PUBLIC ASSESSMENT REPORT

Stavudine Capsules 15 mg and 20 mg

International Nonproprietary Name (INN): **Stavudine**

Abstract

Stavudine Capsules 15 mg and 20 mg, manufactured by Aurobindo Pharma Ltd., Hyderabad – 500 072, India was the subject of an abbreviated new drug application (ANDA) submitted to the U. S. Food and Drug Administration (USFDA) pursuant to section 505(j) of the U. S. Federal Food, Drug, and Cosmetic Act.

This ANDA was reviewed under the President's Emergency Plan for AIDS Relief (PEPFAR). Based upon the information presented to date the USFDA concluded that Stavudine Capsules 15 mg and 20 mg are safe and effective for use as recommended in the submitted labeling and, therefore, this ANDA was approved on December 29, 2008.

Stavudine Capsules 15 mg and 20 mg, on the basis of USFDA approval, were placed on the WHO Prequalification Programme list of manufacturers and suppliers whose HIV-related products have been found acceptable, in principle, for procurement by UN Agencies (WHO Prequalification Programme: Priority Essential Medicines, 63rd Edition, 1 February 2008).

Products appearing on the WHO Prequalification Programme list with the note "USFDA" are added to the list based on scientific assessment and inspections conducted by the USFDA. Products listed as USFDA approved are eligible for purchase with PEPFAR funds.

Stavudine Capsules 15 mg and 20 mg are indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. Detailed conditions for the use of these products are described in the Summary of Product Characteristics (SPC) and Scientific Discussion, Parts 4 and 6 of this Public Assessment Report.

The active pharmaceutical ingredient (API) of Stavudine Capsules is the reverse transcriptase inhibitor stavudine, a synthetic thymidine nucleoside analogue, which is a well-established substance for the treatment of HIV/AIDS in combination with other products.

Stavudine has been investigated in several clinical trials and longitudinal studies, in both treatment-naïve and treatment-experienced patients. These studies have demonstrated significant decreases in viral load and increases in CD4 cell counts.

The most frequent adverse events observed during treatment were changes in distribution of body fat, changes in fat metabolism, development of insulin resistance, neuropathy and/or paraesthesias, nausea and vomiting, rises in serum amylase and lipase, elevation of liver enzymes and total bilirubin, and rash. The most important safety problems with stavudine are severe lactic acidosis and hepatic steatosis with hepatic failure, both of which, if untreated, could be fatal.

The clinical benefit of stavudine is well established based on extensive clinical experience, and the safety pattern is satisfactory in the treatment of HIV.

All Accepted Presentations

Status	INN	Strength	Form	Route of Administration	Packaging	Package size
USFDA approved	Stavudine	15 mg	Capsules	Oral	Bottle	60
USFDA approved	Stavudine	20 mg	Capsules	Oral	Bottle	60

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Stavudine Capsules 15 mg and 20 mg

Read all of this leaflet carefully before you start taking this medicine
--Keep this leaflet. You may need to read it again.
--If you have further questions, ask your doctor, health care provider or pharmacist.
--This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. WHAT STAVUDINE CAPSULES ARE AND WHAT THEY ARE USED FOR

Stavudine belongs to a group of antiviral medicines, also known as antiretrovirals, called nucleoside analogue reverse transcriptase inhibitors (NRTIs). These medicines are used to treat Human Immunodeficiency Virus (HIV) infection.

Stavudine is used in antiretroviral combination therapy for the treatment of HIV infection. Stavudine reduces the amount of HIV virus in your body and keeps it at a low level. It also increases CD4 cell counts. CD4 cells are a type of white blood cell that play an important role in maintaining a healthy immune system to help fight infection. Response to treatment with stavudine varies between patients. Your doctor or health care provider will be monitoring the effectiveness of your treatment.

Stavudine Capsules may improve your condition but are not a cure for HIV infection. HIV infection is a disease spread by contact with blood or sexual contact with an infected individual. Treatment with Stavudine Capsules has not been shown to reduce the risk of passing HIV infection on to others by sexual contact or by blood transfer. Therefore, you must continue to take appropriate precautions to avoid giving the HIV virus to others.

During your treatment, other infections linked to your weakened immunity (called "opportunistic infections") may arise. These will require specific and sometimes preventive treatment.

2. BEFORE YOU TAKE STAVUDINE CAPSULES

Do not take Stavudine Capsules if:
--You are allergic (hypersensitive) to stavudine or any of the other ingredients of Stavudine Capsules (see Part 6 below, "What Stavudine Capsules 15 mg and 20 mg contain).

Take special care with Stavudine Capsules
Before using this medicine, tell your doctor or health care provider:
• if you suffer from kidney disease or liver disease (such as hepatitis)

• if you have had peripheral neuropathy (persistent tingling or numbness or pain in the feet and/or hands)
• if you have suffered from pancreatitis (inflammation of the pancreas).

The class of medicines to which stavudine belongs (NRTIs) can cause a condition called *lactic acidosis* (a build-up of lactic acid in the body), together with an enlarged liver. Lactic acidosis, if it occurs, usually develops after a few months of treatment. Lactic acidosis can cause dehydration and coma. Deep, rapid breathing, drowsiness, and nonspecific symptoms such as nausea, vomiting and stomach pain, may indicate the development of lactic acidosis. In addition, lactic acidosis may lead to rare cases of liver failure, renal failure, or fatal hepatitis.

