Stavudine capsules, USP

30 mg and 40 mg

[Patient Information Leaflet Included]

WARNING. Lactic acidosis and severe hyperlactatemia with fatal outcomes have been reported in patients receiving this drug, including patients with HIV infection. In some patients, increased lactic acidosis and hyperlactatemia have occurred in the setting of clinical deterioration or severe pre-existing medical conditions (e.g., viral ranidications, sepsis, major surgery, severe trauma, procedures or prolonged periods of stress). Lactic acidosis is a medical emergency, including ventilatory support. It may develop at any time during the treatment period, but is more common in the first months of treatment. Physical and metabolic alterations associated with severe hyperlactatemia include pallor, hypoxia, hyperventilation, hypotension, abdominal pain, and disorientation. Adverse drug reactions may be additive. Lactic acidosis is frequently associated with hyperglycemia, but this may not be present. The mortality rate has been 30% or greater. In most reported cases, elevations, in serum transaminase and other aminotransferase activities have also been noted. Drug withdrawal is recommended if symptoms or signs suggestive of lactic acidosis or severe hyperlactatemia are observed. Other significant metabolic alterations associated with severe hyperlactatemia include a shift of plasma bicarbonate to the intracellular compartment, respiratory acidosis, and anuria. These clinical events have usually followed the administration of larger than recommended doses.

Stavudine is a white-to-off-white crystalline solid with a molecular formula C₉H₁₂N₄O₆ and a molecular weight of 224.2. The solubility of stavudine is 0.001% in purified water at 37°C. It is a prodrug that is rapidly absorbed from the gastrointestinal tract. Stavudine has a high degree of protein binding (95% to 98%) and is extensively metabolized in humans.

Stavudine is a nucleoside reverse transcriptase inhibitor that is converted to its metabolites, which are inactive against HIV-1. Stavudine and its metabolites are eliminated primarily by the kidneys, with a half-life of 5 to 6 hours.

Antiviral Activity:

Stavudine is a competitive inhibitor of HIV-1 reverse transcriptase, the enzyme that is responsible for polymerizing viral DNA from RNA. It is a substrate for the HIV-1 reverse transcriptase and is phosphorylated to its active form, which inhibits the enzyme's activity.

Mechanism of Action:

Stavudine is a nucleoside analogue that inhibits the reverse transcriptase enzyme of HIV. It is converted to its active form by cellular kinases, which then inhibits the reverse transcriptase enzyme and prevents the synthesis of new viral DNA. Stavudine is also a prodrug that is rapidly absorbed from the gastrointestinal tract.

CLINICAL PHARMACOLOGY: Pharmacokinetics:

Pharmacokinetic parameters of stavudine and its metabolites are presented in Table 1. Stavudine is extensively metabolized in vivo, and the major metabolites are 5'-O-β-D-glucuronide of stavudine and its 5'-O-β-D-glucuronide. The human plasma elimination half-life of stavudine is approximately 5 hours, and the mean terminal half-life of the active metabolite is about 6 hours.

Stavudine is a substrate for the human metabolizing enzyme CYP1A2, which is known to be induced by the drug itself. This induction of CYP1A2 results in an increased clearance of stavudine, and the peak plasma concentrations of stavudine are lower in subjects who have been treated with stavudine for more than 1 month compared to those who have been treated for a shorter period.

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Table 1: Steady State Pharmacokinetic Parameters of Stavudine in Subjects of Different Ethnicity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Caucasian</th>
<th>Black (USA)</th>
<th>Black (Africa)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>56 ± 20</td>
<td>40 ± 15</td>
<td>35 ± 10</td>
<td>47 ± 18</td>
</tr>
<tr>
<td>Tmax</td>
<td>1 ± 0.5</td>
<td>1 ± 0.5</td>
<td>1 ± 0.5</td>
<td>1 ± 0.5</td>
</tr>
<tr>
<td>T1/2</td>
<td>4 ± 1</td>
<td>4 ± 1</td>
<td>4 ± 1</td>
<td>4 ± 1</td>
</tr>
<tr>
<td>Vd</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
</tr>
</tbody>
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In patients weighing ≤ 60 kg:

- Total Bilirubin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard (mg/dL)</th>
<th>Stavudine ≤ 60 kg (mg/dL)</th>
<th>Stavudine &gt; 60 kg (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Bilirubin</td>
<td>0.2 0.3 0.4 0.6 0.8</td>
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</tr>
<tr>
<td>ALT (SGPT)</td>
<td>1 1.5 2 2.5 3 3.5 4</td>
<td>1.5 2 2.5 3 3.5 4</td>
<td>1.5 2 2.5 3 3.5 4</td>
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<tr>
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<td>1 1.5 2 2.5 3 3.5 4</td>
<td>1.5 2 2.5 3 3.5 4</td>
<td>1.5 2 2.5 3 3.5 4</td>
</tr>
<tr>
<td>Lipase (I.ULN)</td>
<td>0.5 1 1.5 2 2.5 3 3.5</td>
<td>0.5 1 1.5 2 2.5 3 3.5</td>
<td>0.5 1 1.5 2 2.5 3 3.5</td>
</tr>
</tbody>
</table>

Stavudine capsules are available containing 30 mg or 40 mg of stavudine. The 30 mg capsule has a hard shell capsule with an off-white cap and a white opaque body usually printed with N 139 in black; in the capsule is an off-white cap with an orange body. They are available in bottles of 100 capsules.

Stavudine capsules USP (standalone, also known as 467) are formulated with the following inactive ingredients:

- Gelatin shell.
- Sodium lauryl sulfate.
- FD&C Blue No. 2 aluminum lake.

Stavudine capsules USP (standalone, also known as 467) may be administered to adult patients with impaired renal function with adjustment in dose as shown in Table 3.

What is stavudine?

Stavudine is a prescription medicine used in combination with other drugs to treat adults and children who are infected with HIV (the immune system disease) in patients with AIDS. Stavudine belongs to a class of drugs called nucleoside reverse transcriptase inhibitors (NRTIs). By reducing the amount of HIV in your body, stavudine helps control your HIV infection and may slow the progression of AIDS.

Stavudine does not cure HIV or AIDS and you should continue to take other medicines to treat or manage HIV-related conditions, including opportunistic infections or other conditions caused by your weakened immune system. Use of stavudine alone may increase your risk for pancreatitis.

Stavudine capsules are available in bottles of 60 capsules, 120 capsules, or 180 capsules containing 30 mg or 40 mg of stavudine. Stavudine capsules are supplied in bottles of 100 capsules containing 30 mg or 40 mg of stavudine. Stavudine capsules are available in bottles of 100 capsules containing 30 mg or 40 mg of stavudine.

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