Product Information as approved by the CHMP on 17 February 2011, pending endorsement by the European Commission

Only text for Zerit 15 mg hard capsules is shown. The same changes apply to other strengths.

Deleted text highlighted in ~~**red strikethrough**~~, added text highlighted in **red bold**.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zerit 15 mg hard capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 15 mg of stavudine.

Excipients:
80.84 mg of lactose anhydrous per capsule.
40.42 mg of lactose monohydrate per capsule.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
The hard capsule is red and yellow, opaque and imprinted with "BMS" over a BMS code "1964" on one side and "15" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zerit is indicated in combination with other antiretroviral medicinal products for the treatment of HIV infected **adult** patients **and paediatric patients (over the age of 3 months) only when other antiretrovirals can not be used. The duration of therapy with Zerit should be limited to the shortest time possible (see section 4.2).**

4.2 Posology and method of administration

~~**Posology**~~

The therapy should be initiated by a doctor experienced in the management of HIV infection (see also section 4.4).

~~**For optimal absorption, Zerit should be taken on an empty stomach (i.e. at least 1 hour prior to meals) but, if this is not possible, it may be taken with a light meal. Zerit may also be administered by carefully opening the hard capsule and mixing the contents with food.**~~

For patients starting therapy with Zerit, the duration should be limited to the shortest time possible followed by a switch to an alternative appropriate therapy whenever possible. Patients continuing treatment with Zerit should be assessed frequently and switched to an alternative appropriate therapy whenever possible (see section 4.4).

Posology

Adults: the recommended oral dosage is:

Patient weight	Zerit dosage
< 60 kg	30 mg twice daily (every 12 hours)
≥ 60 kg	40 mg twice daily

Paediatric population:
Adolescents, children and infants over the age of 3 months: the recommended oral dosage is:

Patient weight	Zerit dosage
< 30 kg ≥ 30 kg	1 mg/kg twice daily (every 12 hours) adult dosing

The powder formulation of ZERIT should be used for infants under the age of 3 months. **Adult patients that have problems swallowing capsules should ask their doctor about the possibility of changing to the powder formulation of this medicine.**

Please refer to the Summary of Product Characteristics of the powder formulation.

Dose adjustments

Peripheral neuropathy: if symptoms of peripheral neuropathy develop (usually characterised by persistent numbness, tingling, or pain in the feet and/or hands) (see section 4.4) patients should be switched to an alternative treatment regimen, if appropriate. In the rare cases when this is inappropriate, dose reduction of stavudine may be considered, while the symptoms of peripheral neuropathy are under close monitoring and satisfactory virological suppression is maintained. The possible benefits of a dose reduction should be balanced in each case against the risks - which may result from this measure (lower intracellular concentrations).

Special populations

Elderly: Zerit has not been specifically investigated in patients over the age of 65.

Hepatic impairment: no initial dosage adjustment is necessary.

Renal impairment: the following dosages are recommended:

Patient weight	Zerit dosage (according to creatinine clearance)	
	26-50 ml/min	≤ 25 ml/min (including dialysis dependence*)
< 60 kg	15 mg twice daily	15 mg every 24 hours
≥ 60 kg	20 mg twice daily	20 mg every 24 hours

* Patients on haemodialysis should take Zerit after the completion of haemodialysis, and at the same time on non-dialysis days.

Since urinary excretion is also a major route of elimination of stavudine in paediatric patients, the clearance of stavudine may 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 proportional to the reduction for adults should be considered. **There are no dosage recommendations for paediatric patients under the age of 3 months with renal impairment.**

Method of administration

For optimal absorption, Zerit should be taken on an empty stomach (i.e. at least 1 hour prior to meals) but, if this is not possible, it may be taken with a light meal. Zerit may also be administered by carefully opening the hard capsule and mixing the contents with food.

4.3 Contraindications

Hypersensitivity to ~~stavudine~~**the active substance** or to any of the excipients.

4.4 Special warnings and precautions for use

Stavudine therapy is associated with several severe side effects, such as lactic acidosis, lipoatrophy and polyneuropathy, for which a potential underlying mechanism is mitochondrial toxicity. Given these potential risks, a benefit-risk assessment for each patients should be made and an alternative antiretroviral should be carefully considered (see *Lactic acidosis, Lipodystrophy and metabolic abnormalities,* and *Peripheral neuropathy* below and section 4.8).

Lactic acidosis: lactic acidosis, usually associated with hepatomegaly and hepatic steatosis has been reported with the use of nucleoside reverse transcriptase inhibitors (NRTIs). Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, renal failure, or motor paralysis.
Lactic acidosis generally occurred after a few or several months of treatment.
Treatment with NRTIs should be discontinued if there is symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.
Caution should be exercised when administering NRTIs to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.
Patients at increased risk should be followed closely (see also section 4.6).

Liver disease: hepatitis or liver failure, which was fatal in some cases, has been reported. The safety and efficacy of stavudine has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse **~~events~~reactions**. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

In the event of rapidly elevating transaminase levels (ALT/AST, > 5 times upper limit of normal, ULN), discontinuation of Zerit and any potentially hepatotoxic medicinal products should be considered.