Lactic acidosis is a rare but serious side effect that occurs more often in women, particularly if very overweight. If you have liver disease you may also have a higher risk of lactic acidosis. While you are taking Stavudine Capsules, your doctor or health care provider will monitor you closely for any signs that suggest you may be developing lactic acidosis.

Stavudine may cause peripheral neuropathy and paresthesia, conditions which can cause a persistent numbness, tingling, or pain in the feet and/or hands and or muscle weakness. Tell your doctor or health care provider as soon as possible if you notice any of these signs.

Tell your doctor or health care provider if you have a history of liver disease. Patients with chronic hepatitis B or C who are treated with antiretroviral agents are at increased risk for severe and potentially fatal liver adverse events and may require blood tests for control of liver function.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infections, signs and symptoms of inflammation from those previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection (such as fever), tell your doctor or health care provider immediately.

Redistribution, accumulation, or loss of body fat may occur in patients receiving antiretroviral therapy. Contact your doctor or health care provider if you notice changes in body fat.

You must take your prescribed dose of stavudine every day. This medicine helps to control your condition but is not a cure for HIV infection. You may continue to develop other infections and other illnesses associated with HIV disease. Maintain regular contact with your doctor or health care provider. Do not stop taking your medicine without first talking to your doctor or health care provider.

Taking other medicines
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. These may affect the action of Stavudine Capsules, or Stavudine Capsules may affect their action.

Stavudine Capsules should ***not*** be taken in combination with:

- Zidovudine, which interferes with the activity of stavudine
- Didanosine, which can increase the risk of peripheral neuropathy, pancreatitis, and lactic acidosis when used in combination with stavudine
- Zalcitabine, because of an increased risk of neuropathy

- Doxirubicin, which interferes with stavudine

Taking Stavudine Capsules with food and drink
Stavudine Capsules may be taken with or without food.

Pregnancy
If you become pregnant, or are planning to become pregnant, see your doctor or health care provider to discuss the potential adverse effects, and the benefits and risks of your antiretroviral therapy to you and your child. Lactic acidosis (sometimes fatal) has been reported in pregnant women who received stavudine in combination with other antiretroviral treatment. Do not take Stavudine Capsules in combination with didanosine during pregnancy because of the high incidence of peripheral neuropathy, pancreatitis, and lactic acidosis.

If you have taken Stavudine Capsules during your pregnancy, your doctor or health care provider may request regular visits to monitor the development of your child. These visits may include blood tests and/or other diagnostic tests.

In children whose mother took nucleoside and nucleotide analogues during pregnancy, the benefit from the reduced chance of being infected with HIV is greater than the risk of suffering from side effects related to the medicines.

Breast-feeding
HIV-infected women should not breastfeed under any circumstances in order to avoid transmission of HIV to the baby.

Driving and using machines
No information on the effects of stavudine on the ability to drive and use machines is available.

3. HOW TO TAKE STAVUDINE CAPSULES

Always take your prescribed dose of Stavudine Capsules exactly as your doctor or health care provider tells you. You should check with your doctor, health care provider or pharmacist if you are not sure.

The usual daily dose for adults and children whose body weight is between 30–60 kg (66-132 lbs) is 30 mg twice daily with approximately 12 hours between each dose.

The usual daily dose for adults whose body weight is equal to or more than 60 kg (132 lbs) is 40 mg twice daily with approximately 12 hours between each dose.

Stavudine Capsules may be taken with or without food.

Stavudine Capsules will always be taken in combination with other antiretroviral medications. Please be sure to follow the instructions within the supplied package leaflets.

If you take more Stavudine Capsules than you should
If you take too many capsules or if someone accidentally swallows some, there is no immediate danger. However, contact your doctor or health care provider, or the nearest hospital emergency department, for further advice as soon as possible.

If you forget to take your prescribed dose of Stavudine Capsules
If you accidentally miss a dose, take your normal dose when the next one is due. *Do not* take a double dose to make up for forgotten individual doses. If you have any further questions on the use of this product, ask your doctor, health care provider or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Stavudine Capsules can cause side effects, although not everybody gets them. When treating HIV infection, it is not always possible to differentiate between unwanted effects caused by Stavudine Capsules, by those caused by any other medicines you may be taking at the same time, or by HIV disease. For this reason, it is important that you promptly inform your doctor or health care provider of any change in your health.

Short-term adverse reactions to combination antiretroviral therapy are common. After you start taking Stavudine Capsules, temporary reactions (such as pain in upper abdomen, nausea, diarrhea, and/or headache) may occur. These reactions are usually mild and disappear within a few weeks.

Common long-term side effects include peripheral neuropathy (pain or tingling in the feet or hands), changes in fat distribution, and abnormalities in the body's chemical processes. Rare and very rare long-term adverse reactions include lactic acidosis, fatty deposits in the liver, pancreatitis, and liver failure.

