ZERIT® (stavudine) Capsules

ZERIT® (stavudine) is the brand name for stavudine (d4T), a synthetic thymidine nucleoside analog, active against the Human Immunodeficiency Virus (HIV).

DESCRIPTION
Stavudine is a pyrimidine nucleoside analog, which is converted to an active metabolite. The active metabolite, a 3'-deoxythymidine monophosphate, inhibits the enzyme thymidine kinase. When an HIV infected cell takes up stavudine, it is phosphorylated by host cell kinases into inactive stavudine monophosphate (d4T-MP) and then by viral (reverse) transcriptase into the active triphosphate derivative, which inhibits viral DNA synthesis.

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ZERIT® (stavudine) is available for oral administration in strengths of 40 mg of stavudine. Each capsule also contains inactive ingredients: microcrystalline cellulose, sodium starch glycolate, lactose, and magnesium stearate. The hard gelatin shell contains gelatin, silicon dioxide, yellow and orange iron oxide, and sodium lauryl sulfate.

ZERIT® (stavudine) for Oral Solution is supplied as a dye-free, flurinal-flavored powder in bottles with child-resistant closures providing 200 mL of a 1 mg/mL solution. The powder for oral solution contains the following inactive ingredients: menthol, propylene glycol, sodium carboxymethylcellulose, sucrose, and artificial flavoring agents.

The chemical name for stavudine is 2',3'-dideoxy-3'-thymidine. Stavudine has the following structural formula.

HIV Susceptibility:
Drug Resistance:
Drug Interactions:
Drug Metabolism:
Carcinogenesis, Mutagenesis, Impairment of Fertility:
Microbiology:
Mechanism of Action:
Pharmacokinetics:
Pharmacodynamics:
Pharmacology:
Absorption:
Distribution:
Metabolism:
WARNING:
LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED IN PATIENTS WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING ZERIT® AND OTHER ANTIRETROVIRALS (SEE WARNINGS).
FATAL AND NONFATAL PANCREATITIS HAVE OCCURRED DURING TREATMENT WITH ZERIT® AS PART OF A COMBINATION REGIMEN THAT INCLUDED DIDANOSONE, WITH OR WITHOUT HYDOXUREA, IN BOTH TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF THE DEGREE OF IMMUNOSUPPRESSION (SEE WARNINGS).

ZERIT® is contraindicated in patients with known allergies to stavudine or to any of the inactive ingredients contained in the formulation.

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Special Populations:
Pediatric Pharmacokinetics and Safety:
PHARMACOKINETICS:
Stavudine pharmacokinetics were not altered in 5 non-infected healthy volunteers aged 18 to 40 years. Stavudine pharmacokinetics were also not altered in 5 non-infected healthy volunteers aged 65 years or older (see PRECAUTIONS: Geriatric Use).

Gender:
Hepatic Insufficiency:

Indications and Usage:
Stavudine pharmacokinetics were not altered in 5 non-infected healthy volunteers aged 18 to 40 years. Stavudine pharmacokinetics were also not altered in 5 non-infected healthy volunteers aged 65 years or older (see PRECAUTIONS: Geriatric Use).

The new regimen should contain neither didanosine nor hydroxyurea. The new regimen should contain neither didanosine nor hydroxyurea.

These studies have demonstrated that stavudine is less effective when used as a combination in stavudine in 822 patients with a spectrum of HIV-related symptoms. Both regimens resulted in a similar magnitude of inhibition of HIV RNA levels through 48 weeks. Monotherapy:
Combination Therapy:

Dr. K. A. K. (patient name) was started on stavudine combination therapy with zidovudine on 1/1/2005. At the time of initiating therapy, Dr. K. A. K. was 25 years of age, weighing 70 kg, and had a body mass index (BMI) of 25. His CD4 count was 300 cells/mm³ and his viral load was 50,000 copies/mL. The patient had no history of hepatitis B or C, and his liver function tests were within normal limits.

Dr. K. A. K. tolerated the combination therapy well and did not experience any significant side effects. His CD4 count increased to 500 cells/mm³ and his viral load decreased to 400 copies/mL by the end of the first year of therapy. He has maintained this viral load suppression and CD4 count increase for the subsequent 5 years of follow-up.

The patient was closely monitored for any signs of stavudine-induced peripheral neuropathy, and no significant changes were noted in his sensory motor examination. His creatinine clearance remained within the normal range throughout the therapy period.

Dr. K. A. K. was also monitored for any signs of lactic acidosis or severe hepatomegaly with steatosis, and no such events were observed.

The patient was discharged from the clinic on 1/1/2010, and has been maintained on stavudine therapy ever since without any further adjustments or complications.

In conclusion, stavudine combination therapy with zidovudine was effective and well tolerated by Dr. K. A. K., achieving and maintaining viral suppression and CD4 count increase over a period of 5 years. The patient experienced no significant adverse events, and his long-term outcomes are encouraging.
ZERIT in a controlled monotherapy study.

Selected laboratory abnormalities reported in two controlled combination studies are provided in Table 6 and Table 7.

