SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Zerit. This scientific discussion has been updated until 1 September 2005. For information on changes after this date please refer to module 8B.

1. Introduction

Zerit contains the active substance stavudine, a antiviral agent, which inhibits the replication of the Human Immunodeficiency Virus (HIV) in human cells *in vitro*. Stavudine is a thymidine 2'-deoxynucleoside analogue. It is structurally similar to three other drugs which had been previously approved for the treatment of HIV disease: ZDV (zidovudine), ddC (zalcitabine) and ddI (didanosine). All of these compounds act as inhibitors of HIV reverse transcriptase and of viral DNA synthesis.
Zerit is presented either as a capsule in four strengths or as a powder for oral solution.
Zerit capsules are supplied in strengths containing 15 mg, 20 mg, 30 mg and 40 mg of stavudine. The composition of the capsules is virtually identical, differing only with respect to the capsule shell colour by use of iron oxide dyes (red, yellow and/or black) and titanium dioxide. Capsules are packaged in white high-density polyethylene bottles with a child resistant screw cap (60 capsules per bottle) or in blister pack with 14 capsules per strip and 4 strips (56 capsules) per carton.
Zerit powder for oral solution is supplied in one strength, which provides 1 mg of stavudine per ml of reconstituted solution (200 ml per bottle). The container consists of a high-density polyethylene bottle with a child resistant screw cap, and a fill mark (200 ml of solution after reconstitution). A 30 ml measuring cup is supplied in the cardboard carton.
Zerit 37.5 mg, 50 mg, 75 mg and 100 mg prolonged release hard capsules were approved in November 2002. In February 2005, the Marketing Authorisation Holder requested to withdraw the marketing authorisation of Zerit prolonged-release hard capsules for manufacturing reasons.
Zerit is indicated in combination with other antiretroviral medicinal products for the treatment of HIV infected patients.

2. Chemical, pharmaceutical and biological aspects

Stavudine is a chiral molecule with four possible stereoisomers of which the one used has the 1'*R*, 4'S configuration at the two stereogenic centres. This is equivalent to the ß-D-configuration of the anomeric carbon of the sugar moiety.
The synthesis of stavudine involves four steps starting from ß-D-thymidine, for which one of the three stereogenic centres is removed during synthesis.
The enantiomeric purity of the active substance is dependent on the purity of the starting material, thymidine. The specifications for thymidine only contain tests for specific rotation and it is not known whether these methods are appropriate to detect enantiomeric impurities. Therefore the applicant provided additional information on the methods and specifications applied in assessing the enantiomeric purity of the active substance. The routine controls of thymidine and stavudine themselves were considered insufficient to ensure enantiomeric purity to accommodate future changes of sources of thymidine. To resolve this issue, the vendors of the starting material committed themselves to the applicant that he will be kept abreast of eventual manufacturing changes introduced. In addition, in the event of a change in the process for a new vendor (ß-D-thymidine), the applicant will perform a full qualification, including enantiomeric purity, of this new ß-D-thymidine. Further data from the applicant have shown that the manufacturing process produces stavudine exclusively.
The hydrolytic degradation of stavudine has also caused some concerns, as it is the main degradation pathway during the synthesis, purification, formulation and product shelf-life. Clarification was requested regarding the mass balance of the hydrolysis of stavudine in the solid state, also to avoid an overestimation of the purity of the stavudine reference standard. Regarding the carbohydrate mass balance upon degradation of stavudine, the lack of data has been accepted considering the complicated chemistry involved and the efforts made to elucidate it. Alternative methods used to confirm the purity of the reference standard were considered relevant although the applicant was asked to present at the hearing details on these methods and results obtained. Data obtained from 400 MHz Proton Nuclear Magnetic Resonance (NMR) Spectroscopy have demonstrated the validity of the assignment of the

purity of the reference standard by HPLC. Therefore the purity of the reference standard would make it possible to detect significant amount of the carbohydrate degradants.
During discussion following the hearing, the applicant agreed on a tightening of the release specifications for thymine.
Since the use of wet granulation resulted in hydrolytic degradation on storage at elevated temperatures, **Zerit capsules** are manufactured using standard excipients and a dry granulation process (slugging or roller-compaction) and then milling, followed by encapsulation.
It has been demonstrated that capsules containing 5 mg, 10 mg, 20 mg and 40 mg exhibited an equivalent *in vitro* dissolution profile. Although capsules used in clinical trials differed in composition, the bioavailability is considered unlikely to be affected because of the high water solubility of stavudine (>83 mg/ml).
Zerit powder for oral solution is manufactured according to a conventional manufacturing process for this pharmaceutical form. During the assessment procedure of the application, the applicant was requested to confirm the uniformity of individual doses delivered by the dosing device to be used with the reconstituted oral solution. The results submitted showed a satisfactory deviation of no more than 2% of the deliverable volume from any of the markings on the cup. During discussion following the hearing, the applicant agreed on the specifications (at release and shelf-life) of both preservatives (methylparaben and isopropylparaben) in this formulation.
Concerning the Spray-Dried Cherry Flavour (FMC 20194), the further documentation submitted describing the chromatographic method used for the identification of the main constituents is satisfactory.
For both pharmaceutical forms, results of stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