Lipodystrophy and metabolic abnormalities: combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and NRTIs has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances.

In randomized controlled trials of treatment-naive patients, clinical lipoatrophy developed in a higher proportion of patients treated with stavudine compared to other nucleosides (tenofovir or abacavir). Dual energy x-ray absorptiometry (DEXA) scans demonstrated overall limb fat loss in stavudine treated patients compared to limb fat gain or no change in patients treated with other NRTIs (abacavir, tenofovir or zidovudine). The incidence and severity of lipoatrophy are cumulative over time with stavudine-containing regimens. In clinical trials, switching from stavudine to other nucleosides (tenofovir or abacavir) resulted in increases in limb fat with modest to no improvements in clinical lipoatrophy. Given the potential risks of using **~~ZERIT~~ Zerit** including lipoatrophy or lipodystrophy, a benefit-risk assessment for each patient should be made and an alternative antiretroviral carefully considered. Patients receiving Zerit should be frequently examined and questioned for signs of lipoatrophy. When such development is found, discontinuation of Zerit should be considered.

Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

Peripheral neuropathy: up to 20% of patients treated with Zerit will develop peripheral neuropathy, often starting after some months of treatment. Patients with a history of neuropathy, or with other risk factors (for example alcohol, ~~**medications**~~**medicines** such as isoniazid) are at particular risk. Patients should be monitored for symptoms (persistent numbness, tingling or pain in feet/hands) and if present patients should be switched to an alternate treatment regimen (see section 4.2 and Not recommended combinations, below).

Pancreatitis: patients with a history of pancreatitis had an incidence of approximately 5% on Zerit, as compared to approximately 2% in patients without such a history. Patients with a high risk of pancreatitis or those receiving products known to be associated with pancreatitis should be closely followed for symptoms of this condition.

Immune reactivation syndrome: in HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), 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 initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis carinii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Osteonecrosis: although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Not recommended combinations: pancreatitis (fatal and nonfatal) and peripheral neuropathy (severe in some cases) have been reported in HIV infected patients receiving stavudine in association with hydroxyurea and didanosine. Hepatotoxicity and hepatic failure resulting in death were reported during postmarketing surveillance in HIV infected patients treated with antiretroviral agents and hydroxyurea; fatal hepatic events were reported most often in patients treated with stavudine, hydroxyurea and didanosine. Hence, hydroxyurea should not be used in the treatment of HIV infection.

~~***Lactose intolerance:* the hard capsule contains lactose (120 mg). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicine.**~~

Elderly: Zerit has not been specifically investigated in patients over the age of 65.

Paediatric population

Infants under the age of 3 months: safety data are available from clinical trials up to 6 weeks of treatment in 179 newborns and infants < 3 months of age (see section 4.8).
Special consideration should be given to the antiretroviral treatment history and the resistance profile of the HIV strain of the mother.

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 (see also section 4.8). The main adverse ~~**events**~~**reactions** reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). 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, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Lactose intolerance: **the hard capsule contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicine.**

4.5 Interaction with other medicinal products and other forms of interaction

Since stavudine is actively secreted by the renal tubules, interactions with other actively secreted medicinal products are possible, e.g. with trimethoprim. No clinically relevant pharmacokinetic interaction has, however, been seen with lamivudine.

Zidovudine and stavudine are phosphorylated 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.

In vitro studies indicate that the activation of stavudine is inhibited by doxorubicin and ribavirin but not by other medicinal products used in HIV infection which are similarly phosphorylated, (e.g. didanosine, zalcitabine, ganciclovir and foscarnet) therefore, coadministration of stavudine with either doxorubicin or ribavirin should be undertaken with caution. Stavudine's influence on the phosphorylation kinetics of nucleoside analogues other than zidovudine has not been investigated.

Clinically significant interactions of stavudine or stavudine plus didanosine with nelfinavir have not been observed.

Stavudine does not inhibit the major cytochrome P450 isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4; therefore, it is unlikely that clinically significant drug interactions will occur with ~~**drugs**~~**medicines** metabolised through these pathways.

Because stavudine is not protein-bound, it is not expected to affect the pharmacokinetics of protein-bound ~~**drugs**~~**medicines**.

There have been no formal interaction studies with other medicinal products.

Paediatric population

Interaction studies have only been performed in adults

4.6 Fertility, pregnancy and lactation

Pregnancy

Zerit should not be used during pregnancy unless clearly necessary.
Clinical experience in pregnant women is limited, but congenital anomalies and abortions have been reported.

In study AI455-094, performed in South-Africa, 362 mother-infant pairs were included in a prevention of mother-to-child-transmission study. Treatment naive pregnant women were enrolled into the study at gestation week 34-36 and given antiretroviral treatment until delivery. Antiretroviral prophylaxis, the same medications as given to the mother, was given to the new-born infant within 36 hours of delivery and continued for 6 weeks. In the stavudine containing arms, the neonates were treated for 6 weeks with stavudine 1 mg/kg BID. The follow-up time was up to 24 weeks of age.

