

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZERIT safely and effectively. See full prescribing information for ZERIT.

ZERIT® (stavudine) Capsules

ZERIT® (stavudine) for Oral Solution

Initial U.S. Approval: 1994

WARNING: LACTIC ACIDOSIS and HEPATOMEGALY with STEATOSIS; PANCREATITIS

See full prescribing information for complete boxed warning.

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

RECENT MAJOR CHANGES

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

- Recommended dosage for adults:
 - less than 60 kg: 30 mg every 12 hours (2.1)
 - at least 60 kg: 40 mg every 12 hours (2.1)
- Recommended dosage for pediatric patients:
 - newborns from birth to 13 days old: 0.5 mg/kg every 12 hours (2.2)
 - at least 14 days old and weighing less than 30 kg: 1 mg/kg every 12 hours (2.2)
 - weighing at least 30 kg: adult dose (2.2)
- Renal impairment: Dose adjustment is recommended for CrCl ≤50 mL/min. (2.3)
- Oral solution: Requires preparation by a pharmacist. (2.4)

DOSAGE FORMS AND STRENGTHS

- Capsules: 15 mg, 20 mg, 30 mg, 40 mg (3, 16.1)
- Oral solution: 1 mg/mL following constitution (3, 16.2)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 11/2011

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FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS and HEPATOMEGALY with STEATOSIS; PANCREATITIS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including stavudine and other antiretrovirals. Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk [see *Warnings and Precautions (5.1)*].

Fatal and nonfatal pancreatitis have occurred during therapy when ZERIT was part of a combination regimen that included didanosine in both treatment-naïve and treatment-experienced patients, regardless of degree of immunosuppression [see *Warnings and Precautions (5.4)*].

INDICATIONS AND USAGE

ZERIT[®] (stavudine), in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV)-1 infection [see *Clinical Studies (14)*].

DOSAGE AND ADMINISTRATION

The interval between doses of ZERIT (stavudine) should be 12 hours. ZERIT may be taken with or without food.

Recommended Adult Dosage

The recommended adult dosage is based on body weight as follows:

- For patients weighing less than 60 kg: 30 mg every 12 hours.
- For patients weighing at least 60 kg: 40 mg every 12 hours.

Recommended Pediatric Dosage

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

Dosage Adjustment

Renal Impairment

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

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

| Creatinine Clearance (mL/min) | Recommended ZERIT Dose by Patient Weight | |
|----------------------------------|---|-----------------------------------|
| | at least 60 kg | less than 60 kg |
| greater than 50 | 40 mg every 12 hours | 30 mg every 12 hours |
| 26–50 | 20 mg every 12 hours | 15 mg every 12 hours |
| 10–25 | 20 mg every 24 hours | 15 mg every 24 hours |
| Hemodialysis | 20 mg every 24 hours [*] | 15 mg every 24 hours [*] |

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

Pediatric Patients: Since urinary excretion is also a major route of elimination of stavudine in pediatric patients, the clearance of stavudine may be altered in children with renal impairment. There are insufficient data to recommend a specific dose adjustment of ZERIT in this patient population.

Method of Preparation for Oral Solution

Prior to dispensing, the pharmacist must constitute the dry powder with purified water to a concentration of 1 mg stavudine per mL of solution, as follows:

1. Add 202 mL of purified water to the container.
2. Shake container vigorously until the powder dissolves completely. Constitution in this way produces 200 mL (deliverable volume) of 1 mg/mL stavudine solution. The solution may appear slightly hazy.
3. Dispense solution in original container with measuring cup provided. Instruct patient to shake the container vigorously prior to measuring each dose and to store the tightly closed container in a refrigerator, 2°C to 8°C (36°F to 46°F). Discard any unused portion after 30 days.

DOSAGE FORMS AND STRENGTHS

- ZERIT 15 mg capsules with dark red cap and light yellow body, printed with black ink “BMS 1964” on the cap and with black ink “15” on the body.
- ZERIT 20 mg capsules with light brown cap and light brown body, printed with black ink “BMS 1965” on the cap and with black ink “20” on the body.
- ZERIT 30 mg capsules with dark orange cap and light orange body, printed with black ink “BMS 1966” on the cap and with black ink “30” on the body.
- ZERIT 40 mg capsules with dark orange cap and dark orange body, printed with black ink “BMS 1967” on the cap and with black ink “40” on the body.
- ZERIT for oral solution is a dye-free, fruit-flavored powder that provides 1 mg of stavudine per milliliter solution after constitution.

