutations 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

Several studies have demonstrated that prolonged stavudine treatment can select and/or maintain mutations associated with zidovudine resistance. HIV-1 isolates with one or more zidovudine-resistance-associated mutations (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) exhibited reduced susceptibility to stavudine *in vitro*.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults

The pharmacokinetic properties of stavudine administered as an extended-release capsule have been evaluated in healthy adult volunteers and HIV-infected adults. The slow release of stavudine from the extended-release capsule maintains measurable plasma concentrations for 24 hours after once-daily dosing. With once-daily dosing of the extended-release capsule, there is approximately 50% lower fluctuation of plasma concentration than observed with twice-daily dosing of the immediate-release formulation of stavudine.

Absorption

In a crossover study in healthy volunteers, equivalent values for stavudine AUC (total daily exposure) were observed for the extended-release and immediate-release formulations. AUC increased proportionally with dose in the oral dose range of 37.5 to 100 mg.

In parallel groups of HIV-infected patients, stavudine exposure was on average 23% lower following administration of 100 mg once daily of the extended-release formulation compared with 40 mg twice daily of the immediate-release formulation. The maximum plasma concentration (C_{max}) for the extended-release capsule is 43% of the value for the immediate-release capsule, and the time to

reach C_{max} (T_{max}) is approximately 3 hours for the extended-release capsule compared with 1 hour for the immediate-release capsule. No significant accumulation of stavudine was observed after repeated administration of the extended-release capsule every 24 hours. Steady-state pharmacokinetic parameters of ZERIT XR in HIV-infected adults are compared with those of the immediate-release formulation in Table 1.

Effects of food on oral absorption:

Compared to the fasted condition, the administration of stavudine extended-release capsules with a high-fat meal (945 kcal), a light meal (373 kcal), yogurt (26 kcal, 2 tablespoons), or applesauce (32 kcal, 2 tablespoons) did not significantly alter the stavudine AUC and C_{max}.

Distribution

Volume of distribution and the ratio of cerebrospinal fluid (CSF) to plasma levels are shown in Table 2. 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.

Table 1: Pharmacokinetic Parameters of Stavudine in HIV-Infected Adults, ZERIT XR versus ZERIT Immediate-Release (IR): Absorption

Parameter	ZERIT XR 100 mg QD Mean ± SD (n=19[a])	ZERIT IR 40 mg BID Mean ± SD (n=8[a])
AUC (ng.h/mL)	1966 ± 629	2568 ± 454
C_{max} (ng/mL)	228 ± 62	536 ± 146
C_{min} (ng/mL)	24 ± 17	8 ± 9

[a] Parallel groups for XR and IR formulations in HIV-infected adults.
AUC=area under the curve over 24 hours.
C_{max}=maximum plasma concentration
C_{min}=trough or minimum plasma concentration.

Table 2: Pharmacokinetic Parameters of Stavudine in HIV-Infected Adults[a]: Distribution and Clearance

Parameter	Mean ± SD	n
Volume of distribution (L)[b]	46 ± 21	44
Total body clearance (mL/min)[b]	594 ± 164	44
Renal clearance (mL/min)[b]	237 ± 98	39
Urinary recovery of stavudine (% of dose)[b]	42 ± 14	39
Ratio of CSF to plasma concentration (as %)[c]	59 ± 35	8[a]

[a] Ratio of CSF to plasma concentration was determined in HIV-infected pediatric patients.

[b] Over 12-24 hours following 1-hour IV infusion.

[c] At median time of 2.5 hours (range 2-3 hours) following multiple oral doses.

Metabolism

The metabolism of stavudine has not been elucidated in humans.

Elimination

In humans, renal elimination accounts for about 40% of the overall clearance of stavudine (Table 2). The mean renal clearance is about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration. The remaining 60% of the drug is presumably eliminated by endogenous pathways. The elimination half-life of stavudine is 1.6 hours.