3. Toxico-pharmacological aspects

Stavudine, a thymidine nucleoside analogue, *in vitro* exhibits an anti-retroviral activity against both HIV-1 and HIV-2. Stavudine is phosphorylated by cellular kinases to stavudine triphosphate which exerts antiviral activity. Stavudine triphosphate inhibits HIV replication by the two following mechanisms:

- It inhibits HIV reverse transcriptase (RT) by competing with the natural substrate, thymidine triphosphate.
- It inhibits viral DNA synthesis by causing DNA chain termination.

In addition, stavudine triphosphate may inhibit cellular DNA polymerases, particularly mitochondrial DNA polymerase γ.
The concentration required for 50% inhibition of HIV-1 or HIV-2 *in vitro* ranged between 0.009 to 0.3 μM. Antiviral activity of stavudine towards other viruses such as human hepatitis B appeared to be low. A consequence of stavudine's ability to inhibit mitochondrial DNA polymerase γ may be the induction of peripheral neuropathy, which is the main dose-limiting effect in patients. This effect has also been reported with the other nucleoside analogues. This phenomenon is reflected *in vitro* by decreased viability of neurones and undifferentiated cells as well as morphological alterations, but cannot be reproduced *in vivo* in experimental animal models.

Pharmacodynamics
Studies on pharmacodynamic effects with respect to the proposed indication consisted almost exclusively of bibliographic data and referred to *in vitro* experimental models. No studies have been conducted in animal models of HIV-infection.
Studies intended to investigate potential secondary pharmacological effects revealed no unexpected effects.
Data showing *in vitro* and *in vivo* development of resistance using different HIV-strains, substrains and host cells, and the induction of an eventual cross-resistance with other potential therapeutic nucleosides were sparse.

Pharmacokinetics
The pharmacokinetic profile of stavudine was determined in several animal species and included distribution and elimination studies. Concerning the metabolism of stavudine, data and theoretical

considerations support the metabolism of the pyrimidine moiety via endogenous pathways. During the assessment procedure of Zerit, the lack of data related to the metabolic fate of stavudine with respect of the sugar moiety was pointed out. The applicant submitted further data on the elimination of radiolabelled stavudine studies performed in rat and monkey to further investigate the fate of the sugar moiety. These data showed that the kidneys excrete the sugar moiety in one of three forms, as yet not identified further. This deficiency was accepted on the basis of the wide safety margin obtained in the repeat-dose toxicity studies.

Toxicology
Single oral doses of stavudine (up to approximately 500 times the recommended human dose) in animals did not reveal severe toxicities.

The repeat-dose toxicity of stavudine was studied in adequately designed studies in animals. Two effects of long-term administration of stavudine, erythroid (decreased red blood cell count, sometimes accompanied by decreased haemoglobin and haematocrit) and hepatic alterations (liver enlargement with centrilobular hepatocellular hypertrophy), are clearly indicated. Two additional possible targets, for which there is much weaker evidence of toxicity, are leukopoiesis and the lymphatic system. Safety margins calculated on the basis of systemic exposure are very wide. The dose limiting clinical toxicity of stavudine, peripheral neuropathy is not evident in repeat-dose toxicity studies, or in investigations specifically directed towards the study of this particular effect. Likewise, increases in serum transaminases, a phenomenon associated with the clinical use of stavudine, are inconsistent and sporadic.
Some concerns were raised related to the increase in liver weight as result of cellular hypertrophy and endoplasmic reticulum proliferation. As stavudine has no inducing effect on cytochromes P450, the increase in liver weight is likely due to induction of some other protein or enzyme system.

Reproductive toxicity studies performed in animals, with high doses of stavudine were associated with decreased implantation efficiency. Maternal and/or foetal toxicity was not observed at doses giving significantly higher exposure than during clinical therapy. Until additional data become available, stavudine should only be given during pregnancy after special consideration. Stavudine was excreted in the milk of lactating rats. The data available on stavudine excretion into human breast milk are insufficient to assess the risk to the infant. Therefore, mothers should be instructed to discontinue breast-feeding prior to receiving Zerit.
It is recommended that HIV-infected women should not breast-feed their infants under any circumstances to avoid transmission of HIV.

Genotoxic potential has been shown for stavudine. It is 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. Whether a threshold for the genotoxicity exists is difficult to assess, as well as its clinical relevance.