Very commonly reported (greater than 1 in every 10 patients treated) side effects are peripheral neuropathy and paresthesia (persistent numbness or tingling or pain in the feet and/or hands).

Commonly reported (greater than 1 in every 100 patients treated) side effects are rash, nausea and vomiting, headache, changes in distribution of body fat (e.g. loss of fat from legs, arms and face, increased fat in the abdomen ("belly") and around the internal organs, breast enlargement and fatty lumps on the back of the neck ("buffalo hump"), disturbance of fat metabolism (increased fats in the blood), resistance to insulin, and decreased liver function (increased liver enzymes).

The following side effects are uncommon (between 1 in 1,000 and 1 in 100 patients treated): pancreatitis, diabetes mellitus.

There are rare reports (between 1 in 10,000 to 1 in 1,000 patients treated) of fatty deposits in the liver, hepatitis, liver failure, and lactic acidosis.

There are very rare reports (less than 1 in 10,000 patients treated) of thrombocytopenia (decrease in blood cells related to clotting).

Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipemia (increased fats in the blood), and resistance to insulin.
If you experience any of these side effects, or if you notice any side effects not listed in this leaflet, tell your doctor, health care provider or pharmacist as soon as possible.

5. HOW TO STORE STAVUDINE CAPSULES

Keep out of the reach and sight of children.

Store at 20° to 25°C (68° to 77°F).

Store in the original container in order to protect from moisture and light.

Do not use Stavudine Capsules after the expiration (expiry) date stated on the label. The expiration date refers to the last day of that month.

Do not use Stavudine Capsules if there is any sign that the packaging has been opened or tampered with, or if you notice any visible signs of deterioration such as fading in color or discoloration of any of the capsules.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines that are no longer required. Proper disposal of medicine will help protect the environment.

6. FURTHER INFORMATION

What Stavudine Capsules contain
The active ingredient in Stavudine Capsules is stavudine. Each capsule also contains inactive ingredients: microcrystalline cellulose, sodium starch glycolate, anhydrous lactose, and magnesium stearate. The hard gelatin shell consists of gelatin, sodium lauryl sulfate, titanium dioxide, yellow iron oxide, red iron oxide, and black iron oxide. (Black iron oxide is used for printing on the capsules.)

What Stavudine Capsules 15 mg and 20 mg look like and contents of the packages

Stavudine Capsules 15 mg are dark red/light yellow opaque gelatin capsules filled with white to off-white granular powder and imprinted with an ‘E’ on the dark red opaque cap and the number ‘76’ on the light yellow opaque body with black ink. Stavudine Capsules 15 mg are packaged in bottles of 60 capsules.

Stavudine Capsules 20 mg are light brown opaque gelatin capsules filled with white to off-white granular powder and imprinted with an ‘E’ on the light brown opaque cap and the number ‘77’ on the light brown opaque body with black ink. Stavudine Capsules 20 mg are packaged in bottles of 60 capsules.

Supplier
Aurobindo Pharma Ltd., Hyderabad – 500 072, India

SUMMARY OF PRODUCT CHARACTERISTICS

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Stavudine Capsules 15 mg and 20 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Stavudine Capsule 15 mg contains 15 mg of stavudine.
Each Stavudine Capsule 20 mg contains 20 mg of stavudine.
For excipients see 6.1

3. PHARMACEUTICAL FORM

Stavudine Capsules 15 mg are dark red opaque/light yellow opaque size '4' hard gelatin capsules filled with white to off-white granular powder and imprinted with 'E' on dark red opaque cap and '76' on light yellow opaque body with black ink.

Stavudine Capsules USP, 20 mg are light brown opaque/light brown opaque size '3' hard gelatin capsules filled with white to off-white granular powder and imprinted with 'E' on light brown opaque cap and '77' on light brown opaque body with black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Stavudine is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

4.2 Posology and method of administration

Stavudine Capsules 15 mg and 20 mg are for oral use.

Therapy should be prescribed by a physician experienced in the management of HIV-1 infection.

The recommended dose of stavudine in adults is:

- 40 mg twice daily for patients ≥60 kg
- 30 mg twice daily for patients <60 kg

The recommended dose of stavudine for pediatric use is:
• Newborn to 13 days: 0.5 mg/kg/dose every 12 hours
• From 14 days old and weight up to 30 kg: 1 mg/kg/dose every 12 hours
• Patients weighing 30 kg or more should receive the recommended adult dosage.

The interval between doses of stavudine should be 12 hours.

Stavudine may be taken with or without food.

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. These symptoms may be difficult to detect in young children. If these symptoms develop during treatment, stavudine therapy should be interrupted. Symptoms may resolve if therapy is withdrawn promptly. In some cases, symptoms may worsen temporarily following discontinuation of therapy. If symptoms resolve completely, patients may tolerate resumption of treatment at one-half the recommended dose:

- 20 mg twice daily for patients ≥60 kg
- 15 mg twice daily for patients <60 kg

If peripheral neuropathy recurs after resumption of Stavudine Capsules, permanent discontinuation should be considered.

Liver Disease: No dose adjustment is necessary.

