

Arrow - Stavudine

Stavudine Capsules 40mg

Presentation

Arrow - Stavudine is a white capsule containing white to off-white powder, with "STN-40" on both the cap and the body printed in black. Each capsule contains 40 mg of Stavudine.

This product is not able to deliver all approved dose regimens.

Uses

Actions

Stavudine is a synthetic thymidine analogue active against the Human Immunodeficiency virus (HIV). Stavudine inhibits the replication of HIV in human cells *in vitro*. It is phosphorylated by cellular kinases to stavudine triphosphate which inhibits HIV reverse transcriptase by competing with the natural substrate, deoxythymidine triphosphate. It also inhibits viral DNA synthesis by causing DNA chain termination due to a lack of the 3'-hydroxyl group necessary for DNA elongation. Stavudine triphosphate reduces synthesis of mitochondrial DNA by inhibiting cellular polymerase gamma, but is 100-fold less active against cellular DNA polymerase alpha and beta.

Although the clinical efficacy is well established, a relationship between *in vitro* susceptibility of HIV to stavudine and inhibition of HIV replication in humans or clinical response to therapy has not been well established.

Stavudine triphosphate has an intracellular half-life of 3.5 hours in CEM T-cells and peripheral blood mononuclear cells.

Reductions in sensitivity to stavudine of some HIV-1 strains has been observed in *in vitro* selection studies and in some pairs of pre-treatment and post-treatment HIV-1 isolates from clinical studies. Some stavudine post-treatment isolates were resistant to didanosine and/or zidovudine. The relationship between stavudine treatment and the appearance of resistance to didanosine and zidovudine is unexplained.

In vitro studies of HIV-1 demonstrated additive antiviral effect with the combination of stavudine with didanosine (molar ratios of stavudine to didanosine of 0.05, 0.10, 0.16 and 0.5). Stavudine and zalcitabine combinations exhibited a synergistic effect *in vitro*. In cell culture studies in lymphocytes, thymidine kinase, which is essential for the phosphorylation of stavudine, has been found to have a low affinity for stavudine compared with zidovudine. In CEM-SS cells, an antagonist antiviral effect was seen at a molar ratio of 20 (stavudine to zidovudine), while at molar ratios of 100 and 500 an additive antiviral effect was apparent. The clinical relevance of this is unknown.

Pharmacokinetics

Adults

Absorption

Stavudine is rapidly absorbed following oral administration. Mean absolute bioavailability is 86%. Peak plasma concentrations (C_{max}) occur ≤ 1 hour after dosing and increase in a dose-related manner. No significant accumulation of stavudine was observed with repeated administration every 6, 8 or 12 hours.

A study in asymptomatic, HIV-infected patients demonstrated that systemic exposure (area under the plasma concentration-time curve) is similar whether stavudine is administered under fasting conditions or after a standardised, high-fat meal. Mean \pm SD C_{MAX} of stavudine was reduced from 1.44(0.49 *mcg* /mL in the fasting state to 0.75(0.16 *mc g*/mL after the meal, and the median time to reach C_{MAX} was prolonged from 0.6 to 1.5 hours. The mean plasma profiles in the fed and fasted states intersected approximately 1.5 hours post-dose and mean plasma stavudine concentrations thereafter were between 50% and 100% higher in the fed compared to fasted subjects. From six hours post-dose, mean plasma concentrations were comparable. The relationship between plasma concentration and intracellular antiviral activity is now known.

Distribution

The mean apparent volume of distribution following single oral doses is 66L. Stavudine crosses the blood brain barrier. Serum protein binding is negligible. Stavudine distributes equally between red blood cells and plasma. Cerebrospinal fluid levels were detectable in 4 healthy subjects 4 to 5 hours after a single 40mg oral dose of stavudine. The mean (range) CSF concentration was 0.063mcg/mL (0.044-0.071 mcg/mL). The mean (range) CSF concentration expressed as a percent of the corresponding plasma concentration was 40% (31-45%).