CONTRAINDICATIONS

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

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

Particular caution should be exercised when administering 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 unexplained weight loss); respiratory symptoms (tachypnea and dyspnea); or neurologic symptoms, including motor weakness [see *Warnings and Precautions (5.3)*] might be indicative of the development of symptomatic hyperlactatemia or lactic acidosis syndrome.

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

Hepatic Toxicity

The safety and efficacy of ZERIT have not been established in HIV-infected patients with significant underlying liver disease. During combination antiretroviral therapy, patients with preexisting liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities, including severe and potentially fatal hepatic adverse events, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

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

Use with Interferon and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as stavudine. Although no evidence of a pharmacokinetic or pharmacodynamic (eg, loss of HIV-1/HCV virologic suppression) interaction was seen when ribavirin was coadministered with stavudine in HIV-1/HCV co-infected patients [see *Drug Interactions* (7)], **hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon and ribavirin.** Patients receiving interferon with or without ribavirin and stavudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of stavudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (eg, Child-Pugh >6) (see **the full prescribing information for interferon and ribavirin**).

Neurologic Symptoms

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

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

Patients should be monitored for the development of peripheral neuropathy. Stavudine-related peripheral neuropathy may resolve if therapy is withdrawn promptly. If peripheral neuropathy

develops permanent discontinuation of ZERIT should be considered. In some cases, symptoms may worsen temporarily following discontinuation of therapy.

Pancreatitis

Fatal and nonfatal pancreatitis have occurred during therapy when ZERIT was part of a combination regimen that included didanosine in both treatment-naive and treatment-experienced patients, regardless of degree of immunosuppression. The combination of 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; avoid use in combination with didanosine.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy.

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

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including ZERIT. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to

indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

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

ADVERSE REACTIONS

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

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

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

Clinical Trial Experience in Adults

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

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

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

| Adverse Reaction | Percent (%) | |
|------------------|--|---|
| | ZERIT ^b (40 mg twice daily) (n=412) | zidovudine (200 mg 3 times daily) (n=402) |
| Headache | 54 | 49 |

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

| Adverse Reaction | Percent (%) | |
|---|--|---|
| | ZERIT ^b (40 mg twice daily) (n=412) | zidovudine (200 mg 3 times daily) (n=402) |
| Diarrhea | 50 | 44 |
| Peripheral Neurologic Symptoms/ Neuropathy | 52 | 39 |
| Rash | 40 | 35 |
| Nausea and Vomiting | 39 | 44 |

^a The incidences reported included all severity grades and all reactions regardless of causality.

^b Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.

Pancreatitis was observed in 3 of the 412 adult patients who received ZERIT in study AI455-019.

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

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

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

^a The incidences reported included all severity grades and all reactions regardless of causality.

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

| Adverse Reaction | Percent (%) | | | |
|------------------|--|---|--|---|
| | START 1 | | START 2 ^b | |
| | ZERIT + lamivudine + indinavir (n=100 ^c) | zidovudine + lamivudine + indinavir (n=102) | ZERIT + didanosine + indinavir (n=102 ^c) | zidovudine + lamivudine + indinavir (n=103) |
| | | | | |

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

^c Duration of stavudine therapy = 48 weeks.

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

Table 4: Selected Laboratory Abnormalities in Study AI455-019^{a,b}

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

^a Data presented for patients for whom laboratory evaluations were performed.

^b Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.

ULN = upper limit of normal.

Selected laboratory abnormalities reported in two controlled combination studies are provided in Tables 5 and 6.

Table 5: Selected Laboratory Abnormalities in START 1 and START 2 Studies (Grades 3–4)

| Parameter | Percent (%) | | | |
|------------------------|--|---|--|---|
| | 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 6: Selected Laboratory Abnormalities in START 1 and START 2 Studies (All Grades)

| Parameter | Percent (%) | | | |
|-----------------|--|---|--|---|
| | 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 |

Clinical Trial Experience in Pediatric Patients

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

Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of ZERIT. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions have been chosen for inclusion due to their seriousness, frequency of reporting, causal connection to ZERIT, or a combination of these factors.

Body as a Whole: abdominal pain, allergic reaction, chills/fever, and redistribution/accumulation of body fat [see *Warnings and Precautions* (5.5)].

Digestive Disorders: anorexia.

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

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

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

Metabolic Disorders: lipoatrophy, lipodystrophy [see *Warnings and Precautions* (5.5)], diabetes mellitus and hyperglycemia.