Renal Impairment: It is recommended that stavudine dosing be modified in patients with reduced creatinine clearance according to the schedule shown below.*

Creatinine clearance (mL/min)	Recommended dosage of Stavudine in patients by weight	
	< 60 kg	> 60 kg
> 50	30 mg every 12 hours	40 mg every 12 hours
26-50	15 mg every 12 hours	20 mg every 12 hours
10-25	15 mg every 24 hours	20 mg every 24 hours

*Since urinary excretion is also a major route of elimination of stavudine in pediatric patients, the clearance of stavudine may likewise be altered in children with renal impairment. Although there is insufficient data to recommend a specific dose adjustment of stavudine in children, a reduction in the dose and/or an increase in the interval between doses should be considered.

Hemodialysis Patients: The recommended dose is 20 mg every 24 hours (≥60 kg) or 15 mg every 24 hours (<60 kg) and should be administered after the completion of each haemodialysis and at the same time of day on non-dialysis days.

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

Stavudine is not recommended for use as monotherapy or dual therapy because of rapid emergence of resistant virus.

Patients treated with stavudine in combination with didanosine may have an increased risk for developing pancreatitis, peripheral neuropathy, liver function abnormalities, and lactic acidosis. The combination of stavudine and didanosine has also been implicated in the deaths of several

HIV-1 infected pregnant women secondary to severe lactic acidosis (with or without hepatic steatosis and pancreatitis) after prolonged use. In general, drug regimens containing didanosine and stavudine should be used only when other NRTI drug combinations have failed or have caused unacceptable toxicities and where potential benefit outweighs the risks of toxicities. Therefore, due to the presence of didanosine in the following treatment regimens, stavudine should not be used with didanosine and lamivudine, or didanosine and abacavir.

Transmission of HIV
Antiretroviral therapy has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Patients must be counseled to continue to use precautions while being treated with stavudine and other antiretroviral therapy.

Neuropathy
Therapy with stavudine can be associated with severe dose-related neuropathy or paresthesia, usually manifested by numbness, tingling, or pain in the feet or hands. Stavudine-related peripheral neuropathy may resolve over 1-3 weeks if therapy is withdrawn. When stavudine is used in combination with didanosine, the incidence of neuropathy is higher than when stavudine is used alone. Stavudine use should not be continued in patients who develop neuropathy unless the potential benefits outweigh the risk of this toxicity.

Lipodystrophy and metabolic abnormalities
Combination antiretroviral therapy may lead to abnormal redistribution of body fat including central obesity, dorsocervical fat pad enlargement, peripheral and facial subcutaneous fat wasting (lipoatrophy), and breast enlargement. Use of stavudine is particularly associated with an increased risk of developing lipoatrophy. Substitution of stavudine with abacavir or tenofovir leads to modest recovery of subcutaneous limb fat.

Stavudine as part of combination antiretroviral therapy also increases the likelihood of developing increases in fasting triglycerides, total cholesterol, low-density lipoprotein cholesterol and a decrease in high-density lipoprotein cholesterol.

Use of stavudine may be associated with an increased risk of insulin resistance and diabetes mellitus. This is likely to be mediated through indirect effects of stavudine on lipoatrophy development. Direct drug effects have not been demonstrated, but cannot be ruled out.

Lactic acidosis
Lactic acidosis and hepatic steatosis with hepatic failure are rare but severe complications associated with NRTI therapy, including stavudine, that may occur after a few to several months of treatment. Lactic acidosis has a high mortality rate. Hyperlactatemia is defined as a venous lactate level > 2 mmol/L but false positive results due to faulty collection are common. If lactate is elevated the test should be repeated with particular attention to patient rest and hydration. Patients with elevated serum lactate levels may be asymptomatic, critically ill, or may have non-specific symptoms such as dyspnea, fatigue, nausea, diarrhea, vomiting and abdominal pain. Lactic acidosis may be associated with pancreatitis, liver failure, renal failure and motor paralysis.

Risk factors other than use of stavudine include concomitant use of didanosine, zalcitabine, female gender, and obesity. Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. It is therefore imperative that this combination is not used during pregnancy.

Lactic acid levels < 5 mmol/L may not require treatment or may be managed with substitution of stavudine with another antiretroviral drug. Symptomatic patients usually have levels > 5 mmol/L and require discontinuation of all treatment including stavudine. Lactic acid levels > 10 mmol/L usually are a medical emergency carrying a high risk of death. Seriously ill patients require supportive treatment, which may include intravenous hydration, mechanical ventilation, and/or dialysis. Recovery may be protracted.

Pancreatitis
Pancreatitis is a rare event that may occur during therapy with stavudine in combination with didanosine. The combination of stavudine and didanosine and any other agents that are toxic to the pancreas should be discontinued immediately in patients with suspected pancreatitis.

Mitochondrial dysfunction
Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues. The main adverse events reported are hematological disorders (anemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behavior). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed in utero to nucleoside and nucleotide analogues, even HIV-negative children, require full investigation for possible mitochondrial dysfunction in case of relevant signs or symptoms, including clinical and laboratory follow-up. (These findings do not affect current international recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.)

Immune reconstitution syndrome
In HIV infected individuals with severe immunodeficiency at the time of institution of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of therapy. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterium infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Optimal therapy has not been determined. Anti-inflammatory therapy may attenuate symptoms but many cases may resolve spontaneously.