Metabolism

The metabolism of stavudine in humans has not been elucidated. After incubation of human liver slices with [14 C]- stavudine for 6 hours, 87% of the radioactivity was accounted for by the parent compound, 2% was metabolised to thymine, and 7% was associated with unidentified polar compounds.

Excretion

The mean terminal elimination half-life is 1.44 hours following single oral doses, and is independent of dose. Renal elimination accounts for approximately 40% of overall clearance. Mean renal clearance is approximately twice the mean endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration.

Paediatric Patients

Studies in HIV-infected paediatric patients demonstrated a mean absolute bioavailability of stavudine of 78.5% and 69.2% following oral administration of capsule and solution formulations, respectively. Pharmacokinetic profiles are similar after the first-dose and in steady-state, with no accumulation of stavudine at the dosages employed (0.125 to 2mg/kg every 12 hours). Mean volume of distribution is

0.68L/kg following intravenous infusions. Cerebrospinal fluid concentrations correspond to 16% to 97% of simultaneous plasma concentrations. Mean terminal elimination half-life after a single oral dose is 0.91 hours.

Renal Insufficiency

The clearance of stavudine decreases as creatinine clearance decreases; therefore, it is recommended that the dosage of stavudine be modified in patients with reduced renal function. (See Dosage and Administration).

Hepatic Insufficiency

Stavudine pharmacokinetics are not significantly altered in patients with stable moderate to severe hepatic insufficiency (Child-Pugh Class B or C with cirrhosis). Therefore, no modifications of dosing are recommended for patients with stable hepatic insufficiency. Stavudine pharmacokinetics have not been assessed in patients with unstable hepatic insufficiency.

Clinical Trials

Study AI455-019

This was a Phase 3, multi-centre, randomised, double blind trial of stavudine vs. continued zidovudine in HIV-infected adults with CD4 counts of 50 to 500 cells/mm³, who had received at least 24 weeks of prior zidovudine treatment. Stavudine was administered in dosages of 40mg twice a day for patients weighing ≥60kg and 30mg twice a day for those weighing <60kg. The zidovudine dosage was 200mg three times a day.

The final analysis included data from 822 patients with a median baseline CD4 count of 235 cells/mm³ (range: 10 to 735 cells/mm³), and a median duration of prior zidovudine treatment of 88 weeks (range: 11 to 365 weeks). Fourteen percent of subjects had AIDS at baseline, while 50% had minor HIV-related symptoms and 36% were asymptomatic.

Patients on stavudine received a median duration of 79 weeks of therapy as compared to 53 weeks for patients on zidovudine (P<0.0001). Two hundred and thirty-one events of clinical progression, defined as the development of an AIDS-defining event or death (26 events/100 patients-years of follow-up), occurred in the stavudine group as compared to 262 events (32 events/100 patient-years) in the zidovudine group. The relative risk for the progression of HIV-related disease was reduced in the stavudine group as compared to the zidovudine group (RR=0.78, log rank p=0.006). The Kaplan-Meier estimate of the two-year survival rate for patients on stavudine was 87%, while that for patients on zidovudine was 83% (RR=0.74, log rank p=0.07). Stavudine was also associated with an immediate improvement in mean CD4 cell counts, which was sustained above baseline for approximately 16 weeks. A difference of approximately 40-50 cells/mm³ was apparent between stavudine and zidovudine treated patients and was maintained over 96 weeks of follow-up (p<0.03 at week 12) also favoured stavudine over zidovudine.

Stavudine Parallel Track Program

(Study AI455-900)

This program provided access to stavudine for HIV-infected patients with CD4 cell counts $<300/\text{mm}^3$, who had failed, or were intolerant of, or had contraindications to, therapy with zidovudine and didanosine. The program was randomised, double-blind, comparative trial of stavudine, 20 or 40mg twice daily for patients weighing $\geq 60\text{kg}$ (15 or 30mg twice daily for patients weighing 40 to $<60\text{kg}$, and 10 or 20mg twice daily for patients weighing $<40\text{kg}$).