Special Populations

Renal Impairment

The extended-release formulation of stavudine should not be used in patients with creatinine clearance ≤50 mL/min. (see **DOSAGE AND ADMINISTRATION: Dosage Adjustment**).

The effects of renal dysfunction on the pharmacokinetics of the extended-release capsule have not been investigated. Data from two studies with an immediate-release formulation of stavudine indicated that the apparent oral clearance of stavudine decreased and the terminal elimination half-life increased as creatinine clearance decreased. The applicability of the results from the immediate-release formulation to the extended-release formulation needs to be further investigated.

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 of an immediate-release formulation of stavudine.

Pediatric Patients

The pharmacokinetics of stavudine administered as ZERIT XR have not been studied in pediatric patients (see **PRECAUTIONS: Pediatric Use)**.

Geriatric

Stavudine pharmacokinetics have not been studied in patients >65 years of age (see **PRECAUTIONS: Geriatric Use**).

Gender

The effects of gender on the pharmacokinetics of the extended-release capsule have not been investigated. For the immediate-release capsule, a population pharmacokinetic analysis of data collected during a controlled clinical study in HIV-infected patients showed no clinically important differences between males (n=291) and females (n=27).

Race

The effects of race on the pharmacokinetics of the extended-release capsule have not been investigated. For the immediate-release capsule, a population pharmacokinetic analysis of data collected during a controlled clinical study in HIV-infected patients showed no clinically important differences between races (n=233 Caucasian, 29 African-American, 41 Hispanic, 1 Asian, and 4 other).

Drug Interactions (see PRECAUTIONS: Drug Interactions)

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

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

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 3 and 4 summarize the effects on AUC and C_{max}, with a 95% confidence interval (CI) when available, following coadministration of an immediate-release formulation of ZERIT with didanosine, lamivudine, and nelfinavir. The results of these studies may be expected to apply to ZERIT XR. No clinically significant pharmacokinetic interactions were observed.

Table 3: Results of Drug Interaction Studies with Stavudine (Immediate-Release Formulation): 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 q12h for 4 days	40 mg q12h for 4 days	10	↔	↑ 17%
Lamivudine, 150 mg single dose	40 mg single dose	18	↔ (92.7-100.6%)	↑ 12% (100.3-126.1%)
Nelfinavir, 750 mg q8h for 56 days	30-40 mg q12h for 56 days	8	↔	↔

↑ indicates increase.

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

[a] HIV-infected patients.

Table 4: Results of Drug Interaction Studies with Stavudine (Immediate-Release Formulation): Effects of Stavudine on Coadministered Drug Plasma AUC and C_{max} Values

Drug	Stavudine Dosage	n[a]	AUC of Coadministered Drug (95% CI)	C_{max} of Coadministered Drug (95% CI)
Didanosine, 100 mg q12h for 4 days	40 mg q12h for 4 days	10	↔	↔
Lamivudine, 150 mg single dose	40 mg single dose	18	↔ (90.5-107.6%)	↔ (87.1-110.6%)
Nelfinavir, 750 mg q8h for 56 days	30-40 mg q12h for 56 days	8	↔	↔

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

[a] HIV-infected patients.

INDICATIONS AND USAGE

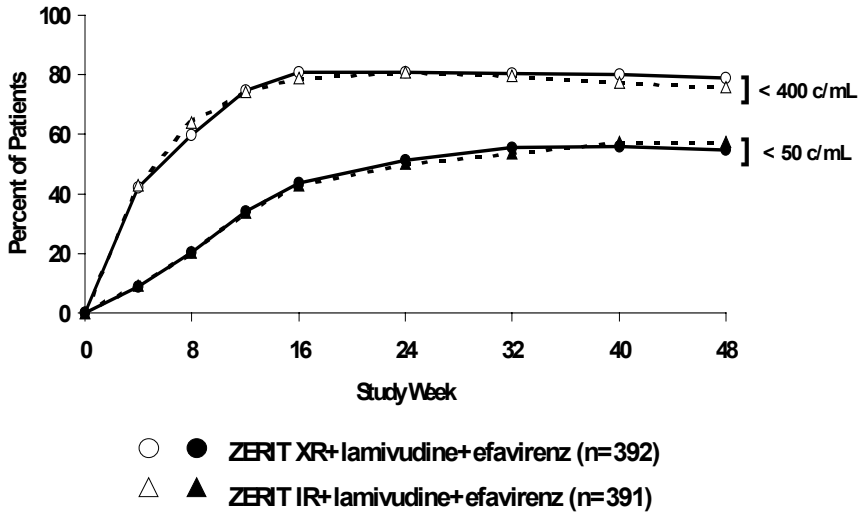
ZERIT XR, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection (see Clinical Studies).