The mother-infant pairs were randomised to receive either stavudine (N= 91), didanosine (N= 94), stavudine + didanosine (N= 88) or zidovudine (N= 89).
95% Confidence intervals for the mother-to-child-transmission rates were 5.4-19.3% (stavudine), 5.2-18.7% (didanosine); 1.3-11.2% (stavudine + didanosine); and 1.9-12.6% for zidovudine.

Preliminary safety data from this study (see also section 4.8), showed an increased infant mortality in the stavudine + didanosine (10%) treatment group compared to the stavudine (2%), didanosine (3%) or zidovudine (6%) groups, with a higher incidence of stillbirths in the stavudine + didanosine group. Data on lactic acid in serum were not collected in this study.

However, lactic acidosis (see section 4.4), sometimes fatal, has been reported in pregnant women who received the combination of didanosine and stavudine with or without other anti-retroviral treatment. Embryo-foetal toxicities were seen only at high exposure levels in animals. Preclinical studies showed placental transfer of stavudine (see section 5.3). Until additional data become available, Zerit should be given during pregnancy only after special consideration; there is insufficient information to recommend Zerit for prevention of mother-to-child transmission of HIV. Furthermore, 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.

Breastfeeding

It is recommended that HIV infected women should not breast-feed under any circumstances in order to avoid transmission of HIV.
The data available on stavudine excretion into human breast milk are insufficient to assess the risk to the infant. Studies in lactating rats showed that stavudine is excreted in breast milk. Therefore, mothers should be instructed to discontinue breast-feeding prior to receiving Zerit.

Fertility

No evidence of impaired fertility was seen in rats at high exposure levels (up to 216 times that observed at the recommended clinical dose).

4.7 Effects on ability to drive and use machines

~~**Based on the pharmacodynamic properties of stavudine it is unlikely that Zerit affects the ability to drive or operate machinery.**~~
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

a. Summary of the safety profile

Stavudine therapy is associated with several severe ~~**side effects**~~**adverse reactions**, such as lactic acidosis, lipoatrophy and polyneuropathy, for which a potential underlying mechanism is mitochondrial toxicity. Given these potential risks, a benefit-risk assessment for each patient should be made and an alternative antiretroviral should be carefully considered (see section 4.4 and below).

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported in < 1% of patients taking stavudine in combination with other antiretrovirals (see section 4.4).

Motor weakness has been reported rarely in patients receiving combination antiretroviral therapy including Zerit. Most of these cases occurred in the setting of symptomatic hyperlactatemia or lactic

acidosis syndrome (see section 4.4). The evolution of motor weakness may mimic the clinical presentation of Guillain-Barré syndrome (including respiratory failure). Symptoms may continue or worsen following discontinuation of therapy.

Hepatitis or liver failure, which was fatal in some cases, has been reported with the use of stavudine and with other nucleoside analogues (see section 4.4).

Lipoatrophy was commonly reported in patients treated with stavudine in combination with other antiretrovirals (see section 4.4).

Peripheral neuropathy was seen in combination studies of Zerit with lamivudine plus efavirenz; the frequency of peripheral neurologic symptoms was 19% (6% for moderate to severe) with a rate of discontinuation due to neuropathy of 2%. The patients usually experienced resolution of symptoms after dose reduction or interruption of stavudine.

Pancreatitis, occasionally fatal, has been reported in up to 2-3% of patients enrolled in monotherapy clinical studies (see section 4.4). Pancreatitis was reported in < 1% of patients in combination therapy studies with Zerit.

b. Tabulated summary of adverse reactions

Adverse reactions ~~-~~of moderate or greater severity with at least a possible relationship to treatment regimen (based on investigator attribution) reported from 467 patients treated with Zerit in combination with lamivudine and efavirenz in two randomised clinical trials and along-term follow-up study (follow-up: median 56 weeks ranging up to 119 weeks) are listed below. Also listed are adverse reactions observed post-marketing in association with stavudine-containing antiretroviral treatment~~—~~. The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 **to** < 1/10); uncommon (≥ 1/1,000 **to** < 1/100); rare (≥ 1/10,000 **to** < 1/1,000); very rare (< 1/10,000)**~~; or not known (cannot be estimated from the available data)~~**. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders:	~~**frequency not known**~~ **rare**: anaemia* **very rare: neutropenia** *, thrombocytopenia~~**, neutropenia***~~*
Endocrine disorders:	uncommon: gynaecomastia
Metabolism and nutrition disorders:	common: lipoatrophy**, lipodystrophy**, asymptomatic hyperlactatemia~~,~~ uncommon: lactic acidosis (in some cases involving motor weakness), anorexia ~~**frequency not known**~~ **rare: hyperglycaemia*** **very rare**: diabetes mellitis~~**, hyperglycaemia***~~
Psychiatric disorders:	common: depression uncommon: anxiety, emotional lability
Nervous system disorders:	common: peripheral neurologic symptoms including peripheral neuropathy, paresthesia, and peripheral neuritis; dizziness; abnormal dreams; headache, insomnia; abnormal thinking; somnolence ~~**frequency not known**~~ **very rare**: motor weakness* (most often reported in the setting of symptomatic hyperlactatemia or lactic acidosis syndrome)
Gastrointestinal disorders:	common: diarrhoea, abdominal pain, nausea, dyspepsia uncommon: pancreatitis, vomiting
Hepatobiliary disorders:	uncommon: hepatitis or jaundice ~~**frequency not known: liver failure, hepatitis and**~~ **rare:** hepatic steatosis * **very rare: liver failure***
Skin and subcutaneous tissue disorders:	common: rash, pruritus uncommon: urticaria
Musculoskeletal and connective tissue disorders:	uncommon: arthralgia, myalgia
General disorders and administration site conditions:	common: fatigue uncommon: asthenia