The Parallel Track Program began patient enrollment and randomisation in October 1992. The final analysis was conducted on 12,551 patients randomised through May 20, 1994. Prior to randomisation, over 99% of patients had received zidovudine for a median of 96 weeks, and 98% of patients had received didanosine for a median of 26 weeks. Ninety-five percent of the patients were male, and 84% were white. The median CD4 cell count at entry was 44 cells/ mm^3 (range: 0 to 940). For the 11,784 patients who had received stavudine, the median duration of drug treatment was 22 weeks (range: <1 to 87 weeks).

In an intent-to-treat analysis of all randomised subjects, the 1-year survival rates were similar for the two dose groups (74% for each group). Death occurred within 30 days of dosing in fewer patients receiving the 40mg BID dose as compared with the 20mg BID dose ($p=0.03$).

Indications

Arrow - Stavudine is indicated for the treatment of HIV-infected patients (over the age of 5 months) for whom zidovudine therapy is not, or is no longer, appropriate.

Dosage and Administration

This product is not able to deliver all approved dose regimens.

Adults (12 years of age or older)

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

40mg every 12 hours for patients $\geq 60\text{kg}$

30mg every 12 hours for patients $<60\text{kg}$

Paediatric Patients

1mg/kg every 12 hours for patients $<30\text{kg}$

30mg every 12 hours for patients ≥ 30 to $<60\text{kg}$

When stavudine is taken with food, peak plasma levels are altered, but overall exposure is unchanged (see Pharmacokinetics). The clinical significance of this is unknown.

Dosage Adjustment in Patients with Peripheral Neuropathy

Patients should be monitored for the development of peripheral neuropathy, which is usually characterised by numbness, tingling, or pain in the feet or hands. If these symptoms develop, stavudine therapy should be interrupted. Symptoms may

resolve if therapy is withdrawn promptly. Some patients may experience a temporary worsening of symptoms following discontinuation of therapy. If symptoms resolve satisfactorily, resumption of treatment with stavudine may be considered using half the recommended dosage schedule.

Dosage Adjustment in Patients with Hepatic Impairment

In patients with stable hepatic impairment, no initial adjustment of dosage is necessary. In the event of rapidly elevating aminotransferase levels, consideration should be given to discontinuation of all nucleoside analogue therapy.

Dosage Adjustment in Patients with Renal Impairment

Adult

Stavudine may be administered to adult patients with impaired renal function. The following dosages are recommended:

Creatinine Clearance (mL/min)	Recommended Stavudine Dosage by Patient Weight	
	≥ 60kg	<60kg
>50*	40mg every 12 hours *	30mg every 12 hours
26-50	20mg every 12 hours	15mg every 12 hours
<25 ⁺	20mg every 24 hours	15mg every 24 hours

* Normal dose, no adjustment necessary

⁺ For patients undergoing haemodialysis, the daily dose of stavudine should be administered after the completion of a scheduled haemodialysis sessions. On nondialysis days, stavudine should be administered at the same time of day as it is on dialysis days.

Paediatric Patients

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

Contraindications

ARROW - STAVUDINE is contraindicated in patients with hypersensitivity to stavudine or to any component of the formulation.

Warnings and Precautions

Warnings

Peripheral Neuropathy

An important toxicity of stavudine is peripheral neuropathy which is dose related and occurs more frequently in patients with advanced HIV infection, a history of

neuropathy, or concurrent neurotoxic drug therapy, including didanosine (see Adverse Effects). This complication occurred with 24-week rates of 19 and 24 percent of the 11,784 patients with very advanced HIV disease who received the two dose levels of stavudine in the Parallel Track Program. In the AI455-019 study, the peripheral neuropathy rate was 14% and 4% in the stavudine and zidovudine-treated groups, respectively.