Musculoskeletal: myalgia.

Nervous System: insomnia, severe motor weakness (most often reported in the setting of lactic acidosis) [see *Warnings and Precautions* (5.1, 5.3)].

Use with Didanosine- and Hydroxyurea-Based Regimens

When stavudine is used in combination with other agents with similar toxicities, the incidence of these toxicities may be higher than when stavudine is used alone. Thus, patients treated with

ZERIT in combination with didanosine, with or without hydroxyurea, may be at increased risk for pancreatitis and hepatotoxicity, which may be fatal, and severe peripheral neuropathy [see *Warnings and Precautions* (5)]. The combination of ZERIT and hydroxyurea, with or without didanosine, should be avoided.

7 DRUG INTERACTIONS

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

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

Doxorubicin: *In vitro* data indicate that the phosphorylation of stavudine is inhibited at relevant concentrations by doxorubicin. The clinical significance of this interaction is unknown; therefore, concomitant use of stavudine with doxorubicin should be undertaken with caution.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Reproduction studies have been performed in rats and rabbits with exposures (based on C_{max}) up to 399 and 183 times, respectively, of that seen at a clinical dosage of 1 mg/kg/day and have revealed no evidence of teratogenicity. The incidence in fetuses of a common skeletal variation, unossified or incomplete ossification of sternebra, was increased in rats at 399 times human exposure, while no effect was observed at 216 times human exposure. A slight post-implantation loss was noted at 216 times the human exposure with no effect noted at approximately 135 times the human exposure. An increase in early rat neonatal mortality (birth to 4 days of age) occurred

at 399 times the human exposure, while survival of neonates was unaffected at approximately 135 times the human exposure. A study in rats showed that stavudine is transferred to the fetus through the placenta. The concentration in fetal tissue was approximately one-half the concentration in maternal plasma. Animal reproduction studies are not always predictive of human response.

There are no adequate and well-controlled studies of stavudine in pregnant women. Stavudine should be used during pregnancy only if the potential benefit justifies the potential risk.

Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. It is unclear if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in nonpregnant individuals receiving nucleoside analogues [see *Boxed Warning* and *Warnings and Precautions (5.1)*]. **The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk.** Healthcare providers caring for HIV-infected pregnant women receiving stavudine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to stavudine and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Studies in lactating rats demonstrated that stavudine is excreted in milk. Although it is not known whether stavudine is excreted in human milk, there exists the potential for adverse effects from stavudine in nursing infants. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving ZERIT.**

8.4 Pediatric Use

Use of stavudine in pediatric patients from birth through adolescence is supported by evidence from adequate and well-controlled studies of stavudine in adults with additional pharmacokinetic and safety data in pediatric patients [see *Dosage and Administration (2.2)* and *Adverse Reactions (6.2)*].

Adverse reactions and laboratory abnormalities reported to occur in pediatric patients in clinical studies were generally consistent with the safety profile of stavudine in adults. These studies include ACTG 240, where 105 pediatric patients ages 3 months to 6 years received ZERIT 2 mg/kg/day for a median of 6.4 months; a controlled clinical trial where 185 newborns received ZERIT 2 mg/kg/day either alone or in combination with didanosine from birth through 6 weeks of age; and a clinical trial where 8 newborns received ZERIT 2 mg/kg/day in combination with didanosine and nelfinavir from birth through 4 weeks of age.

Stavudine pharmacokinetics have been evaluated in 25 HIV-1-infected pediatric patients ranging in age from 5 weeks to 15 years and in weight from 2 to 43 kg after IV or oral administration of single doses and twice-daily regimens and in 30 HIV-1-exposed or -infected newborns ranging in age from birth to 4 weeks after oral administration of twice-daily regimens [see *Clinical Pharmacology* (12.3, Table 9)].

8.5 Geriatric Use

Clinical studies of ZERIT (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 ZERIT cannot be ruled out.

In a monotherapy Expanded Access Program for patients with advanced HIV-1 infection, peripheral neuropathy or peripheral neuropathic symptoms were observed in 15 of 40 (38%) elderly patients receiving 40 mg twice daily and 8 of 51 (16%) elderly patients receiving 20 mg twice daily. Of the approximately 12,000 patients enrolled in the Expanded Access Program, peripheral neuropathy or peripheral neuropathic symptoms developed in 30% of patients receiving 40 mg twice daily and 25% of patients receiving 20 mg twice daily. Elderly patients should be closely monitored for signs and symptoms of peripheral neuropathy.