Clinical Studies

AI455-099

Study AI455-099 was a 48-week, randomized, double-blind study comparing ZERIT XR (100 mg once daily) with ZERIT immediate-release (40 mg twice daily), each in combination with lamivudine (150 mg twice daily) plus efavirenz (600 mg once daily), in 783 treatment-naive patients, with a median CD4 cell count of 277 cells/mm^3 (range 61 to 1215 cells/mm^3) and a median plasma HIV-1 RNA of 4.80 $\log_{10}$ copies/mL (range 2.6 to 5.9 $\log_{10}$ copies/mL) at baseline. Patients were primarily males (69%) and non-white (58%) with a median age of 33 years (range 18 to 69 years). Mean increases in CD4 cell count were 202 cells/mm^3 for patients treated with ZERIT XR and 182 cells/mm^3 for patients treated with the ZERIT immediate-release regimen. Outcomes of treatment through 48 weeks for treated patients are shown in Figure 1 and Table 5.

Figure 1: Virologic Response Through Week 48, AI455-099[a,b]



[a] Percent of patients at each time point who had achieved and maintained HIV RNA <400 or <50 copies/mL and did not meet any criteria for treatment failure (eg, virologic failure or discontinuation for any reason).

[b] Plasma HIV-RNA levels were quantified at baseline with the AMPLICOR HIV-1 MONITOR® standard assay (assay limit <400 copies/mL) and on-treatment with the AMPLICOR HIV-1 MONITOR ultrasensitive assay (assay limit <50 copies/mL). Samples from subjects in North America were tested with version 1.0 of the assay, and samples from subjects outside North America were tested with version 1.5.

AMPLICOR HIV-1 MONITOR® is a registered trademark of a member of the Roche Group.

Table 5: Treatment Outcomes Through Week 48, AI455-099

Outcome	ZERIT XR + lamivudine + efavirenz n=392	ZERIT IR + lamivudine + efavirenz n=391
Virologic responder[a]		
HIV RNA <400 [<50] copies/mL	79 % [55%]	76% [57%]
Virologic failure[b]	10%	10%
Rebound	5%	6%
No confirmed response	4%	4%
Death	<1%	<1%
Discontinued due to adverse event	4%	3%
Discontinued due to other reasons[c]	7%	10%

[a] Achieved virologic response (two consecutive plasma HIV-1 RNA levels <400 [<50] copies/mL) and maintained it to Week 48.
[b] Includes viral rebound and failing to achieve confirmed <400 copies/mL by Week 48.
[c] Includes lost to follow-up, withdrawal, pregnancy, on-study protocol violation, noncompliance, and administrative decision.
IR=immediate-release.

AI455-096

Study AI455-096 was a pilot 48-week, randomized, double-blind study comparing ZERIT XR (100 mg once daily) with ZERIT immediate-release (40 mg twice daily), each in combination with lamivudine (150 mg twice daily) plus efavirenz (600 mg once daily), in 150 treatment-naive patients, with a median CD4 cell count of 285 cells/mm^3 (range 63 to 962 cells/mm^3) and a median plasma HIV-1 RNA of 4.65 $\log_{10}$ copies/mL (range 2.3 to 5.9 $\log_{10}$ copies/mL) at baseline. Patients were primarily males (75%) and white (70%) with a median age of 34 years (range 20 to 69 years). The results of this pilot study were similar to the findings of AI455-099.

