

DATA SHEET

1 PRODUCT NAME

Zerit[®] stavudine capsules 40mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Zerit 40 mg hard capsules

Each hard capsule contains 40 mg of stavudine.

Excipients with known effect

Each hard capsule contains 159.06 mg of lactose anhydrous.

Each hard capsule contains 79.53 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Product Strength and Pack	Capsule Shell Colour	Markings on Capsule (in black ink)
40mg 60's (bottle) 56's (carton)	Dark orange	BMS 1967 40

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Zerit (stavudine) is indicated for the treatment of HIV infection in adults (12 years of age or older) and paediatric patients greater than 30kg in weight, in combination with other anti-retrovirals

4.2 Dose and method of administration

Adults (12 years of age or older)

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

40mg every 12 hours for patients ≥ 60 kg

30mg every 12 hours for patients < 60 kg

Paediatric Patients

1mg/kg every 12 hours for patients < 30 kg *

30mg every 12 hours for patients ≥ 30 to < 60 kg

* Zerit capsules should not be used in patients < 30kg because an appropriate dose cannot be given with the currently available capsule strengths.

When Zerit is taken with food, peak plasma levels are altered, but overall exposure is unchanged (see 5.2 Pharmacokinetic properties). 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, Zerit 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 Symptoms may resolve if therapy is withdrawn promptly.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 Zerit 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 treatment with Zerit should be suspended and consideration should be given to discontinuation of all nucleoside analogue therapy.

Dosage Adjustment in Patients with Renal Impairment

Adult:

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

Creatinine Clearance (mL/min)	Recommended Zerit 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 Zerit should be administered after the completion of a scheduled haemodialysis session. On nondialysis days, Zerit 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 Zerit in this patient population, a reduction in the dose and/or an increase in the interval between doses should be considered.

4.3 Contraindications

Zerit is contraindicated in patients with hypersensitivity to stavudine or to any component of the formulation.

Co-administration of Zerit with didanosine is contraindicated due to the potential for serious and/or life-threatening events notably lactic-acidosis, liver function abnormalities, pancreatitis, and peripheral neuropathy.

4.4 Special warnings and precautions for use

Warnings

Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, Zerit and zidovudine. Zerit therapy is associated with several severe side effects, such as lactic acidosis, lipoatrophy and polyneuropathy, for which a potential underlying mechanism is mitochondrial toxicity

Peripheral Neuropathy: An important toxicity of Zerit is peripheral neuropathy which is dose related and occurs more frequently in patients with advanced HIV infection, a history of neuropathy, or concurrent neurotoxic medicine therapy, including didanosine (see 4.8 Undesirable effects).

Peripheral neuropathy, which was severe in some cases, has been reported in HIV-infected patients receiving hydroxyurea in combination with antiretroviral agents, including didanosine. 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 4.2 Dose and method of administration). Patients with a history of peripheral neuropathy are at increased risk for development of neuropathy. If Zerit must be administered in this clinical setting, careful monitoring is essential.

Motor weakness has been reported rarely in patients receiving combination antiretroviral therapy including stavudine. Most of these cases occurred in the setting of lactic acidosis. The evolution of motor weakness may mimic the clinical presentation of Guillain-Barré syndrome (including respiratory failure). If motor weakness develops Zerit should be discontinued. Symptoms may continue or worsen following discontinuation of therapy.

Pancreatitis: Fatal and nonfatal pancreatitis have occurred during therapy when Zerit was part of a combination regimen that included didanosine or didanosine and hydroxyurea in both treatment-naïve and treatment-experienced patients, regardless of degree of immunosuppression. The combination of Zerit and didanosine and any other agents that are toxic to the pancreas should be suspended in patients with suspected pancreatitis. Reinstitution of Zerit 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. In addition, deaths

attributed to hepatotoxicity have occurred in patients receiving the combination of Zerit, Videx (didanosine) and hydroxyurea. Particular caution should be exercised when administering Zerit to any patient known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Zerit 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).

Generalized 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 Zerit. 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 Zerit 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 Zerit. 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, generalized and/or focal mycobacterial infections and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated, and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Lipoatrophy

On the basis of mitochondrial toxicity, Zerit has been shown to cause loss of subcutaneous fat, which is most evident in the face, limbs, and buttocks. The incidence and severity of lipoatrophy are related to cumulative exposure, and is often not reversible when Zerit treatment is stopped. Patients receiving Zerit should be frequently examined and questioned for signs of lipoatrophy. When such development is found, treatment with Zerit should be discontinued.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. In some cases, for lipids, there is evidence of a treatment effect. While for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

While a small number of patients have received >2 years of therapy with Zerit (stavudine) capsules, patients should be informed that the long term effects of Zerit 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 Zerit be adjusted in patients with reduced renal function (creatinine clearance ≤ 50 mL/min; see 4.2 Dose and method of administration).