4.5 Interaction with other medicinal products and other forms of interaction

Stavudine and zidovudine compete for phosphorylation by the cellular enzyme, thymidine kinase, which preferentially phosphorylates zidovudine, thereby decreasing the phosphorylation of stavudine to its active triphosphate form. Zidovudine is therefore not recommended to be used in combination with stavudine.

Stavudine should not be used with didanosine because of a high incidence of peripheral neuropathy, pancreatitis and lactic acidosis unless the potential benefit clearly outweigh the risk of toxicities.

Stavudine is contraindicated in combination with zalcitabine because of the risk of severe neuropathy.

Co-administration with methadone results in a 25% reduction in stavudine area under the concentration curve.

In vitro studies indicate that the activation of stavudine is inhibited by doxorubicin and ribavirin.

Stavudine does not inhibit the major cytochrome P450 isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

4.6 Pregnancy and lactation

Pregnancy
Stavudine is assigned FDA Pregnancy Category C status (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). No increased risk of birth defects have been reported for stavudine (www.apregistry.com). Fatal lactic acidosis has been reported in pregnant women who received stavudine in combination with didanosine and other antiretroviral drugs—the combination of stavudine and didanosine should be avoided during pregnancy.

Nursing Mothers: Because of the potential for postnatal HIV transmission and adverse effects caused by stavudine in nursing infants, HIV-infected mothers should be instructed not to breastfeed.

4.7 Effects on ability to drive and use machines

No studies on the effects of stavudine on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Short-term adverse reactions are common. At the beginning of therapy, epigastric pain, nausea, diarrhea, and headache may occur. These reactions are usually mild and disappear within a few weeks even if treatment is continued.

Common long-term adverse reactions include neuropathy, lipodystrophy/lipoatrophy, and metabolic abnormalities. Rare and very rare long-term adverse reactions include lactic acidosis, hepatic steatosis, pancreatitis and liver failure.

The following adverse events have been reported in controlled clinical trials and case series during treatment of HIV infection with stavudine. Adverse events considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), and very rare (<1/10,000).

Blood and lymphatic systems disorders
Very rare: thrombocytopenia

Metabolic and nutrition disorders
Very common: changes in distribution of body fat including central obesity, dorsocervical fat enlargement, peripheral and facial subcutaneous fat wasting, breast enlargement; increases in

fasting triglycerides, total cholesterol, low-density lipoprotein cholesterol, decrease in high-density lipoprotein cholesterol; development of insulin resistance.
Uncommon: diabetes mellitus
Rare: lactic acidosis

Nervous system disorders
Very common: neuropathy and/or paresthesias
Common: headache

Gastrointestinal disorders
Common: nausea and vomiting; elevations in serum amylase, lipase, bilirubin, and liver enzymes
Uncommon: pancreatitis, hepatobiliary disorders
Rare: hepatic steatosis, hepatitis and liver failure

Skin and subcutaneous tissue disorders
Common: rash

4.9 Overdose

Overdose with stavudine has not been reported. Stavudine can be removed by hemodialysis. Experience with adults treated with 12 to 24 times the recommended daily dose revealed no acute toxicity.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiretroviral, ATC code: J05AF04

Stavudine (2',3'-didehydro-2',3'-didoxythymidine) is a nucleoside analogue of thymidine. It is phosphorylated by thymidine kinase, thymidylate kinase, and pyrimidine kinase to the active metabolite stavudine triphosphate. Stavudine shows antiviral activity *in vitro* against HIV–1 and HIV–2. The 50% inhibitory concentration for stavudine against laboratory and clinical isolates ranges from 0.009 to 4.100 μM.

Stavudine triphosphate inhibits the activity of HIV reverse transcriptase by both competing with the natural substrate deoxythymidine triphosphate, and by its incorporation into viral DNA, causing a termination of DNA chain elongation because stavudine lacks the essential 3'-OH group. In addition to the inhibitory effect on HIV reverse transcriptase, stavudine triphosphate inhibits cellular DNA polymerase beta and gamma and has been shown to be able to reduce the synthesis of mitochondrial DNA.

Clinical efficacy
Stavudine has been investigated in several randomized, prospective clinical trials combined with other antiretroviral drugs. These studies have demonstrated significant decreases in plasma HIV RNA and increases in CD4 cell counts when used in combination with additional nucleoside analogues and either a NNRTI or a PI. In intention-to-treat analyses > 75% of subjects have plasma HIV RNA < 50 copies/mL after 48 weeks of antiretroviral combination treatment.

Isolates with thymidine-analogue associated mutations caused by the thymidine-analogues, zidovudine and stavudine, at positions M41L, K65R, D67N, K70R, L210W, T215Y/F, and

K219Q/E) in the reverse transcriptase gene have reduced susceptibility to nucleoside analogues including stavudine.

Patients who are infected with known stavudine-resistant HIV or patients who have previously experienced virological failure on a stavudine-containing regimen may not respond sufficiently to further treatment with a combination regimen containing stavudine.

Stavudine should not be used with didanosine and lamivudine, or didanosine and abacavir, because of inferior efficacy compared to other combination regimens.