CONTRAINDICATIONS

ZERIT XR is contraindicated in patients with clinically significant hypersensitivity to stavudine or to any of the components contained in the formulation.

WARNINGS

1. Lactic Acidosis/Severe Hepatomegaly with Steatosis/Hepatic Failure:

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including stavudine and

other antiretrovirals. Although relative rates of lactic acidosis have not been assessed in prospective well-controlled trials, longitudinal cohort and retrospective studies suggest that this infrequent event may be more often associated with antiretroviral combinations containing stavudine. Female gender, obesity, and prolonged nucleoside exposure may be risk factors. Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk (see **PRECAUTIONS: Pregnancy**).

Particular caution should be exercised when administering stavudine to any patient with known risk factors for liver disease; however, cases of lactic acidosis have also been reported in patients with no known risk factors. Generalized fatigue, digestive symptoms (nausea, vomiting, abdominal pain, and unexplained weight loss); respiratory symptoms (tachypnea and dyspnea); or neurologic symptoms (including motor weakness, see **2. Neurologic Symptoms**) might be indicative of the development of symptomatic hyperlactatemia or lactic acidosis syndrome.

Treatment with ZERIT XR 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).

An increased risk of hepatotoxicity may occur in patients treated with stavudine in combination with didanosine and hydroxyurea compared to when stavudine is used alone. Deaths attributed to hepatotoxicity have occurred in patients receiving this combination. Patients treated with this combination should be closely monitored for signs of liver toxicity.

2. Neurologic Symptoms:

Motor weakness has been reported rarely in patients receiving combination antiretroviral therapy including stavudine. Most of these cases occurred in the setting of lactic acidosis. The evolution of motor weakness may mimic the clinical presentation of Guillain-Barré syndrome (including respiratory failure). Symptoms may continue or worsen following discontinuation of therapy.

Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been reported in patients receiving stavudine therapy. Peripheral neuropathy has occurred more frequently in patients with advanced HIV disease, with a history of neuropathy, or in patients receiving other drugs that have been associated with neuropathy, including didanosine (see **ADVERSE REACTIONS**). Stavudine-related peripheral neuropathy may resolve if therapy is withdrawn promptly, although in some cases, symptoms may worsen temporarily following discontinuation of therapy. Switching the patient with peripheral neuropathy to an alternate treatment regimen should be

considered. If switching to an alternate regimen is not suitable and if symptoms resolve satisfactorily after temporary withdrawal, treatment with ZERIT XR may be resumed at 50% of the recommended dosage (see **DOSAGE AND ADMINISTRATION**). The efficacy of regimens containing reduced dose ZERIT XR has not been fully evaluated. If peripheral neuropathy recurs, permanent discontinuation of ZERIT XR should be considered.

3. Pancreatitis:

Fatal and nonfatal pancreatitis have occurred during therapy when stavudine was part of a combination regimen that included didanosine, with or without hydroxyurea, in both treatment-naive and treatment-experienced patients, regardless of degree of immunosuppression. The combination of ZERIT XR and didanosine (with or without hydroxyurea) and any other agents that are toxic to the pancreas should be suspended in patients with suspected pancreatitis. Reinstitution of ZERIT XR 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.

PRECAUTIONS

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. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Information for Patients (see Patient Information Leaflet)

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 ZERIT XR therapy may be required.

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 disease or a history of peripheral neuropathy, and that dose modification and/or discontinuation of ZERIT XR may be required if toxicity develops.

Patients should be informed that when ZERIT XR is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when ZERIT XR is used alone. An increased risk of pancreatitis, which may be fatal, may occur in patients treated with the combination of stavudine and didanosine, with or without hydroxyurea. Patients treated with this combination should be closely monitored for symptoms of pancreatitis. An increased risk of hepatotoxicity, which may be fatal, may occur in patients treated with stavudine in combination with didanosine and hydroxyurea. Patients treated with this combination should be closely monitored for signs of liver toxicity.

