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, for oral use
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 ZERIT and didanosine. Coadministration of ZERIT with didanosine is contraindicated. (4, 5.1)**
- **Fatal and nonfatal pancreatitis have occurred when ZERIT was part of a combination regimen that included didanosine. Coadministration of ZERIT with didanosine is contraindicated. (4, 5.4)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	12/2017
Contraindications (4)	12/2017
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5)	12/2017

----------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)
- For oral solution: Requires preparation by a pharmacist. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

- Capsules: 15 mg, 20 mg, 30 mg, 40 mg (3, 16)
- For oral solution: 1 mg/mL following constitution (3, 16)

----------CONTRAINDICATIONS----------

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

----------WARNINGS AND PRECAUTIONS----------

- Hepatic toxicity: May be severe, fatal. Consider interruption or discontinuation. Avoid use in combination with hydroxyurea. Coadministration of ZERIT with didanosine is contraindicated. Risk of hepatic decompensation exists when used in combination with interferon and ribavirin; closely monitor and consider discontinuation of stavudine. (4, 5.2, 7)
- 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)
- Patients may develop localized loss of body fat, monitor for signs and symptoms of lipoatrophy. 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. (6.1)

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----------

- The combination of ZERIT and hydroxyurea should be avoided. (7)
- 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. (4, 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: 12/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS and HEPATOMEGALY with STEATOSIS; PANCREATITIS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including stavudine and other antiretrovirals. Fatal lactic acidosis has been reported in pregnant women who received the combination of ZERIT and didanosine with other antiretroviral agents. Coadministration of ZERIT and didanosine is contraindicated because of increased risk of serious and/or life-threatening events [see *Warnings and Precautions (5.1)*]. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur.

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 [see *Warnings and Precautions (5.4)*].

1. INDICATIONS AND USAGE

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

2. DOSAGE AND ADMINISTRATION

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

2.1 Recommended Adult Dosage

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

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

2.2 Recommended Pediatric Dosage

- For newborns from birth to 13 days old: 0.5 mg/kg given every 12 hours.

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

2.3 Dosage Adjustment

Renal Impairment

Adult Patients: 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	Recommended ZERIT Dose by Patient Weight	
(mL/min)	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.

2.4 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.

3. 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.

4. CONTRAINDICATIONS

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

Co-administration of ZERIT with didanosine is contraindicated due to the potential for serious and/or life-threatening events notably lactic acidosis, hepatotoxicity, peripheral neuropathy, and pancreatitis [*see Warnings and Precautions (5.1, 5.2, 5.3, 5.4*)].

5. WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including stavudine and other antiretrovirals. Although relative rates of lactic acidosis have not been assessed in prospective well-controlled trials, longitudinal cohort and retrospective studies suggest that this infrequent event may be more often associated with antiretroviral combinations containing stavudine. Female gender, obesity, and prolonged nucleoside exposure may be risk factors. Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. Coadministration of ZERIT and didanosine is contraindicated [*see Contraindications (4)* and *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 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.

5.2 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. Coadministration of ZERIT and didanosine is

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