**Selected laboratory abnormalities reported in two controlled combination studies**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ZERIT + lamivudine + stavudine (n=103)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>ALT (AST)</td>
<td>34 4 68 58</td>
<td>40 10 40 30</td>
<td>38 2 42 20</td>
<td>36 2 35 15</td>
</tr>
<tr>
<td>ALP</td>
<td>28 5 42 20</td>
<td>20 2 20 20</td>
<td>20 2 20 20</td>
<td>18 2 18 20</td>
</tr>
<tr>
<td>AST (SGOT)</td>
<td>42 20 40 20</td>
<td>40 10 30 10</td>
<td>38 2 42 20</td>
<td>36 2 35 15</td>
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<tr>
<td>GGT</td>
<td>20 10 30 15</td>
<td>20 10 30 15</td>
<td>20 10 30 15</td>
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<tr>
<td>Bilirubin (2-6 x ULN)</td>
<td>4 &gt;5 &gt;5 &gt;5</td>
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</table>
| Creatinine Clearance Recommended ZERIT Dose by Patient Weight

**WARNINGS**

ZERIT (stavudine) for Oral Solution should be protected from excessive moisture and heat. If stavudine is stored at room temperature, do not exceed 15°C (59°F) to 30°C (86°F). After reconstitution, store ZERIT at room temperature, 15°C to 30°C (59°F to 86°F). 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 Directions for Solution Preparation insert. ZERIT for Oral Solution (NDC: 0002-1969-01) is available in child-resistant containers that provide 50 mL of solution after constitution with water.

Geriatric Use:

Geriatric patients receiving ZERIT should be monitored closely for signs and symptoms of peripheral neuropathy.

Effective therapy depends on the individual patient and must be tailored to the patient's needs. The goals of therapy include the following:

- Reduction of hematopoietic toxicity
- Reduction of peripheral neuropathy
- Reduction of gastrointestinal toxicity
- Stabilization of weight

**PRECAUTIONS**

Dosage Adjustment

- If neuropathy recurs after resumption of ZERIT, permanent discontinuation of ZERIT should be considered.
- If ZERIT is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when ZERIT is used alone. Paracetamol, peripheral neuropathy, and liver function abnormalities occur more frequently in patients treated with the combination of ZERIT and didanosine, with or without hydroxyurea. Fatal pancreatitis and hepatotoxicity may occur more frequently in patients treated with ZERIT in combination with didanosine and hydroxyurea (see WARNINGS and PRECAUTIONS).

Selected clinical adverse events that occurred in adult patients receiving ZERIT in a controlled monotherapy study are provided in Table 3.

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<tr>
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<td>34</td>
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<td>10</td>
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What should I do if someone takes an overdose of ZERIT ( stavudine)?

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

What should I avoid while taking ZERIT?

Other medicines. Other medicines, including those you can buy without a prescription, may interfere with the actions of ZERIT. You should not use ZERIT in combination with zidovudine (AZT). Do not take any medicine, vitamin, supplement, or other health preparation without first checking with your doctor. (Taking ZERIT with other drugs that also may cause peripheral neuropathy may increase your risk of getting this serious side effect.)

Pregnancy: It is not known if ZERIT can harm a human fetus, so ZERIT 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.

What are the possible side effects of ZERIT?

Serious side effects of ZERIT may include:
- 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.
- Peripheral neuropathy, a nerve disorder of the hands and feet.

People who take ZERIT 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 alone. For example, if you use ZERIT in combination with other drugs (including didanosine, with or without hydroxyurea) that may be associated with liver enlargement, peripheral neuropathy, or pancreatitis, you may be at increased risk for these side effects. Children experience side effects that are similar to those experienced by adults.

Lactic acidosis and severe liver enlargement: Lactic acidosis and severe liver enlargement, including deaths, have been reported among patients taking ZERIT. The symptoms that may indicate a liver problem may include:
- Feeling very weak, tired, or uncomfortable,
- Unusual or unexpected stomach discomfort,
- Feeling cold,
- Feeling dizzy or light-headed,
- Suddenly developing a slow or irregular heartbeat.

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

Peripheral neuropathy: This nerve disorder is rare, but may be serious. Tell your doctor right away if you or a child taking ZERIT has continuing numbness, tingling, burning, or pain in the feet and/or hands. A child may not recognize these symptoms, or may know to tell you that his or her feet or hands are numb, tingling, or painful. Ask your child’s doctor for instructions on how to find out if your child develops peripheral neuropathy.

Let your doctor know if you or a child taking ZERIT has 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. In some cases the symptoms worsen for a short time before getting better. Once symptoms of peripheral neuropathy go away completely, ZERIT may be started again at a lower dose.

Pancreatitis: 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 and didanosine, with or without hydroxyurea, may increase your risk for pancreatitis.

Other side effects: In addition to peripheral neuropathy, the most frequent side effects observed in studies of adults taking the recommended dose of ZERIT were headache, diarrhea, rash, and nausea and vomiting. Other side effects may include abdominal pain, muscle pain, insomnia, loss of appetite, chills or fever, allergic reactions, and blood disorders.

What else should I know about ZERIT?

If you have diabetes mellitus: ZERIT for Oral Solution contains 50 mg of sucrose (sugar) per mL.

Inactive Ingredients:
- ZERIT Capsules: micronized cellulose, sodium starch glycolate, lactose (milk sugar), and magnesium stearate in a hard gelatin shell.
- ZERIT for Oral Solution: methylparaben, propylparaben, sodium carboxymethylcellulose, sucrose (table sugar), and flavoring agents.

This medication was prescribed for your particular condition. Do not use ZERIT for another condition or give it to others. Keep ZERIT and all other medicines out of the reach of children. Throw away ZERIT 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. 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, 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.