Patients should be informed that ZERIT XR (stavudine) is not a cure for HIV infection, and that they may continue to acquire illnesses associated with HIV infection, including opportunistic infections. Patients should be advised to remain under the care of a physician when using ZERIT XR. They should be advised that ZERIT XR therapy has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination. Patients should be informed that the long-term effects of ZERIT XR are unknown at this time.

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.

Patients should be informed that redistribution or accumulation of body fat may occur in individuals receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Patients should be advised of the importance of adherence to any antiretroviral regimen, including those that contain ZERIT XR.

Drug Interactions (see also CLINICAL PHARMACOLOGY)

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

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.

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 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.

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.

Pregnancy

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

There are no adequate and well-controlled studies of stavudine in pregnant women. 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 **WARNINGS: Lactic Acidosis/Severe Hepatomegaly with Steatosis/Hepatic Failure**). **The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk.**

Health care 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.

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed 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 breast-feed if they are receiving ZERIT XR.**

Pediatric Use

The safety and efficacy of ZERIT XR in pediatric patients have not been established. Please consult the complete prescribing information for ZERIT (stavudine) Capsules and ZERIT for Oral Solution for dosage and administration of stavudine to pediatric patients.

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 in which patients with advanced HIV infection were treated with ZERIT immediate-release, 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. ZERIT immediate-release, with dose adjustment, is recommended for patients with creatinine clearance ≤50 mL/min (see **DOSAGE AND ADMINISTRATION: Dosage Adjustment**).

ADVERSE REACTIONS

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

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

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

Patients should be monitored for the development of neuropathy, which is usually manifested by numbness, tingling, or pain in the feet or hands. Stavudine-related peripheral neuropathy may resolve if therapy is withdrawn promptly, although in some cases, symptoms may worsen temporarily following discontinuation of therapy. Switching the patient with peripheral neuropathy to an alternate treatment regimen should be considered. If switching to an alternate regimen is not suitable and if symptoms resolve satisfactorily after temporary withdrawal, treatment with ZERIT XR may be resumed at 50% of the recommended dosage (see **DOSAGE AND ADMINISTRATION**). The efficacy of regimens containing reduced dose ZERIT XR has not been fully evaluated. If peripheral neuropathy recurs, permanent discontinuation of ZERIT XR should be considered. In clinical trials, less than 1% of 466 patients treated with ZERIT XR for a median duration of 56 weeks (ranging up to 120 weeks) discontinued therapy because of peripheral neuropathy.

When stavudine is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when stavudine is used alone. Pancreatitis, peripheral neuropathy, and liver function abnormalities occur more frequently in patients treated with the combination of stavudine and didanosine, with or without hydroxyurea. Fatal pancreatitis and hepatotoxicity may occur more frequently in patients treated with stavudine in combination with didanosine and hydroxyurea (see **WARNINGS** and **PRECAUTIONS**).

In the pooled database from trials AI455-099 and AI455-096 and an ongoing long-term follow-up study for patients completing these two trials (median duration of therapy 56 weeks, ranging up to 120 weeks), the rates of discontinuation of therapy due to adverse events were 5% for the ZERIT XR regimen and 7% for the ZERIT immediate-release regimen.

Selected drug-related (considered by the investigator to be of possible, probable, or unknown relationship to any component of the regimen) clinical adverse events in these trials are presented in Table 6.