Patients should be monitored for the development of neuropathy, which may resolve if therapy is withdrawn promptly. Symptoms may temporarily worsen in some cases following discontinuation of therapy. Resumption of treatment at a reduced dosage may be considered if symptoms resolve satisfactorily. (See Dosage and Administration). Patients with a history of peripheral neuropathy are at increased risk for development of neuropathy. If stavudine must be administered in this clinical setting, careful monitoring is essential.

Pancreatitis

Fatal and nonfatal pancreatitis have occurred during therapy when stavudine was part of a combination regimen that included didanosine in both treatment-naïve and treatment-experienced patients, regardless of degree of immunosuppression. The combination of stavudine and didanosine and any other agents that are toxic to the pancreas should be suspended in patients with suspected pancreatitis. Reinstitution of stavudine after a confirmed diagnosis of pancreatitis should be undertaken with particular caution and close patient monitoring. The new regimen should contain neither didanosine nor hydroxyurea.

Lactic Acidosis/Severe Hepatomegaly with Steatosis/Hepatic Failure

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 antiretroviral agents.

A majority of cases have been in women. 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 Pregnancy). Particular caution should be exercised when administering stavudine to any patient known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with stavudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Generalised fatigue, digestive symptoms such as nausea, vomiting, abdominal pain, sudden unexplained weight loss; respiratory symptoms (tachypnea, dyspnoea); or neurological symptoms (including motor weakness) might be indicative of lactic acidosis development.

Hepatic Dysfunction

Hepatitis or liver failure, which was fatal in some cases, have been reported with stavudine. In patients with pre-existing liver dysfunction, discontinuation of all nucleoside analogues should be considered when worsening liver disease occurs.

Hepatotoxicity and hepatic failure resulting in death were reported during postmarketing surveillance in HIV-infected patients treated with antiretroviral agents in combination with hydroxyurea. Fatal hepatic events were reported most often in patients treated with the combination of hydroxyurea, didanosine and stavudine. This combination should be avoided.

The safety and efficacy of stavudine have not been established in patients with significant underlying liver disorders. During combination antiretroviral therapy, patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities, including severe and potentially fatal hepatic events, and should be monitored according to standard practice.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients with combination antiretroviral therapy, including stavudine. In patients with severe immune deficiency at the time of institution of combination antiretroviral therapy, an inflammatory reaction to indolent or residual opportunistic pathogens may arise and cause serious clinical conditions or aggravation of symptoms. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated, and treatment instituted when necessary.

Fat Redistribution

Redistribution/accumulation of body fat (lipodystrophy/lipoatrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequence of these events are currently unknown. A causal relationship has not been established.

While a small number of patients have received >2 years of therapy with stavudine, patients should be informed that the long term effects of stavudine have been fully evaluated. Physicians should be alert to the development of other adverse events noted on long term exposure to other nucleoside analogue reverse transcriptase inhibitors, such as myopathy.

Precautions

Renal Impairment

The clearance of stavudine decreased as creatinine clearance decreased; therefore, it is recommended that the dosage of stavudine be adjusted in patients with reduced renal function (creatinine clearance (≤ 50 mL/min; see Dosage and Administration).

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no data on the carcinogenicity of stavudine. In *in vitro* assay there was an increase in the frequency of transformed foci in mouse fibroblast cells, with and without metabolic activation. Another nucleoside analogue reverse transcriptase inhibitor causes vaginal neoplasms at high doses in mice and 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. Stavudine increased the frequency of chromosome aberrations in human lymphocytes without metabolic activation. In vivo micronucleus assay showed clastogenic activity in bone marrow cells following stavudine administration to mice at dosages of 600 to 2,000 mg/kg/day for 3 days.

Fertility was not impaired in rats with exposures (based on C_{max}) up to 216 times that observed at 1mg/kg/day, the approximate clinical dosage.