ZERIT is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function. Dose adjustment is recommended for patients with renal impairment [see *Dosage and Administration* (2.3)].

Renal Impairment

Data from two studies in adults indicated that the apparent oral clearance of stavudine decreased and the terminal elimination half-life increased as creatinine clearance decreased. Based on these

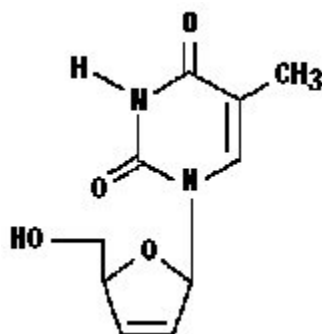
observations, it is recommended that the ZERIT dosage be modified in patients with reduced creatinine clearance and in patients receiving maintenance hemodialysis [see *Dosage and Administration* (2.3) and *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

Experience with adults treated with 12 to 24 times the recommended daily dosage revealed no acute toxicity. Complications of chronic overdosage include peripheral neuropathy and hepatic toxicity. Stavudine can be removed by hemodialysis; the mean \pm SD hemodialysis clearance of stavudine is 120 ± 18 mL/min. Whether stavudine is eliminated by peritoneal dialysis has not been studied.

11 DESCRIPTION

ZERIT[®] is the brand name for stavudine (d4T), a synthetic thymidine nucleoside analogue, active against the human immunodeficiency virus type 1 (HIV-1). The chemical name for stavudine is 2',3'-didehydro-3'-deoxythymidine. Stavudine has the following structural formula:



Stavudine 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.

Capsules: ZERIT is available as capsules for oral administration containing either 15, 20, 30, or 40 mg of stavudine. Each capsule also contains inactive ingredients microcrystalline cellulose, sodium starch glycolate, lactose, and magnesium stearate. The hard gelatin shell consists of gelatin, titanium dioxide, and iron oxides. The capsules are printed with edible inks.

Powder for Oral Solution: ZERIT is available as a dye-free, fruit-flavored powder in bottles with child-resistant closures providing 200 mL of a 1 mg/mL stavudine oral solution upon constitution with water per label instructions. The powder for oral solution contains the following inactive ingredients: methylparaben, propylparaben, sodium carboxymethylcellulose, sucrose, and antifoaming and flavoring agents.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

The pharmacokinetics of stavudine have been evaluated in HIV-1-infected adult and pediatric patients (Tables 7, 8, and 9). Peak plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) increased in proportion to dose after both single and multiple doses ranging from 0.03 to 4 mg/kg. There was no significant accumulation of stavudine with repeated administration every 6, 8, or 12 hours.

Absorption

Following oral administration, stavudine is rapidly absorbed, with peak plasma concentrations occurring within 1 hour after dosing. The systemic exposure to stavudine is the same following administration as capsules or solution. Steady-state pharmacokinetic parameters of ZERIT (stavudine) in HIV-1-infected adults are shown in Table 7.

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

| Parameter | ZERIT 40 mg BID Mean \pm SD (n=8) |
|-------------------------------|--|
| AUC ₀₋₂₄ (ng•h/mL) | 2568 \pm 454 |
| C _{max} (ng/mL) | 536 \pm 146 |
| C _{min} (ng/mL) | 8 \pm 9 |

AUC₀₋₂₄ = Area under the curve over 24 hours.
C_{max} = Maximum plasma concentration.
C_{min} = Trough or minimum plasma concentration.

Distribution

Binding of stavudine to serum proteins was negligible over the concentration range of 0.01 to 11.4 µg/mL. Stavudine distributes equally between red blood cells and plasma. Volume of distribution is shown in Table 8.

Metabolism

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

Elimination

Following an 80-mg dose of ¹⁴C-stavudine to healthy subjects, approximately 95% and 3% of the total radioactivity was recovered in urine and feces, respectively. Radioactivity due to parent drug in urine and feces was 73.7% and 62.0%, respectively. The mean terminal elimination half-life is approximately 2.3 hours following single oral doses. Mean renal clearance of the parent compound is approximately 272 mL/min, accounting for approximately 67% of the apparent oral clearance.

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

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

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

^a Following 1-hour IV infusion.
^b Following single oral dose.
^c Assuming a body weight of 70 kg.
^d Over 12–24 hours.