Table 6: Selected Clinical Adverse Events[a] of Any Severity From Combination Studies of ZERIT XR (Pooled Data)[b]

Adverse Events	ZERIT XR + lamivudine + efavirenz n=466	ZERIT IR + lamivudine + efavirenz n=467
Body as a whole		
Headache	12%	8%
Fatigue	6%	4%
Digestive system		
Diarrhea	10%	10%
Nausea	10%	9%
Dyspepsia	4%	3%
Vomiting	3%	4%
Metabolic & nutritional system		
Lipodystrophy	3%	4%
Nervous system		
Dizziness	30%	30%
PNS/Neuropathy	16%	19%
Abnormal dreams	13%	14%
Somnolence	8%	8%
Insomnia	8%	6%
Abnormal thinking	3%	2%
Depression	2%	1%
Skin & appendages		
Rash	16%	12%
Pruritus	4%	4%

[a] Considered by the investigator to be of possible, probable, or unknown relationship to any component of the drug regimen.

[b] Patients received either ZERIT XR 100 mg once daily or ZERIT immediate-release 40 mg twice daily each in combination with lamivudine 150 mg twice daily and efavirenz 600 mg once daily. Median duration of treatment was 56 weeks (ranging up to 120 weeks).

IR = immediate-release; PNS = peripheral neurologic symptoms (includes neuropathy, paresthesia, and peripheral neuritis).

In clinical trials, lactic acidosis syndrome/symptomatic hyperlactatemia (LAS/SHL), sometimes fatal, was reported. LAS/SHL occurred in 3 of 466 patients treated with ZERIT XR and in 6 of 467 patients treated with ZERIT immediate-release. The overall incidence of LAS/SHL for these trials was 8.8/1000 patient years.

Elevations in liver function tests or progression of liver disease, sometimes fatal, that resulted in discontinuation of study drug were observed in 3 of 466 patients in the ZERIT XR arm and 3 of 467 patients in the ZERIT immediate-release arm of clinical trials. All six patients were co-infected with hepatitis B or C.

Pancreatitis was observed in 1 of 466 patients treated with ZERIT XR and 4 of 467 patients treated with ZERIT immediate-release in clinical trials. Pancreatitis resulting in death was observed in patients treated with stavudine plus didanosine, with or without hydroxyurea, in controlled clinical studies and in postmarketing reports.

Selected laboratory abnormalities reported in antiretroviral-naive adult patients receiving either ZERIT XR or ZERIT immediate-release in the pooled database from two controlled combination studies and an ongoing long-term follow-up study for patients completing these studies are provided in Table 7.

Table 7: Selected Laboratory Abnormalities from Combination Studies of ZERIT XR (Pooled Data)[a]

Parameter	ZERIT XR + lamivudine + efavirenz n=466	ZERIT IR + lamivudine + efavirenz n=467
AST (>5 x ULN)	2%	3%
ALT (>5 x ULN)	3%	3%
Lipase (≥2.1 x ULN)	4%	3%
Total bilirubin (≥2.6 x ULN)	<1%	0
Neutropenia (ANC <750/mm^3)	5%	5%
Anemia (hemoglobin <8 g/dL)	<1%	<1%
Thrombocytopenia (platelets <50,000/mm^3)	1%	2%

[a] Patients received either ZERIT XR 100 mg once daily or ZERIT immediate-release 40 mg twice daily each in combination with lamivudine 150 mg twice daily and efavirenz 600 mg once daily. Median duration of treatment was 56 weeks (ranging up to 120 weeks).

IR=immediate-release; ULN = upper limit of normal; ANC = absolute neutrophil count.

Observed During Clinical Practice

The following events have been identified during post-approval use of the immediate-release formulations 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 stavudine, or a combination of these factors.

Body as a Whole—abdominal pain, allergic reaction, chills/fever, and redistribution/accumulation of body fat (see **PRECAUTIONS**: **Fat Redistribution**).
Digestive Disorders—anorexia.

Hematologic Disorders—anemia, leukopenia, and thrombocytopenia.
Exocrine Gland Disorders—pancreatitis [including fatal cases (see **WARNINGS**)].
Liver—symptomatic hyperlactatemia/lactic acidosis and hepatic steatosis (see **WARNINGS**), hepatitis and liver failure.
Musculoskeletal—myalgia.
Nervous System—insomnia, severe motor weakness (most often reported in the setting of lactic acidosis, see **WARNINGS**).