Carcinogenesis, Mutagenesis

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.

Information for patients

Patients should be informed that Zerit is not a cure for HIV infection, and that they may continue to experience illness associated with AIDS or HIV infection, including opportunistic infections. Zerit 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 Zerit.

Patients should be informed that an important toxicity of Zerit 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 Zerit is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when Zerit is used alone. An increased risk of pancreatitis, which may be fatal, may occur in patients treated with the combination of Zerit (stavudine) and Videx (didanosine) with or without hydroxyurea. Patients treated with Zerit 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 Zerit in combination with Videx with or without hydroxyurea. 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 Zerit are unknown. They should be advised that Zerit therapy has not been shown to reduce the risk of transmission of HIV to others.

4.5 Interaction with other medicines and other forms of interaction

The combination of hydroxyurea, didanosine and stavudine should be avoided in HIV-infected patients due to an increased risk of fatal hepatic events (**see 4.4 Special warnings and precautions for use**).

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 medicine as a single dose on Day 2. Both medicines at the same doses were taken together every 12 hours from day 3-7. The pharmacokinetic profiles of each medicine 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 5.1 Pharmacodynamic properties). Therefore, use of zidovudine in combination with Zerit 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 Zerit (stavudine) and didanosine when co-administered in a clinical trial. The interaction of other medicines with Zerit has not been studied in a systematic manner. Clinical trials utilising combination therapy including stavudine are ongoing and will provide information regarding any possible medicine interactions.

4.6 Fertility, 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 4.4 Special warnings and precautions for use Lactic Acidosis/Severe Hepatomegaly with Steatosis/Hepatic Failure**). . Health care providers caring for HIV-infected pregnant women receiving stavudine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

Breast feeding

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 medicines 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 Zerit.

Lactose Intolerance

Zerit capsules contain lactose (120 and 240 mg depending on capsule strength). This amount is probably insufficient to induce specific symptoms of intolerance.

Impairment of Fertility:

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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Stavudine may cause dizziness and/or somnolence. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

When Zerit is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when Zerit is used alone. Pancreatitis, peripheral neuropathy and liver function abnormalities occur more frequently in patients treated with the combination of Zerit and Videx. Fatal pancreatitis and hepatotoxicity may occur more frequently in patients treated with Zerit in combination with Videx (see 4.4 Special warnings and precautions for use).

Many of the serious adverse clinical events from patients receiving Zerit 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 Zerit is dose-related peripheral neuropathy (see Table 1). Patients with advanced HIV infection, a history of peripheral neuropathy, or concurrent neurotoxic medicine therapy, including didanosine, are at increased risk for developing this complication during therapy with Zerit. 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 Zerit may be considered at a reduced dosage if symptoms resolve satisfactorily (see 4.2 Dose and method of administration).

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

	Study No: AI455-019		Parallel Track Program	
	Zerit 40 mg BID N = 412	Zidovudine 200 mg TID N = 402	Zerit 20 mg BID N = 5879	Zerit 40 mg BID 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 Zerit, as with other nucleoside analogues. These reports, which were usually associated with severe hepatic steatosis, have been reported postmarketing (see 4.4 Special warnings and precautions for use).

Hepatic Dysfunction

Hepatitis or liver failure, which was fatal in some cases, have 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 4.4 Special warnings and precautions for use).

Observed during Clinical Practice

The following events have been identified during post-approval use of Zerit. 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 Zerit, or a combination of these factors.

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

Digestive Disorders – anorexia

Blood and Lymphatic System Disorders – macrocytosis, thrombocytopenia, neutropenia, anemia

Exocrine Gland Disorders – pancreatitis [including fatal cases (see 4.4 Special warnings and precautions for use)]

Haematological Disorders – anaemia, leucopenia, thrombocytopenia

Liver – lactic acidosis and hepatic steatosis (see Precautions), hepatitis, liver failure and hepatotoxicity resulting in death (see 4.4 Special warnings and precautions for use).

Musculoskeletal - myalgia

Nervous system – insomnia, severe motor weakness (most often reported in the setting of symptomatic hyperlactaemia or lactic acidosis), peripheral neuropathy (see 4.4 Special warnings and precautions for use)

Metabolic Disorders – lipoatrophy, lipodystrophy, diabetes mellitus, hyperglycaemia.