Pregnancy and Lactation

Pregnancy

There are no adequate and well-controlled studies of stavudine in pregnant women. Stavudine should be used in pregnancy only if the potential benefits 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 not known if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in nonpregnant individuals receiving nucleoside analogues (see "Warnings" Lactic Acidosis/Severe Hepatomegaly with Steatosis/Hepatic Failure). 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. Health care providers caring for HIV-infected pregnant women receiving stavudine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

No evidence of teratogenicity was observed in rats and rabbits with exposures (based on C_{max}) up to 399 and 183 times, respectively, of that observed at 1mg/kg/day, the approximate human dosage. The incidence of a common skeletal variation, unossified or incomplete ossification of sternebrae, was increased in rat fetuses at 299 times the human exposure but not at 216 times human exposure. Early rat neonatal mortality (birth to 4 days of age) was increased at 399 times the human exposure and unaffected at 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 maternal plasma. Animal reproduction studies are not always predictive of human response.

Lactation

Studies in lactating rats showed that stavudine is excreted in breast milk. It is not known whether stavudine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions from

stavudine in nursing infants, mothers should be instructed to discontinue nursing if they are receiving stavudine.

Lactose Intolerance

ARROW - STAVUDINE capsules contain lactose. This amount is probably insufficient to induce specific symptoms of intolerance.

Effects on ability to drive and use machines

There is no indication that stavudine affects this ability.

Adverse Effects

When stavudine is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when stavudine is used alone. Pancreatitis, peripheral neuropathy and liver function abnormalities occur more frequently in patients treated with the combination of stavudine and didanosine. Fatal pancreatitis and hepatotoxicity may occur more frequently in patients treated with stavudine in combination with didanosine (see Warnings).

Many of the serious adverse clinical events from patients receiving stavudine in clinical trials were consistent with the course of HIV infection. Concurrent therapy with other medications was permitted in these trials. Therefore, it is difficult to distinguish which events were related to stavudine, the disease itself, or other therapies.

Peripheral Neuropathy

The major clinical toxicity of stavudine is dose-related peripheral neuropathy (see Table 1). Patients with advanced HIV infection, a history of peripheral neuropathy, or concurrent neurotoxic drug therapy, including didanosine, are at increased risk for developing this complication during therapy with stavudine. Stavudine-related peripheral neuropathy may resolve if therapy is promptly withdrawn. In some cases, symptoms may worsen temporarily following discontinuation of therapy. Resumption of treatment with stavudine may be considered at a reduced dosage if symptoms resolve satisfactorily (see Dosage & Administration).

Table 1: Incidence of peripheral neuropathy* in controlled clinical trials

	Study No: AI455-019		Parallel Track Program	
	Stavudine 40mg twice a day N = 412	Zidovudine 200mg three times a day N = 402	Stavudine 20mg twice a day N = 5879	Stavudine 40mg twice a day N = 5905
Peripheral Neuropathy	14%	4%	19%	24%

* Peripheral neuropathy requiring or leading to dose modification, regardless of severity.

Pancreatitis

Pancreatitis was reported in up to 2% of patients in clinical trials. Pancreatitis was generally attributed to advanced disease or to prior or concurrent treatment with medications known to be associated with pancreatitis. The occurrences were not dose-related, and were occasionally fatal. Patients with a history of pancreatitis appear to be at increased risk of recurrence. Physicians should monitor patients at high risk of pancreatitis or those receiving medicinal agents known to be associated with pancreatitis. Routine monitoring of serum amylase may be warranted.

Lactic Acidosis

Lactic acidosis, which may be fatal, has been reported rarely in patients receiving stavudine, as with other nucleoside analogues. These reports, which were usually associated with severe hepatic steatosis, have been reported postmarketing (see Warnings & Precautions).

Hepatic Dysfunction

Hepatitis or liver failure, which was fatal in some cases, has been reported postmarketing (see Warnings & Precautions). Patients at high risk include those with pre-existing liver disease, prior use of hepatotoxic agents or hepatitis infection. Modest elevations of hepatic transaminases not requiring dose modification were reported in 10-13% of patients in clinical trials.

During postmarketing surveillance in HIV-infected patients treated with 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 Warnings & Precautions).