OVERDOSAGE

Experience with adults treated with the immediate-release formulation at 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.

DOSAGE AND ADMINISTRATION

ZERIT XR may be taken with or without food.

Adults: The recommended daily dose of ZERIT XR is based on body weight and is administered in a once-daily schedule as follows:

100 mg once daily for patients ≥60 kg.

75 mg once daily for patients <60 kg.

For patients who have difficulty swallowing intact capsules, the capsule can be carefully opened and the contents mixed with 2 tablespoons of yogurt or applesauce. Patients should be cautioned not to chew or crush the beads while swallowing.

Pediatrics: ZERIT XR has not been studied in pediatric patients. Please consult the complete prescribing information for ZERIT (stavudine) Capsules and ZERIT for Oral Solution for dosage and administration of stavudine to pediatric patients.

Dosage Adjustment

Peripheral Neuropathy

Patients should be monitored for the development of peripheral neuropathy, which is usually manifested by numbness, tingling, or pain in the feet or hands (see **WARNINGS**). If these symptoms develop during treatment, stavudine therapy should be interrupted. Symptoms may resolve if therapy is

withdrawn promptly, although in some cases, symptoms may worsen temporarily following discontinuation of therapy. Switching the patient to an alternate treatment regimen should be considered. If switching to an alternate regimen is not suitable and if symptoms resolve satisfactorily after temporary withdrawal, treatment with ZERIT XR may be resumed at 50% of the recommended dosage (see **WARNINGS**):

50 mg once daily for patients ≥60 kg.

37.5 mg once daily for patients <60 kg.

If peripheral neuropathy recurs, permanent discontinuation of ZERIT XR should be considered.

Renal Impairment

ZERIT XR has not been studied in patients with renal impairment. Please consult the complete prescribing information for ZERIT (stavudine) Capsules and ZERIT for Oral Solution for dosage and administration of stavudine to patients with creatinine clearance ≤50 mL/min.

HOW SUPPLIED

ZERIT® XR (stavudine) Extended-Release Capsules are available in the strengths and configurations of high-density polyethylene bottles shown in Table 8. Bottles have child-resistant closures and contain desiccant.

Table 8: ZERIT XR Capsules

Product Strength	Capsule Shell Color	Markings on Capsule (in dark blue ink)	Capsules per Bottle	NDC No.
37.5 mg	Red and yellow	BMS 37.5 mg 1555	30	0003-1555-12
50 mg	Orange	BMS 50 mg 1556	30	0003-1556-12
75 mg	Red	BMS 75 mg 1557	30	0003-1557-12
100 mg	Rich yellow	BMS 100 mg 1558	30	0003-1558-12

US Patent No.: 4,978,655. Patent also pending (stavudine extended-release capsules).

Storage

ZERIT XR Capsules should be stored in tightly closed containers at 25° C (77° F). Excursions between 15° C and 30° C (59° F and 86° F) are permitted (see USP Controlled Room Temperature).

Bristol-Myers Squibb Virology
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Issued _____

PATIENT INFORMATION

ZERIT® XR

(generic name = **stavudine**, also known as **d4T**) **Rx only**

Extended-Release Capsules

What is ZERIT XR?

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

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

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

Because ZERIT XR is a new product, there is limited information on its long-term use. In ZERIT XR Capsules, the active ingredient (stavudine) is enclosed in beads that slow the release of the drug into your body. This slow release allows ZERIT XR to be taken once a day in contrast to other forms of ZERIT that are taken twice a day.

Who should not take ZERIT XR?

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

How should I take ZERIT XR?

Your doctor will determine your dose (the amount in each capsule) based on your body weight, kidney and liver function, and any side effects that you may have had with other medicines. ZERIT XR Capsules are taken once a day (every 24 hours). Take ZERIT XR exactly as instructed. Try not to miss a dose, but if you do, take it as soon as possible. If it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. ZERIT XR may be taken with food or on an empty stomach.