5.2 Pharmacokinetic properties

Peak plasma concentrations (Cmax) 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 and Bioavailability
Stavudine is rapidly absorbed following oral administration. Bioavailability is > 90%. Peak plasma concentrations occur within 1 hour after dosing.

Distribution
The estimated volume of distribution is 0.53 l/kg. Protein binding is negligible.

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 ^{14}C-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 ^{14}C-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%, 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-infected patients, renal elimination of unchanged drug accounts for about 40% of the overall clearance regardless of the route of administration. The mean renal clearance was about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration.

5.3 Preclinical safety data

Animal data showed embryo-fetal toxicity at very high exposure levels. Stavudine was genotoxic in *in vitro* tests in human lymphocytes possessing triphosphorylating activity, in mouse fibroblasts, and in an *in vivo* test for chromosomal aberrations.

Stavudine was not carcinogenic in doses of 39 (mice) and 168 (rats) times the expected human exposure at the recommended therapeutic dose. At higher levels of exposure (250 (mice) and 732 (rats) times human exposure), benign and malignant liver tumors occurred in mice and rats and urinary bladder tumors in male rats. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 Excipients

Microcrystalline cellulose, sodium starch glycolate, anhydrous lactose, and magnesium stearate, with a hard gelatin shell consisting of gelatin, sodium lauryl sulfate, titanium dioxide, yellow iron oxide and red iron oxide, and black iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F).

Protect from moisture and light.

Keep out of sight and reach of children.

6.5 Nature and contents of container

Stavudine Capsules 15 mg and 20 mg are packed in bottles of 60 capsules each.

7. SUPPLIER

Aurobindo Pharma Ltd., Hyderabad – 500 072, India.

8. DATE OF USFDA APPROVAL

December 29, 2008

LABELING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Stavudine Capsules 15 mg and 20 mg

1. NAME OF THE MEDICINAL PRODUCT

Stavudine Capsules 15 mg and 20 mg

2. STATEMENT OF ACTIVE SUBSTANCES

Each Stavudine Capsule 15 mg contains 15 mg of stavudine.
Each Stavudine Capsule 20 mg contains 20 mg of stavudine.

3. LIST OF EXCIPIENTS

Microcrystalline cellulose, sodium starch glycolate, anhydrous lactose, and magnesium stearate, with a hard gelatin shell consisting of gelatin, sodium lauryl sulfate, titanium dioxide, yellow iron oxide and red iron oxide, and black iron oxide

4. PHARMACEUTICAL FORM AND CONTENTS

Stavudine Capsules 15 mg are dark red opaque/light yellow opaque size '4' hard gelatin capsules filled with white to off-white granular powder and imprinted with 'E' on the dark red opaque cap and '76' on the light yellow opaque body with black ink, packaged in bottles of 60 capsules.
Stavudine Capsules 20 mg are light brown opaque/light brown opaque size '3' hard gelatin capsules filled with white to off-white granular powder and imprinted with 'E' on the light brown opaque cap and '77' on the light brown opaque body with black ink, packaged in bottles of 60 capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF REACH AND SIGHT OF CHILDREN

Keep out of reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

8. EXPIRATION DATE

<EXP MM/YYYY>

9. SPECIAL STORAGE CONDITIONS

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF SUPPLIER

Aurobindo Pharma Ltd., Hyderabad – 500 072, India

12. MANUFACTURER'S BATCH NUMBER

<Batch> <Lot> <number>

13. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

14. INSTRUCTIONS FOR USE

DISCUSSION

Name of the Finished Pharmaceutical Product:	Stavudine Capsules15 mg and 20 mg
Supplier	Aurobindo Pharma Ltd., Hyderabad– 500 072, India
Active Pharmaceutical Ingredient (API):	Stavudine
International Nonproprietary Name:	Stavudine
Pharmaco-therapeutic group (ATC Code):	Antiviral for systemic use, nucleoside reverse transcriptase inhibitor, J05AF04
Therapeutic indication:	Stavudine is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

1. Introduction

Stavudine is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. Stavudine is not indicated for use in patients with clinically significant hypersensitivity to stavudine or to any of the components contained in the formulation.

It is recommended that therapy be initiated and managed by a physician or professional health care provider who is experienced in the management of HIV/AIDS.

2. Assessment of Quality

Introduction
The assessment was conducted by the USFDA as an abbreviated new drug application (ANDA) reviewed under the President's Emergency Plan for AIDS Relief (PEPFAR).

Composition
Stavudine Capsules 15 mg contain 15 mg of the active pharmaceutical ingredient (API) stavudine. Stavudine Capsules 20 mg contain 20 mg of the active pharmaceutical ingredient (API) stavudine. Other inactive ingredients are microcrystalline cellulose, sodium starch glycolate, anhydrous lactose, and magnesium stearate, with a hard gelatin shell consisting of gelatin, sodium lauryl sulfate, titanium dioxide, yellow iron oxide and red iron oxide, and black iron oxide. Stavudine Capsules 15 mg and 20 mg are packaged in bottles of 60 capsules each. Stavudine Capsules 15 and 20 mg are generic versions of Zerit® Capsules 15 and 20 mg.