Laboratory Abnormalities: lipase elevations

Paediatric Patients

Adverse events and clinical laboratory abnormalities were generally similar to those seen in adults, and generally related to the underlying disease. Medicine-related peripheral neuropathy has not been reported in paediatric patients who have received Zerit 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
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	Disease (median CD4 counts 250 cells/mm³)	
	Stavudine 40 mg BID* N = 412 ^a	Zidovudine 200 mg TID 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	32	35
Arthralgia	23	19
Nervous		
Other peripheral neurological symptoms (not requiring dose changes)	39	35
Insomnia	29	31
Depression	24	20

Anxiety	22	16
Neuropathy requiring dose modification	14	4
Nervousness	12	12
Dizziness	11	8
Respiratory		
Dyspnoea	15	13

Adverse Event	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 BID* N = 412 ^a	Zidovudine 200 mg TID N = 402 ^b
Skin & Appendages	40	35
Rash	18	16
Sweating	15	12
Pruritis	6	5
Maculopapular rash	6	7
Skin benign neoplasm		

* Patients <60kg received 30 mg BID. 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 BID* N = 412 ^a	Zidovudine 200 mg TID N = 402 ^b
AST (SGOT) ≤5 X ULN†	63	49

>5 x ULN	11	10
ALT (SGPT)		
≤5 x ULN	65	46
>5 x ULN	13	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 BID. † x ULN = times upper limit of normal.

Median duration of treatment 1 = 79 weeks; b = 53 weeks.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting>

4.9 Overdose

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors, ATC code: J05AF04

Mechanism of action

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.

HIV-1 isolates with reduced susceptibility to stavudine have been selected in cell culture (strain specific) and were also obtained from patients treated with stavudine. Phenotype analysis of HIV-1 isolates from 61 patients receiving prolonged (6-29 months) stavudine monotherapy showed that post-therapy isolates from four patients exhibited EC₅₀ values more than 4-fold (range 7- to 16-fold) higher than the average pretreatment susceptibility of baseline isolates. Of these, HIV-1 isolates from one patient contained the zidovudine-resistance associated mutation T215Y and K219E, and isolates from another patient contained the multiple nucleoside- resistance-associated mutation Q151M. Mutations in the RT gene of HIV-1 isolates from the other two patients were not detected. The genetic basis for stavudine susceptibility changes has not been identified.

Cross-resistance among HIV-1 reverse transcriptase inhibitors has been observed. Several studies have demonstrated that prolonged stavudine treatment can select and /or maintain thymidine analogue mutations (TAMs) associated with zidovudine resistance. The decrease of susceptibility in cell culture is subtle requiring two or more TAMs (generally M41L and T215Y) before stavudine susceptibility is decreased (> 1.5 fold). These TAMs are seen at a similar frequency with stavudine and zidovudine in virological treatment. The clinical relevance of these findings suggests that stavudine should be avoided in the presence of thymidine analogue mutations, especially M41L and T215Y.

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.

Clinical efficacy and safety

Clinical Trials

Study AI455-019

This was a Phase 3, multi-centre, randomised, double blind trial of Zerit 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. Zerit was administered in dosages of 40mg BID for patients weighing ≥60kg and 30mg BID for those weighing <60kg. The zidovudine dosage was 200mg TID.

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 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 Zerit 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 Zerit, 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/mm³ (range: 0 to 940). For the 11,784 patients who had received Zerit, the median duration of medicine 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 ($p = 0.03$).

5.2 Pharmacokinetic properties

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 $1.44 \pm 0.49 \mu\text{g/mL}$ in the fasting state to $0.75 \pm 0.16 \mu\text{g/mL}$ 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 not 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 0.063µg/mL (0.044-0.071 µg/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 [¹⁴C]-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 Zerit be modified in patients with reduced renal function. (See 4.2 Dose and method of 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.

5.3 Preclinical safety data

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 sternbrae, 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, sodium starch glycolate, lactose and magnesium stearate.

The hard gelatin shell consists of gelatin, methyl and propyl hydroxy benzoates, titanium dioxide and iron oxides.

6.2 Incompatibilities

None.

6.3 Shelf life

Bottle: 36 months

6.4 Special precautions for storage

Zerit capsules should be stored in tightly closed containers below 30°C.

6.5 Nature and contents of container

Capsules:

Zerit (Stavudine) capsules are available in plastic bottles with child-resistant closures or foil pouches in cartons, in the strengths and configurations shown in Section 3.

60 capsules per bottle

56 capsules per carton (not marketed)

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Bristol-Myers Squibb (NZ) Limited
Private Bag 92518
Auckland 1141

Tel: Toll free 0800 167 567

9 DATE OF FIRST APPROVAL

40mg (TT50-5318/1c): 2 September 2004

10 DATE OF REVISION OF THE TEXT

2 June 2017

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections	Updated to SmPC format
4.3	Addition of the contraindication of the co-administration of Zerit with didanosine
4.4	Zerit is associated with several severe side effects, such as lactic acidosis, lipoatrophy and polyneuropathy, for which a potential underlying mechanism is mitochondrial toxicity.
Lactic acidosis	Removal of the text for use of combination of stavudine & didanosine
Fat-redistribution	Replacement of this section with section on “Lipoatrophy” and addition of subsection on Weight and metabolic parameters
4.6	Removal of the text for use of combination of stavudine & didanosine

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