*** adverse reactions observed post-marketing in association with stavudine-containing antiretroviral treatment**

** See Section ***c. Description of selected adverse reactions*** for more details.

c. Description of selected adverse reactions

Immune reactivation syndrome: in HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4).

*Lipodystrophy and metabolic abnormalities***:** combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump). In randomized controlled trials of treatment-naive patients, clinical lipoatrophy developed in a higher proportion of patients treated with stavudine compared to other NRTIs (tenofovir or abacavir). In one study, after 2 years of treatment, about 40%

of stavudine-treated patients had lost greater than 20% of limb fat and after 3 years the amount of limb fat was only about half of the normal amount (4.5 kg vs about 8 kg).. The incidence and severity of lipoatrophy are cumulative over time; lipoatrophy may affect most patients with time and is often not reversible when stavudine treatment is stopped (see section 4.4).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

Osteonecrosis: cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Laboratory abnormalities
Laboratory abnormalities reported in these two trials and an ongoing follow-up study included elevations of ALT (> 5 x ULN) in 3%, of AST (> 5 x ULN) in 3%, of lipase (≥ 2.1 ULN) in 3% of the patients in the Zerit group. Neutropenia (< 750 cells/mm^3) was reported in 5%, thrombocytopenia (platelets < 50,000/mm^3) in 2%, and low haemoglobin (< 8 g/dl) in < 1% of patients receiving Zerit. Macrocytosis was not evaluated in these trials, but was found to be associated with Zerit in an earlier trial (MCV > 112 fl occurred in 30% of patients treated with Zerit).

d. Paediatric population

Adolescents, children and infants: ~~undesirable effects~~ **adverse reactions** and serious laboratory abnormalities reported to occur in paediatric patients ranging in age from birth through adolescence who received stavudine in clinical studies were generally similar in type and frequency to those seen in adults. However, clinically significant peripheral neuropathy is less frequent. These studies include ACTG 240, where 105 paediatric patients ages 3 months to 6 years received Zerit 2 mg/kg/day for a median of 6.4 months; a controlled clinical trial where 185 newborns received Zerit 2 mg/kg/day either alone or in combination with didanosine from birth through 6 weeks of age; and a clinical trial where 8 newborns received Zerit 2 mg/kg/day in combination with didanosine and nelfinavir from birth through 4 weeks of age.

In study AI455-094 (see also section 4.6), the safety follow-up period was restricted to only six months, which may be insufficient to capture long-term data on neurological adverse events and mitochondrial toxicity. Relevant grade 3-4 laboratory abnormalities in the 91 stavudine treated infants were low neutrophils in 7%, low hemoglobin in 1%, ALT increase in 1% and no lipase abnormality. Data on lactic acid in serum were not collected. No notable differences in the frequency of adverse drug reactions were seen between treatment groups. There was, however, an increased infant mortality in the stavudine + didanosine (10%) treatment group compared to the stavudine (2%), didanosine (3%) or zidovudine (6%) groups, with a higher incidence of stillbirths in the stavudine + didanosine group.

Mitochondrial dysfunction: review of the postmarketing safety database shows that adverse ~~events~~ **reactions** indicative of mitochondrial dysfunction have been reported in the neonate and infant population exposed to one or more nucleoside analogues (see also section 4.4). The HIV status for the newborns and infants ≤ 3 months of age was negative, for older infants it tended to be positive. The profile of the adverse events for newborns and infants ≤ 3 months of age showed increases in lactic acid levels, neutropenia, anaemia, thrombocytopenia, hepatic transaminase increases and increased lipids, including hypertriglyceridaemia. The number of reports in older infants was too small to identify a pattern.

4.9 Overdose

Experience in adults treated with up to 12 times the recommended daily dosage revealed no acute toxicity. Complications of chronic overdosage could include peripheral neuropathy and hepatic dysfunction. The mean haemodialysis clearance of stavudine is 120 ml/min. The contribution of this to

the total elimination in an overdose situation is unknown. It is not known whether stavudine is removed by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ~~**Nucleoside**~~ **antivirals for systemic use, nucleoside and nucleotide** reverse transcriptase inhibitor**s**, ATC code: J05AF04

Mechanism of action: stavudine, a thymidine analogue, is phosphorylated by cellular kinases to stavudine triphosphate which inhibits HIV reverse transcriptase by competing with the natural substrate, thymidine 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. Cellular DNA polymerase γ is also sensitive to inhibition by stavudine triphosphate, while cellular polymerases α and β are inhibited at concentrations 4,000-fold and 40-fold higher, respectively, than that needed to inhibit HIV reverse transcriptase.