Control of active pharmaceutical ingredient (API)
Stavudine Capsules 15 mg and 20 mg controls are consistent with cGMP and USP requirements and take into account product- and process-specific needs and information.

Control testing of the finished medicinal product
The release and shelf-life specifications are in line with the requirements of major internationally used pharmacopoeias and guidelines for capsules. The test methods have been adequately validated.

Stability
Stability studies have been conducted and results show that the products conform with the proposed end of shelf life specification including description, disintegration time, dissolution, assay, and degradation products. Stability data for this product in the proposed marketing containers conforms to specifications. Based on the stability data provided the proposed expiration dating is acceptable.

Conclusions
It is concluded that the data submitted ensure acceptable quality of the finished medicinal product when stored under the conditions specified on the label.

3. Assessment of Bioequivalence

Aurobindo Pharma Ltd. requested a waiver of *in vivo* bioequivalence (BE) requirements for its Stavudine Capsules 15 mg and 20 mg. The firm had previously submitted acceptable fasting and fed BE studies for Stavudine Capsules 40 mg. To support the waiver request the firm submitted

an acceptable comparative *in vitro* dissolution testing on its Stavudine Capsules 15 mg and 20 mg versus its correspondence reference listed drug (RLD) and Stavudine Capsules 40 mg which underwent acceptable BE study. The submitted information showed that formulations of the 15 mg and 20 mg strengths are also proportionally similar to 40 mg strength. The USFDA Office of Generic Drugs Division of Bioequivalence deemed Stavudine Capsules 15 mg and 20 mg to be bioequivalent to the reference product, Zerit® Capsules 40 mg (Bristol Myers Squibb).

4. Summary of Product Safety and Efficacy

4.1 Introduction

Background
Stavudine (2',3'-didehydro-2',3'-didoxythymidine) is a nucleoside analogue of thymidine. It is phosphorylated by thymidine kinase, thymidylate kinase, and pyrimidine kinase to the active metabolite stavudine triphosphate. Stavudine shows anti-viral activity in vitro against human immunodeficiency virus type I (HIV–1) and HIV–2. The 50% inhibitory concentration for stavudine against laboratory and clinical isolates ranges from 0.009 to 4.100 μM.

Stavudine triphosphate inhibits the activity of HIV reverse transcriptase by two known mechanisms: by competing with the natural substrate deoxythymidine triphosphate and by its incorporation into viral DNA causing a termination of DNA chain elongation because stavudine lacks the essential 3'-OH group.

In addition to the inhibitory effect on HIV reverse transcriptase, stavudine triphosphate inhibits cellular DNA polymerase beta and gamma and has been shown to be able to reduce the synthesis of mitochondrial DNA.

Product Design
The development strategy for Stavudine 15 mg and 20 mg capsules was concentrated on compatibility of the active ingredient stavudine with the excipients identified to match the dissolution profile of the innovator, thus producing robust formulations.

Efficacy and Safety
Stavudine Capsules 15 mg and 20 mg are considered safe and effective when the guidances and restrictions presented in the Summary of Product Characteristics (SPC), Part 4 in this Public Assessment Report, are taken into consideration. Clinical efficacy of Stavudine Capsules 15 mg and 20 mg are discussed in Section 5.1 ("Pharmacodynamic Properties") in the SPC. Clinical safety is discussed in Section 5.3 ("Pre-clinical Safety") in the SPC. Also see Section 4 of the SPC ("Clinical Particulars") for discussion of contraindications, special precautions, interactions, use in pregnancy, patient exposure (including overdosage), interactions, and adverse events.

Approved Indication
Stavudine is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

Clinical Pharmacology

Pharmacodynamics
Stavudine is a nucleoside analogue of thymidine which possesses virustatic activity against human immunodeficiency virus type 1 (HIV–1) and type 2 (HIV–2) through inhibition of HIV replication in human cells. Stavudine is phosphorylated by cellular kinases to the active

metabolite stavudine triphosphate, which exerts antiviral activity *in vitro*. Because phosphorylation of stavudine depends on cellular rather than viral enzymes, conversion of the drug to the active triphosphate derivative occurs in both virus-infected and uninfected cells.

Stavudine triphosphate inhibits the activity of HIV reverse transcriptase by two known mechanisms: competing with the natural substrate deoxythymidine triphosphate and by incorporation into viral DNA causing a termination of DNA chain elongation because stavudine lacks the essential 3'-OH group. In addition to the inhibitory effect on HIV reverse transcriptase, stavudine triphosphate inhibits cellular DNA polymerase beta and gamma and markedly reduces the synthesis of mitochondrial DNA.

Pharmacokinetics
Peak plasma concentrations (Cmax) 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.

See the Summary of Product Characteristics, Part 4 of this Public Assessment Report, Section 5.2 ("Pharmacokinetic Properties") for a more complete discussion of stavudine pharmacokinetics, including absorption, bioavailability, distribution, metabolism, and elimination.

Drug Interactions, related side effects and contraindications

Stavudine and zidovudine compete for phosphorylation by thymidine kinase, which preferentially phosphorylates zidovudine, thereby decreasing the phosphorylation of stavudine to its active triphosphate form. Use of zidovudine is therefore not recommended in combination with stavudine.