Observed during Clinical Practice

The following events have been identified during post-approval use of stavudine. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness, frequency of reporting, causal connection to stavudine, or a combination of these factors.

Haematological Disorders: thrombocytopenia

Liver: lactic acidosis and hepatic steatosis (see Precautions), hepatitis and liver failure.

Body as a whole: abdominal pain, allergic reaction, chills/fever.

Digestive Disorders: anorexia

Blood and Lymphatic System Disorders: macrocytosis, thrombocytopenia

Exocrine Gland Disorders: pancreatitis [including fatal cases (see Warnings & Precautions)]

Haematological Disorders: anaemia, leucopenia, thrombocytopenia

Liver: lactic acidosis and hepatic steatosis (see Precautions), hepatitis, liver failure and hepatotoxicity resulting in death (see Warnings & Precautions).

Musculoskeletal: myalgia

Nervous system: insomnia, severe motor weakness (most often reported in the setting of lactic acidosis), peripheral neuropathy (see Warnings and Precautions)

Metabolic Disorders: diabetes mellitus, hyperglycaemia.

Paediatric Patients

Adverse events and clinical laboratory abnormalities were generally similar to those seen in adults, and generally related to the underlying disease. Drug-related peripheral neuropathy has not been reported in paediatric patients who have received stavudine monotherapy in controlled clinical trials.

The clinical adverse events reported at an incidence of >5% in stavudine-zidovudine comparative study (Study No: AI455-019) which are considered potential adverse reactions are listed in Table 2.

Table 2: Adverse events reported, as percentage incidence, at an incidence of >5% in the controlled comparative trial (Study No: AI455-019)

Adverse Event	Study No: AI455-019 Comparative Double-Blind Trial in Patients with Less Advanced HIV Disease (<u>median CD4 counts 250 cells/mm³</u>)	
	Stavudine 40 mg twice a day* N = 412^a	Zidovudine 200 mg three times a day N = 402^b
Body as a whole:		
Headache	54	49
Chills/Fever	50	51
Asthenia	35	34
Abdominal pain	34	27
Pain	21	20
Malaise	20	19
Back pain	19	17
Flu syndrome	15	8
Allergic reactions	9	8
Neoplasms	6	5
Cardiovascular		
Chest pain	11	11
Digestive		
Diarrhoea	50	43
Nausea/Vomiting	38	44
Anorexia	19	22
Dyspepsia	12	14
Constipation	6	7

Haemic/lymphatic Lymphadenopathy	20	20
Musculoskeletal Myalgia Arthralgia	32 23	35 19
Nervous Other peripheral neurological symptoms (not requiring dose changes) Insomnia Depression Anxiety Neuropathy requiring dose modification Nervousness Dizziness	39 29 24 22 14 12 11	35 31 20 16 4 12 8
Respiratory Dyspnoea	15	13
Skin & Appendages Rash Sweating Pruritis Maculopapular rash Skin benign neoplasm	40 18 15 6 6	36 16 12 5 7

* Patients <60kg received 30 mg twice a day.

Median duration of treatment ^a = 79 weeks; ^b = 53 weeks

Laboratory Abnormalities

Laboratory abnormalities reported in clinical trials include those shown in the following table.

Table 3: Laboratory abnormalities, reported as percentage incidence, in clinical trials in adults (Study No: AI455-019)

Laboratory Abnormality	Study No: AI455-019 Comparative Double-Blind Trial in Patients with Less Advanced HIV Disease (median CD4 counts 250 cells/mm ³)	
	Stavudine 40 mg twice a day* N = 412^a	Zidovudine 200 mg three times a day N = 402^b
AST (SGOT) ≤5 x ULN† >5 x ULN	63 11	49 10
ALT (SGPT) ≤5 X ULN >5 x ULD	65 13	46 11
Amylase >1.4 x ULN	14	13

Bilirubin >2.5 x ULN	2	3
Neutrophils <750/mm ³	5	9
Platelets <50,000/mm ³	3	3

* Patients < 60 kg received 30 mg twice a day. † x ULN = times upper limit of normal.
Median duration of treatment ^a = 79 weeks; ^b = 53 weeks.