Special Populations

Pediatric

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

Table 9: Pharmacokinetic Parameters (Mean ± SD) of Stavudine in HIV-1-Exposed or -Infected Pediatric Patients

| Parameter | Ages 5 weeks to 15 years | | Ages 14 to 28 days | | Day of Birth | |
|---|--------------------------|----|--------------------|---|--------------|---|
| | Mean ± SD | n | Mean ± SD | n | Mean ± SD | n |
| Oral bioavailability (%) | 76.9 ± 31.7 | 20 | ND | | ND | |
| Volume of distribution (L/kg) ^a | 0.73 ± 0.32 | 21 | ND | | ND | |
| Ratio of CSF: plasma concentrations (as %) ^b | 59 ± 35 | 8 | ND | | ND | |
| Total body clearance (mL/min/kg) ^a | 9.75 ± 3.76 | 21 | ND | | ND | |

Table 9: Pharmacokinetic Parameters (Mean ± SD) of Stavudine in HIV-1-Exposed or -Infected Pediatric Patients

| Parameter | Ages 5 weeks to 15 years | | Ages 14 to 28 days | | Day of Birth | |
|--|--------------------------|----|--------------------|----|--------------|----|
| | | n | | n | | n |
| Apparent oral clearance (mL/min/kg) ^c | 13.75 ± 4.29 | 20 | 11.52 ± 5.93 | 30 | 5.08 ± 2.80 | 17 |
| Elimination half-life, IV dose (h) ^a | 1.11 ± 0.28 | 21 | ND | | ND | |
| Elimination half-life, oral dose (h) ^c | 0.96 ± 0.26 | 20 | 1.59 ± 0.29 | 30 | 5.27 ± 2.01 | 17 |
| Urinary recovery of stavudine (% of dose) ^{c,d} | 34 ± 16 | 19 | ND | | ND | |

^a Following 1-hour IV infusion.

^b At median time of 2.5 hours (range 2–3 hours) following multiple oral doses.

^c Following single oral dose.

^d Over 8 hours.

ND = Not determined.

Renal Impairment

Data from two studies in adults indicated that the apparent oral clearance of stavudine decreased and the terminal elimination half-life increased as creatinine clearance decreased (see Table 10). C_{max} and T_{max} were not significantly altered by renal impairment. The mean ± SD hemodialysis clearance value of stavudine was 120 ± 18 mL/min (n=12); the mean ± SD percentage of the stavudine dose recovered in the dialysate, timed to occur between 2–6 hours post-dose, was 31 ± 5%. Based on these observations, it is recommended that ZERIT (stavudine) dosage be modified in patients with reduced creatinine clearance and in patients receiving maintenance hemodialysis [see *Dosage and Administration* (2.3)].

Table 10: Mean ± SD Pharmacokinetic Parameter Values of ZERIT^a in Adults with Varying Degrees of Renal Function

| | Creatinine Clearance | | | Hemodialysis Patients ^b (n=11) |
|-------------------------------|----------------------|--------------------|-------------------|---|
| | >50 mL/min (n=10) | 26–50 mL/min (n=5) | 9–25 mL/min (n=5) | |
| Creatinine clearance (mL/min) | 104 ± 28 | 41 ± 5 | 17 ± 3 | NA |

Table 10: Mean ± SD Pharmacokinetic Parameter Values of ZERIT^a in Adults with Varying Degrees of Renal Function

| | Creatinine Clearance | | | Hemodialysis Patients ^b (n=11) |
|----------------------------------|----------------------|-----------------------|----------------------|--|
| | >50 mL/min (n=10) | 26–50 mL/min (n=5) | 9–25 mL/min (n=5) | |
| Apparent oral clearance (mL/min) | 335 ± 57 | 191 ± 39 | 116 ± 25 | 105 ± 17 |
| Renal clearance (mL/min) | 167 ± 65 | 73 ± 18 | 17 ± 3 | NA |
| T _{1/2} (h) | 1.7 ± 0.4 | 3.5 ± 2.5 | 4.6 ± 0.9 | 5.4 ± 1.4 |

^a Single 40-mg oral dose.

^b Determined while patients were off dialysis.

T_{1/2} = Terminal elimination half-life.

NA = Not applicable.

Hepatic Impairment

Stavudine pharmacokinetics were not altered in five non-HIV-infected patients with hepatic impairment secondary to cirrhosis (Child-Pugh classification B or C) following the administration of a single 40-mg dose.

Geriatric

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

Gender

A population pharmacokinetic analysis of data collected during a controlled clinical study in HIV-1-infected patients showed no clinically important differences between males (n=291) and females (n=27).