Stavudine should not be used with didanosine because of a high incidence of peripheral neuropathy, pancreatitis and lactic acidosis unless potential benefit clearly outweighs risk of toxicities.

Stavudine is contraindicated in combination with zalcitabine because of the risk of severe neuropathy.

Co-administration of stavudine with methadone results in a 25% reduction in stavudine area under the concentration curve.

In vitro studies indicate that the activation of stavudine is inhibited by doxorubicin and ribavirin.

Stavudine does not inhibit the major cytochrome P450 isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

Clinical Efficacy

Stavudine has been investigated in several randomized, prospective clinical trials combined with other antiretroviral drugs. These studies have demonstrated significant decreases in plasma HIV RNA and increases in CD4 cell counts when used in combination with additional nucleoside analogues and either a non-nucleoside reverse transferase inhibitor (NNRTI) or a protease inhibitor (PI). In intention-to-treat analyses > 75% of subjects have plasma HIV RNA < 50 copies/mL after 48 weeks of antiretroviral combination treatment.

Isolates with thymidine-analogue associated mutations caused by the thymidine-analogues, zidovudine and stavudine, at positions M41L, K65R, D67N, K70R, L210W, T215Y/F, and K219Q/E) in the reverse transcriptase gene have reduced susceptibility to nucleoside analogues including stavudine (www.iasusa.org). Patients infected with known stavudine-resistant HIV or patients who have previously experienced virological failure on a stavudine-containing regimen may not respond sufficiently to further treatment with a combination regimen containing stavudine.

Stavudine should not be used with didanosine and lamivudine, or didanosine and abacavir, due to inferior efficacy compared to other combination regimens.

Clinical studies in special populations

Renal Impairment
Stavudine dosing should be modified in patients with reduced creatinine clearance according to the schedule shown below.

Creatinine clearance (ml/min)	Recommended dosage of stavudine in patients by weight	
	< 60 kg	≥ 60 kg
> 50	30 mg every 12 hours	40 mg every 12 hours
26-50	15 mg every 12 hours	20 mg every 12 hours
10-25	15 mg every 24 hours	20 mg every 24 hours

Since urinary excretion is also a major route of elimination of stavudine in paediatric patients, the clearance of stavudine may likewise be altered in children with renal impairment. Although there is insufficient data to recommend a specific dose adjustment of stavudine in children, a reduction in the dose and/or an increase in the interval between doses should be considered.

Hemodialysis patients
The recommended dose is 20 mg every 24 hours (≥60 kg) or 15 mg every 24 hours (<60 kg) and should be administered after the completion of each hemodialysis and at the same time of day on non-dialysis days (20).

Liver dysfunction
Stavudine pharmacokinetics in patients with hepatic impairment were similar to those in patients with normal hepatic function.

Pediatric

Adolescents, children and infants: Total exposure to stavudine was comparable between adolescents, children and infants [redacted] 14 days receiving the 2 mg/kg/day dose and adults receiving 1 mg/kg/day. Apparent oral clearance was approximately 14 ml/min/kg for infants ages 5 weeks to 15 years, 12 ml/min/kg for infants ages 14 to 28 days, and 5 ml/min/kg for infants on the day of birth. Two to three hours post-dose, CSF/plasma ratios of stavudine ranged from 16% to 125% (mean of 59%±35%).

Clinical Safety

Short-term adverse reactions are common. At the beginning of therapy, epigastric pain, nausea, diarrhea, and headache may occur: these reactions are usually mild and disappear within a few weeks even if treatment is continued.

Common long-term adverse reactions include neuropathy, lipodystrophy/lipoatrophy, and metabolic abnormalities. Rare and very rare long-term adverse reactions include lactic acidosis, hepatic steatosis, pancreatitis, and liver failure.

For a complete list of adverse events reported in clinical trials, see the Summary of Product Characteristics, Part 4 of this Public Assessment Report (Section 4.8, “Undesirable effects”).

Overdose
Stavudine overdose has not been reported. Stavudine can be removed by hemodialysis. Experience with adults treated with 12 to 24 times the recommended daily dose revealed no acute toxicity.

5. Benefit risk assessment and overall conclusion

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the Summary of Product Characteristics (Part 4 of this Public Assessment Report). Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence
Stavudine Capsules 15 mg and 20 mg have been shown to be bioequivalent to the comparator product Zerit® Capsules 15 mg and 20 mg.

Clinical Efficacy and Safety
Stavudine Capsules 15 mg and 20 mg are considered effective and safe to use when the guidances and restrictions presented in the Summary of Product Characteristics (Part 4 of this Public Assessment Report) are taken into consideration.

Benefit Risk Assessment
Based on USFDA assessments of data on quality, bioequivalence, safety, and efficacy, the benefit risk profile of Stavudine Capsules 15 mg and 20 mg was considered acceptable for the following indication: HIV-1 infection in combination with other antiretroviral agents.

Products added to the WHO prequalification list on the basis of USFDA approval rely on scientific assessment and inspections conducted by the USFDA, and are eligible for purchase with PEPFAR funds.

For further information about this medicinal product, please contact:
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