Resistance: stavudine treatment can select for and/or maintain thymidine analogue mutations (TAMs) associated with zidovudine resistance. The decrease of susceptibility *in vitro* 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 suggest that stavudine should be generally avoided in the presence of TAMs, especially M41L and T215Y.
The activity of stavudine is also affected by multi-drug resistance associated mutations such as Q151M. In addition, K65R has been reported in patients receiving stavudine/didanosine or stavudine/lamivudine, but not in patients receiving stavudine monotherapy. V75T is selected *in vitro* by stavudine and reduces susceptibility to stavudine by 2-fold. It occurs in ~1% of patients receiving stavudine.

Clinical efficacy

Zerit has been studied in combination with other antiretroviral agents, e.g. didanosine, lamivudine, ritonavir, indinavir, saquinavir, efavirenz, and nelfinavir.

In antiretroviral naive patients
Study AI455-099 was a 48-week, randomised, double-blind study with Zerit (40 mg twice daily), in combination with lamivudine (150 mg twice daily) plus efavirenz (600 mg once daily), in 391 treatment-naive patients, with a median CD4 cell count of 272 cells/mm^3 (range 61 to 1,215 cells/mm^3) and a median plasma HIV-1 RNA of 4.80 log_{10} copies/ml (range 2.6 to 5.9 log_{10} copies/ml) at baseline. Patients were primarily males (70%) and non-white (58%) with a median age of 33 years (range 18 to 68 years).

Study AI455-096 was a 48-week, randomised, double-blind study with Zerit (40 mg twice daily), in combination with lamivudine (150 mg twice daily) plus efavirenz (600 mg once daily), in 76 treatment-naive patients, with a median CD4 cell count of 261 cells/mm^3 (range 63 to 962 cells/mm^3) and a median plasma HIV-1 RNA of 4.63 log_{10} copies/ml (range 3.0 to 5.9 log_{10} copies/ml) at baseline. Patients were primarily males (76%) and white (66%) with a median age of 34 years (range 22 to 67 years).

The results of AI455-099 and AI455-096 are presented in Table 1. Both studies were designed to compare two formulations of Zerit, one of which was the marketed formulation dosed as currently approved in product labelling. Only the data from the marketed formulation are presented.

Table 1: Efficacy Outcomes at Week 48 (Studies AI455-099 and AI455-096)

Parameter	AI455-099 Zerit + lamivudine + efavirenz **n=391**	AI455-096 Zerit + lamivudine + efavirenz **n=76**
HIV RNA < 400 copies/ml, treatment response, %		
All patients	73	66
HIV RNA < 50 copies/ml, treatment response, %		
All patients	55	38
HIV RNA Mean Change from Baseline, log_{10} copies/ml		
All patients	-2.83 (n=321[a])	-2.64 (n=58)
CD4 Mean Change from Baseline, cells/mm^3		
All patients	182 (n=314)	195 (n=55)

[a] Number of patients evaluable.

Paediatric population

The use of stavudine in adolescents, children and infants is supported by pharmacokinetic and safety data in paediatric patients (see also sections 4.8 and 5.2).

5.2 Pharmacokinetic properties

Adults

Absorption: the absolute bioavailability is 86±18%. After multiple oral administration of 0.5-0.67 mg/kg doses, a C_{max} value of 810±175 ng/ml was obtained. C_{max} and AUC increased proportionally with dose in the dose ranges, intravenous 0.0625-0.75 mg/kg, and oral 0.033-4.0 mg/kg. In eight patients receiving 40 mg twice daily in the fasted state, steady-state AUC_{0-12h} was 1284±227 ng·h/ml (18%) (mean ± SD [% CV]), C_{max} was 536±146 ng/ml (27%), and C_{min} was 9±8 ng/ml (89%). A study in asymptomatic patients demonstrated that systemic exposure is similar while C_{max} is lower and T_{max} is prolonged when stavudine is administered with a standardised, high-fat meal compared with fasting conditions. The clinical significance of this is unknown.

Distribution: the apparent volume of distribution at steady state is 46±21 l. It was not possible to detect stavudine in cerebrospinal fluid until at least 2 hours after oral administration. Four hours after administration, the CSF/plasma ratio was 0.39±0.06. No significant accumulation of stavudine is observed with repeated administration every 6, 8, or 12 hours.
Binding of stavudine to serum proteins was negligible over the concentration range of 0.01 to 11.4 µg/ml. Stavudine distributes equally between red blood cells and plasma.

Metabolism: Unchanged stavudine was the major drug-related component in total plasma radioactivity circulating after an oral 80 mg dose of ^{14}C-stavudine in healthy subjects. The AUC(*inf*) for stavudine was 61% of the AUC(*inf*) of the total circulating radioactivity. Metabolites include oxidised stavudine, glucuronide conjugates of stavudine and its oxidised metabolite, and an *N*-acetylcysteine conjugate of the ribose after glycosidic cleavage, suggesting that thymine is also a metabolite of stavudine.