If you have difficulty swallowing the capsule, it can be carefully opened and the beads inside mixed with 2 tablespoons of yogurt or applesauce. Be careful not to chew or crush the beads while swallowing.

If you have a kidney problem:

ZERIT XR has not been studied in people with kidney problems. Please consult with your doctor for an alternative ZERIT dosing form.

Can children take ZERIT XR?

ZERIT XR has not been studied in children. Please consult with your doctor for an alternative ZERIT dosing form.

What should I do if someone takes an overdosage of ZERIT XR?

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

Can I take other medicines while taking ZERIT XR?

- Do not take zidovudine (AZT) while taking ZERIT XR, because AZT may interfere with the actions of ZERIT XR. Products containing AZT include Combivir®, Retrovir®, and Trizivir®.

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

What about pregnancy and nursing (breast-feeding)?

- It is not known if ZERIT XR can harm a human fetus. Pregnant women have experienced serious side effects when taking stavudine (the active ingredient in ZERIT XR) in combination with didanosine and other HIV medicines. ZERIT XR should be used during pregnancy only after

discussion with your doctor. **Tell your doctor if you become pregnant or plan to become pregnant while taking ZERIT XR.**

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

What are the possible side effects of ZERIT XR?

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

- ***nausea, vomiting, or unusual or unexpected stomach discomfort;***
- ***feeling very weak and tired;***
- ***shortness of breath;***
- ***weakness in arms and legs.***

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

• **Peripheral neuropathy** is a nerve disorder of the hands and feet. If not recognized promptly, this disorder may worsen***. Tell your doctor right away*** *if you have continuing numbness, tingling, burning, or pain in the feet and/or hands.*

Let your doctor know if you have ever had peripheral neuropathy, because this condition occurs more often in patients who have had it previously. Peripheral neuropathy is also more likely to occur in patients taking drugs that affect the nerves and in patients with advanced HIV disease, but it can occur at any disease stage. If you develop peripheral neuropathy, your doctor may tell you to stop taking ZERIT XR. In some cases the symptoms worsen for a short time before getting better. Your

doctor may switch you to a different drug or, once symptoms of peripheral neuropathy go away completely, have you start ZERIT XR again at a lower dose.

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

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

Other side effects. Frequent side effects observed in studies of adults taking ZERIT XR in combination with other HIV drugs (Epivir® and Sustiva®) were dizziness, rash, peripheral neuropathy, abnormal dreams, headache, diarrhea, and nausea. Other side effects may include sleepiness, insomnia, fatigue, abdominal pain, indigestion, itching, vomiting, abnormal thinking, depression, chills or fever, loss of appetite, muscle pain, allergic reactions, and blood disorders. It is not always possible to tell whether unwanted effects are caused by ZERIT XR, other medicines you may be taking at the same time, or the HIV disease itself.

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

How should I store ZERIT XR?

Store ZERIT XR Capsules in a tightly closed container at room temperature away from heat and out of the reach of children and pets. Do NOT store this medicine in a damp place such as a bathroom medicine cabinet or near the kitchen sink.

Inactive Ingredients:

Distilled acetylated monoglycerides, ethylcellulose aqueous dispersion, gelatin, hydroxypropyl methylcellulose, iron oxide colorant, lactose monohydrate (milk sugar), magnesium stearate, microcrystalline cellulose, silicon dioxide, sodium lauryl sulfate, talc, and titanium dioxide.

This medicine was prescribed for your particular condition. Do not use ZERIT XR for another condition or give it to others. Keep ZERIT XR and all other medicines out of the reach of children. Throw away ZERIT XR when it is outdated or no longer needed by flushing it down the toilet or pouring it down the sink.

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

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This Patient Information Leaflet has been approved by the U.S. Food and Drug Administration.

xxxxxxxx Issued xxxxx xxxx Based on xxxxxx (xx/xx)