Interactions

The combination of hydroxyurea, didanosine and stavudine should be avoided in HIV-infected patients due to an increased risk of fatal hepatic events (see Warnings and Precautions).

The co-administration of stavudine and didanosine was studied in an open label study in ten male patients with HIV. The patients were randomised to receive either didanosine 100mg (2 x 50mg tablets) or stavudine 40mg (2 x 20mg capsules) on Day 1, and the other drug as a single dose on Day 2. Both drugs at the same doses were taken together every 12 hours from day 3-7. The pharmacokinetic profiles of each drug were similar for the single dose, the first simultaneous dose and the last simultaneous dose demonstrating that didanosine and stavudine can be given concurrently without affecting the pharmacokinetics of the either agent.

It is postulated that zidovudine may competitively inhibit the intracellular phosphorylation of stavudine (see Uses). Therefore, use of zidovudine in combination with stavudine is not recommended.

Based on in vitro data, the phosphorylation of stavudine has been shown to be inhibited at relevant concentrations by doxorubicin and ribavirin. The clinical significance of this finding is unknown. The coadministration of stavudine with either doxorubicin and ribavirin should be undertaken with caution.

No pharmacokinetic interaction was observed between stavudine and didanosine when co-administered in a clinical trial. The interaction of other drugs with stavudine has not been studied in a systematic manner. Clinical trials utilising combination therapy including stavudine are ongoing and will provide information regarding any possible drug interactions.

Overdosage

Experience with adults treated with 12 to 24 times the recommended daily dosage showed no acute toxicity. Complications of chronic overdosage include peripheral neuropathy and hepatic toxicity.

Stavudine can be removed by haemodialysis. The mean clearance of stavudine by haemodialysis is 120±18 mL/min (mean ± SD). It is now known whether stavudine is removed by peritoneal dialysis.

Pharmaceutical Precautions

Store below 25°C. Protect from moisture.

Medicine Classification

Prescription Medicine

Package Quantities

Bottle: 60 capsules

Further Information

Information for patients

Patients should be informed that stavudine is not a cure for HIV infection, and that they may continue to experience illness associated with AIDS or HIV infection, including opportunistic infections. Stavudine has not been shown to reduce the incidence or frequency of such illness, and patients should be advised to remain under the care of a physician when using stavudine.

Patients should be informed that an important toxicity of stavudine is peripheral neuropathy. Symptoms of peripheral neuropathy include tingling, burning pain, or numbness in the hands or feet. Patients should be advised that this toxicity occurs with greater frequency in patients with a history of peripheral neuropathy. They should be encouraged to report these symptoms to their physicians and advised that dose changes may be necessary. They should also be cautioned about the use of other medications that may produce or exacerbate peripheral neuropathy.

Patients should be informed that when stavudine is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when stavudine is used alone. An increased risk of pancreatitis, which may be fatal, may occur in patients treated with the combination of stavudine and didanosine. Patients treated with stavudine should be informed of symptoms associated with pancreatitis and they should be encouraged to contact their physician to report these symptoms. An increased risk of lactic acidosis and hepatotoxicity, which may be fatal, may occur in patients treated with stavudine in combination with didanosine. Patients treated with this combination should be closely monitored for signs and symptoms that may indicate liver toxicity.

Patients should be told that the long term effects of stavudine are unknown. They should be advised that stavudine therapy has not been shown to reduce the risk of transmission of HIV to others.

ARROW - STAVUDINE capsules contain the active ingredient, stavudine. They also contain the following excipients: lactose anhydrous, sodium starch glycolate, sodium lauryl sulfate and magnesium stearate. The capsule shell consists of gelatin,

titanium dioxide (E171), black printing ink (SW-9008), sodium lauryl sulfate and liquid paraffin.

Name and address

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Date of Preparation

24 November 2009