Elimination: following an oral 80-mg dose of ^{14}C-stavudine to healthy subjects, approximately 95% and 3% of the total radioactivity was recovered in urine and faeces, respectively. Approximately 70% of the orally administered stavudine dose was excreted as an unchanged drug in urine. Mean renal clearance of the parent compound is approximately 272 ml/min, accounting for approximately 67% of the apparent oral clearance, indicating active tubular secretion in addition to glomerular filtration.

In HIV-infected patients,total clearance of stavudine is 594±164 ml/min, and renal clearance is 237±98 ml/min. The total clearance of stavudine appears to be higher in HIV-infected patients, while the renal clearance is similar between healthy subjects and HIV-infected patients. The

mechanism and clinical significance of this difference are unknown. After intravenous administration, 42% (range: 13% to 87%) of dose is excreted unchanged in the urine. The corresponding values after oral single and multiple dose administration are 35% (range: 8% to 72%) and 40% (range: 12% to 82%), respectively. The mean terminal elimination half-life of stavudine is 1.3 to 2.3 hours following single or multiple doses, and is independent of dose. *In vitro*, stavudine triphosphate has an intracellular half-life of 3.5 hours in CEM T-cells (a human T-lymphoblastoid cell line) and peripheral blood mononuclear cells, supporting twice daily dosing.
The pharmacokinetics of stavudine was independent of time, since the ratio between $AUC_{(ss)}$ at steady state and the $AUC_{(0-t)}$ after the first dose was approximately 1. Intra- and interindividual variation in pharmacokinetic characteristics of stavudine is low, approximately 15% and 25%, respectively, after oral administration.

Special Populations

Renal impairment: the clearance of stavudine decreases as creatinine clearance decreases; therefore, it is recommended that the dosage of Zerit be adjusted in patients with reduced renal function (see section 4.2).

Hepatic impairment: stavudine pharmacokinetics in patients with hepatic impairment were similar to those in patients with normal hepatic function.

Paediatric population

Adolescents, children and infants: total exposure to stavudine was comparable between adolescents, children and infants ≥ 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%).

5.3 Preclinical safety data

Animal data showed embryo-foetal toxicity at very high exposure levels. An *ex vivo* study using a term human placenta model demonstrated that stavudine reaches the foetal circulation by simple diffusion. A rat study also showed placental transfer of stavudine, with the foetal tissue concentration approximately 50% of the maternal plasma concentration.
Stavudine was genotoxic in *in vitro* tests in human lymphocytes possessing triphosphorylating activity (in which no no-effect level was established), in mouse fibroblasts, and in an *in vivo* test for chromosomal aberrations. Similar effects have been observed with other nucleoside analogues.
Stavudine was carcinogenic in mice (liver tumours) and rats (liver tumours: cholangiocellular, hepatocellular, mixed hepatocholangiocellular, and/or vascular; and urinary bladder carcinomas) at very high exposure levels. No carcinogenicity was noted at doses of 400 mg/kg/day in mice and 600 mg/kg/day in rats, corresponding to exposures ~ 39 and 168 times the expected human exposure, respectively, suggesting an insignificant carcinogenic potential of stavudine in clinical therapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Lactose
Magnesium stearate
Microcrystalline cellulose
Sodium starch glycolate

Capsule shell:
Gelatin
Iron oxide colorant (E172)
Silicon dioxide
Sodium laurilsulphate
Titanium dioxide (E171)

The capsule shells are marked using edible black printing ink containing:
Shellac
Propylene Glycol
Purified Water
Potassium Hydroxide
Iron Oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25°C (aclar/alu blisters)
Do not store above 30°C. (HDPE bottles)
Store in the original package.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottles with child resistant screw cap (60 hard capsules per bottle), or

aclar/aluminum blisters with 14 hard capsules per card and 4 cards (56 hard capsules) per carton.

Not all packsizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/009/001 - 002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 May 1996
Date of last renewal: 08 ~~**June**~~ **May** 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bristol-Myers Squibb S.r.l., Contrada Fontana del Ceraso, 03012 Anagni (FR), Italy

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

Periodic Safety Update Reports (PSUR's): **The PSUR will be submitted on a two years basis until otherwise agreed by the CHMP.**
~~**The Marketing Authorisation Holder will submit yearly PSUR's**~~

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.
~~**The MAH must ensure that the system of pharmacovigilance, as described in version 3.5 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.**~~

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan of a Risk Management Plan (RMP) presented to be submitted within one month from the Commission decision in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:
- **When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities**
- **Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached**
- **At the request of the European Medicines Agency**

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT (BLISTER)

1. NAME OF THE MEDICINAL PRODUCT

Zerit 15 mg hard capsules
Stavudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 15 mg stavudine.