Race

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

Drug Interaction Studies

Stavudine does not inhibit the major cytochrome P450 isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways. Because stavudine is not protein-bound, it is not expected to affect the pharmacokinetics of protein-bound drugs.

Tables 11 and 12 summarize the effects on AUC and C_{max} , with a 95% confidence interval (CI) when available, following coadministration of ZERIT with didanosine, lamivudine, and nelfinavir. No clinically significant pharmacokinetic interactions were observed.

Table 11: Results of Drug Interaction Studies with ZERIT: 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-1-infected patients.

Table 12: Results of Drug Interaction Studies with ZERIT: 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-1-infected patients.

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 $0.032 \mu\text{M}$) and by causing DNA chain termination following its incorporation into viral DNA. Stavudine triphosphate inhibits cellular DNA polymerases β and γ and markedly reduces the synthesis of mitochondrial DNA.

Antiviral Activity in Cell Culture

The cell culture antiviral activity of stavudine was measured in peripheral blood mononuclear cells, monocytic cells, and lymphoblastoid cell lines. The concentration of drug necessary to inhibit HIV-1 replication by 50% (EC_{50}) ranged from 0.009 to $4 \mu\text{M}$ against laboratory and clinical isolates of HIV-1. In cell culture, stavudine exhibited additive to antagonistic activity in combination with zidovudine. Stavudine in combination with either abacavir, didanosine, tenofovir, or zalcitabine exhibited additive to synergistic anti-HIV-1 activity. Ribavirin, at the 9 – $45 \mu\text{M}$ concentrations tested, reduced the anti-HIV-1 activity of stavudine by 2.5- to 5-fold. The relationship between cell culture susceptibility of HIV-1 to stavudine and the inhibition of HIV-1 replication in humans has not been established.

Resistance

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

Cross-resistance

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Stavudine was not mutagenic in the Ames, *E. coli* reverse mutation, or the CHO/HGPRT mammalian cell forward gene mutation assays, with and without metabolic activation. Stavudine produced positive results in the *in vitro* human lymphocyte clastogenesis and mouse fibroblast assays, and in the *in vivo* mouse micronucleus test. In the *in vitro* assays, stavudine elevated the frequency of chromosome aberrations in human lymphocytes (concentrations of 25 to 250 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.

14 CLINICAL STUDIES

Combination Therapy

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

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

Monotherapy

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Capsules

ZERIT[®] (stavudine) Capsules are available in the following strengths and configurations of plastic bottles with child-resistant closures:

Table 13: Capsule Strength/Configuration

| Product Strength | Capsule Shell Color | Markings on Capsule (in Black Ink) | | Capsules per Bottle | NDC No. |
|------------------|----------------------------|------------------------------------|----|---------------------|--------------|
| 15 mg | Light yellow & dark red | BMS 1964 | 15 | 60 | 0003-1964-01 |
| 20 mg | Light brown | BMS 1965 | 20 | 60 | 0003-1965-01 |
| 30 mg | Light orange & dark orange | BMS 1966 | 30 | 60 | 0003-1966-01 |
| 40 mg | Dark orange | BMS 1967 | 40 | 60 | 0003-1967-01 |

Oral Solution

ZERIT[®] (stavudine) for Oral Solution is a dye-free, fruit-flavored powder that provides 1 mg of stavudine per mL of solution upon constitution with water. Directions for solution preparation are included on the product label and in the *Dosage and Administration (2)* section of this insert. ZERIT for Oral Solution (NDC No. 0003-1968-01) is available in child-resistant containers that provide 200 mL of solution after constitution with water.

Storage

ZERIT 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).

ZERIT for Oral Solution should be protected from excessive moisture and 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). After constitution, store tightly closed containers of ZERIT for Oral Solution in a refrigerator, 2°C to 8°C (36°F to 46°F). Discard any unused portion after 30 days.

17 PATIENT COUNSELING INFORMATION

See MEDICATION GUIDE.

General

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

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

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

Patients should be informed that when ZERIT is used in combination with other agents with similar toxicities, the incidence of adverse reactions may be higher than when ZERIT is used alone.

Patients should be instructed that if they miss a dose, to take it as soon as possible. If it is almost time for the next dose, skip the missed dose and continue the regular dosing schedule.

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

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

Patients with diabetes should be aware that ZERIT for Oral Solution contains 50 mg of sucrose (sugar) per mL.

Lactic Acidosis

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

Hepatic Toxicity

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

Peripheral Neuropathy

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

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

Pancreatitis

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

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

Fat Redistribution

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