3. LIST OF EXCIPIENTS

Lactose and colorants (E171, E172)

4. PHARMACEUTICAL FORM AND CONTENTS

56 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.
Store in the original package.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/009/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zerit 15 mg

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Zerit 15 mg hard capsules
Stavudine

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 any further questions, ask your doctor 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.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ZERIT IS AND WHAT IT IS USED FOR

Zerit belongs to a **particular** group of antiviral medicines, also known as antiretrovirals, called nucleoside reverse transcriptase inhibitors (NRTIs).

These are used to treat Human Immunodeficiency Virus (HIV) infection.

This medicinal product, in combination with other antiretrovirals, reduces the HIV viral load and keeps it at a low level. It also increases CD4 cell counts. These CD4 cells play an important role in maintaining a healthy immune system to help fight infection. Response to treatment with Zerit varies between patients. Your doctor will therefore be monitoring the effectiveness of your treatment.

Zerit may improve your condition, but it is not a cure for your HIV infection. Treatment with Zerit 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 virus to others.
During ~~**your**~~ treatment, other infections linked to ~~**your**~~ **a** weakened immunity (opportunistic infections) may arise. These will require specific and sometimes preventive treatment.

2. BEFORE YOU TAKE ZERIT

Do not take Zerit:
If you are allergic (hypersensitive) to stavudine or any of the other ingredients of Zerit. Contact your doctor or pharmacist for advice.

Take special care with Zerit:
Before treatment with Zerit, you should have told your doctor:
- if you suffer from kidney disease or liver disease (such as hepatitis),
- if you have had peripheral neuropathy (persistent numbness, tingling, or pain in the feet and/or hands), or
- if you have suffered from pancreatitis (inflammation of the pancreas).

The class of medicines to which Zerit belongs (NRTIs) can cause a sometimes fatal condition called lactic acidosis, together with an enlarged liver. This condition usually does not occur until a few

months after onset of treatment. This rare, but very serious side effect occurs more often in women, particularly if very overweight. In addition, rare cases of liver failure/renal failure or fatal hepatitis have been reported.
Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver ~~adverse events~~ **side effects** and may require blood tests for control of liver function.

If you develop one of the following, contact your doctor:
- persistent numbness, tingling or pain in feet and/or hands (this may indicate the beginning of peripheral neuropathy, an adverse effect on the nerves), muscular weakness or
- abdominal pain, nausea or vomiting, or
- rapid deep breathing, drowsiness (which may indicate pancreatitis, liver disturbance such as hepatitis, or lactic acidosis).

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from 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, please inform your doctor immediately.

Redistribution, accumulation, or loss of body fat may occur in patients receiving ~~antiretroviral therapy.~~ **Zerit.** Some NRTIs, such as ~~stavudine~~ **Zerit**, have been associated with a loss of body fat (lipoatrophy). Contact your doctor if you notice changes in body fat.

Bone problems: some patients taking ~~combination antiretroviral therapy~~ **Zerit** may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Except for zidovudine~~, which interferes with the activity of stavudine~~ **and didanosine**, Zerit may be taken with many of the other medicines commonly used in patients with HIV infection. These include the protease inhibitors (such as nelfinavir) and NRTIs. Please tell your doctor if you are taking **hydroxyurea,** doxorubicin or ribavirin as undesirable interactions may occur.

Taking Zerit with food and drink:
For maximum effect, Zerit should be taken on an empty stomach, and preferably at least one hour before a meal. If this is not possible, the capsules may also be taken with a light meal.

Pregnancy and breast-feeding:
Pregnancy
If you become pregnant, or are planning to become pregnant, you must contact your doctor to discuss the potential ~~adverse~~ **side** 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~~ **Zerit** in combination with other antiretroviral treatment.
If you have taken Zerit during your pregnancy, your doctor may request regular visits to monitor the development of your child. Such visits may include blood tests and 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.**~~

Breast-feeding
Tell your doctor if you are breast-feeding. It is recommended that HIV-infected women should not breast-feed under any circumstances in order to avoid transmission of HIV to the baby.

Driving and using machines:
~~**It is unlikely that Zerit affects the ability to drive or operate machinery.**~~
Zerit may cause dizziness and drowsiness.
If you are affected, do not drive and do not use any tools or machines.

Important information about some of the ingredients of Zerit:
These capsules contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE ZERIT

Always take Zerit exactly as your doctor has told you. You should check with your doctor if you are not sure. Your doctor has defined your daily dose based on your weight and individual characteristics. Please follow these recommendations closely as they will give you the best chance to delay development of a resistance to the medicinal product. Do not change the dose on your own. Continue to take this medicine until your doctor tells you otherwise.
For adults whose body weight is 30 kg or more, the usual starting dose is 30 or 40 mg given twice daily (with approximately 12 hours between each dose).
To obtain optimal absorption, the capsules should be swallowed with a glass of water, preferentially at least one hour before a meal and on an empty stomach. If this is not possible, Zerit may also be taken with a light meal.
If you have problems swallowing capsules you should ask your doctor about the possibility of changing to the solution form of this medicine or you could carefully open the capsule and mix its contents with some food.

Use in Children
For children whose body weight is 30 kg or more, the usual starting dose is 30 or 40 mg given twice daily (with approximately 12 hours between each dose).
Children older than 3 months, whose body weight is less than 30 kg, should receive 1 mg/kg twice daily.

If you take more Zerit than you should:
If you have taken too many capsules or if someone accidentally swallows some, there is no immediate danger. However, you should contact your doctor or the nearest hospital for advice.

If you forget to take Zerit:
If you accidentally miss a dose, then simply take your normal dose when the next one is due. Do not take a double dose to make up for a forgotten dose.

If you stop taking Zerit:
The decision to stop using Zerit should be discussed with your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Zerit 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 Zerit, or those caused by any other medicines you may be taking at the same time, or by the

complications of the infection. For this reason, it is important that you inform your doctor of any change in your health.

Therapy for HIV including stavudine often causes changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face (lipoatrophy), and development of fatty lumps on the back of the neck ("buffalo hump"). Loss of body fat has been shown to be not fully reversible after discontinuation of stavudine. It occurs more often with Zerit compared to other HIV medicines. Your doctor should monitor for clinical signs and symptoms of changes in your body shape. Tell your doctor if you notice any changes in your body shape or loss of fat from your legs, arms, and face. When these signs occur, consideration should be given to discontinuing ZERIT treatment.

The frequency of possible side effects listed below is defined using the following convention:

very common:	affects more than 1 user in 10
common:	affects 1 to less than 10 users in 100
uncommon:	affects 1 to less than 10 users in 1,000
rare:	affects 1 to less than 10 users in 10,000
very rare:	affects less than 1 user in 10,000
~~**not known:**~~	~~**frequency cannot be estimated from the available data**~~

Patients treated with Zerit have reported the following side effects:
Common:

- asymptomatic hyperlactatemia (build up of acid in your blood)
- lipoatrophy or lipodystrophy syndrome (body changes due to fat redistribution, accumulation, or loss of body fat),
- depression
- ~~**peipheral**~~ **peripheral** neurologic symptoms including peripheral neuropathy, paresthesia, and peripheral neuritis (numbness, weakness, tingling or pain in the arms and legs)
- dizziness, abnormal dreams, headache
- insomnia (difficulty sleeping), somnolence (sleepiness), abnormal thinking~~,~~
- diarrhoea, abdominal pain (stomach pain of discomfort),
- nausea, dyspepsia (indigestion)
- rash, pruritus (itching)
- fatigue (extreme tiredness)

Uncommon:

- lactic acidosis (build up of acid in your blood) in some cases involving motor weakness (weakness in your arms, legs or hands)
- gynaecomastia (breast enlargement in men)
- anorexia (loss of appetite), anxiety, emotional lability
- pancreatitis (inflammation of the pancreas), vomiting
- hepatitis **(inflamation of the liver)**, jaundice (yellow of the skin or eyes)
- urticaria (itchy rash), arthralgia (joint pain)
- myalgia (aching muscles), asthenia (unusual tiredness or weakness)

~~**Frequency not known:**~~
Rare

- anemia~~**, thrombocytopenia, neutropenia (blood disorders)**~~
- ~~**diabetes mellitis,**~~ hyperglycaemia (high sugar levels in the blood)
- **hepatic steatosis (fat in the liver)**

Very rare

- **thrombocytopenia, neutropenia (blood disorders)**

- **diabetes mellitis**
- motor weakness (most often reported in the setting of symptomatic hyperlacetatemia or lactic acidosis syndrome**)**
- liver failure~~, hepatitis (inflamation of the liver) and hepatic steatosis (fat in the liver)~~

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell you doctor or pharmacist.

5. HOW TO STORE ZERIT

Keep out of the reach and sight of children.

~~**Store below 25°C (aclar/alu blisters)**~~
~~**Do not store above 30°C. (HDPE bottles)**~~
~~**Store in the original package.**~~

Do not use Zerit after the expiry date which is stated on the carton, the bottle label and/or the blister after EXP. The expiry date refers to the last day of that month.

Store below 25°C (aclar/alu blisters)
Do not store above 30°C. (HDPE bottles)
Store in the original package.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Zerit contains

- The active substance is stavudine **(15 mg)**
- The other ingredients of the powder contained in the hard capsule are: lactose (120 mg), magnesium stearate, microcrystalline cellulose and sodium starch glycolate.
- The ingredients of the capsule shell are gelatine, iron oxide colorant (E172), silicon dioxide, sodium laurilsulphate and titanium dioxide colorant (E171).
- The capsule shells are marked using edible black printing ink containing shellac, propylene glycol, purified water, potassium hydroxide and iron oxide (E172).

What Zerit looks like and content of the pack

Zerit 15 mg hard capsules are red and yellow and marked with “BMS 1964” on one side and “15” on the other side.
Zerit 15 mg hard capsules are supplied in blister packs of 56 hard capsules or bottles of 60 hard capsules. To help protect the capsules from excessive moisture, the bottle includes a desiccant canister.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

Manufacturer:
Bristol-Myers Squibb S.r.l.
Contrada Fontana del Ceraso
03012 Anagni (FR) - Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last approved in {month year}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.