Carcinogenicity studies over 24 months have been performed in mice and rats. On the basis of the results from both studies, the liver was identified as the main target organ for the development of neoplasm lesions. The carcinogenic potential of stavudine is of limited relevance to the therapeutic use of Zerit as indicated by the high safety margins (40 to 170) to clinical exposures. Studies conducted in mice and in a non-rodent species revealed no alteration of immune functions and no delayed type of hypersensitivity reaction respectively.
An environmental risk assessment for stavudine has been performed. With regards to the results obtained from Phase I trials, stavudine is not expected to have any significant environmental impact.

4. Clinical aspects

The clinical development programme for stavudine consisted of three non-randomised Phase I trials in adults and one in children, two randomised Phase II trials in adults and one in children and two

randomised double-blind Phase III studies. None of the studies involving children were designated to demonstrate the clinical benefit of Zerit in this population.
Zerit was initially proposed for the treatment of HIV-infected patients in whom zidovudine is not or is no longer appropriate. Efficacy as measured by clinical endpoints was shown in patients after prolonged prior zidovudine monotherapy.
Zerit is intended to be administered orally twice a day at a dose of 40 mgin adults weighing 60 kg or more and at a dose of 30 mg in adults weighing less than 60 kg and children with a weight of 30 kg and more. The recommended starting dose in children with a weight below 30 kg is 1 mg/kg twice daily (every twelve hours). From birth to 13 days old the recommended dose is 0.5 mg/kg twice daily (every 12 hours). This reduced posology is based on average study data and may not correspond to individual variation in kidney maturation.

Pharmacodynamics and Pharmacokinetics
The pharmacodynamic studies consisted of three non-randomised, dose-ranging studies involving 107 patients. From these studies, maximum tolerated dose was determinated to be 2 mg/kg/day and the dose-limiting effect observed was peripheral neuropathy. All doses of stavudine revealed immunological and virological activity.
Preliminary efficacy was assessed in terms of changes in biological markers (CD4 cells count and viral load) in a randomised, open-label study, administering three different stavudine doses (0.1, 0.5 and 2 mg/kg/day three times daily (tid)). This study included 152 HIV patients with CD4 cells counts ≤ 500 cells/mm^3. The overall results suggest a correlation between efficacy and dose, the 0.1 mg/kg/day dose being less active than the higher doses 0.5 and 2 mg/kg/day, but no consistent difference was observed between the 0.5 mg and the 2 mg dosage groups. As for this study the administration was tid, a concern was raised about the absence of clinical data to support the proposed twice daily administration of Zerit. Nevertheless, it has been accepted that the intracellular half-life (3.5 hours) of decay of stavudine in its active form justified a frequency of administration of every twelve hours.
In vivo anti-retroviral activity, as measured by reduced viral-load, has, however, not been demonstrated specifically in patients clinically failing first-line ZDV therapy.
Supportive evidence of maintained activity in case of zidovudine resistance may be derived from *in vitro* data. Eleven zidovudine-resistant clinical isolates have been evaluated. Only one displayed a significant decrease in stavudine sensitivity, although the apparent cross-resistance was not confirmed when the reverse transcriptase gene of this isolate was placed into a recombinant virus.

The pharmacokinetic behaviour of stavudine has been established in HIV subjects with CD4 cell counts ranging up to 500 cells/mm^3. Additional pharmacokinetic data have been obtained from special patient groups including those with renal and hepatic impairment and children.
The pharmacokinetics was proportional to dose and independent of time. Stavudine is rapidly and well absorbed after oral administration, and the absolute bioavailability has been defined to be 86 % ± 18 %.
The apparent volume of distribution of stavudine at steady state is 46 ± 15 l and stavudine has been shown to be distributed into the cerebrospinal fluid (CSF), with a mean CSF/ plasma ratio equivalent to 40% of the corresponding plasma concentration four hours after oral administration.
Stavudine binding to plasma proteins *in vivo* has not been investigated. However, it is known from preclinical studies that stavudine does not bind to plasma proteins.
The metabolism of stavudine has not been elucidated in humans. Stavudine is mainly eliminated through the kidneys where an active secretion pathway is involved. After i.v. administration, 42 ± 7 % of dose is excreted unchanged in the urine. The corresponding values after oral single and multiple dose administration are 34 ± 5 % and 40 ± 12 %. Therefore, potential interactions with other drugs that are eliminated by active secretion through the kidneys could not be ruled out. It has been demonstrated in animals that the non-renal routes of elimination include intracellular recapture (approximately 20%) and cleavage to thymine and ribose (approximately 30%). However, the enzyme responsible for the eventual cleavage of stavudine has not been identified.
The terminal plasma elimination half-life is 1.3 ± 0.2 hours after administration of a single dose of stavudine, 1.4 ± 0.2 hours after multiple doses and is independent of dose. The intracellular half-life of stavudine triphosphate when estimated *in vitro* is 3.5 hours.
Total clearance of stavudine is 600 ± 90 ml/min and renal clearance is 240 ± 50 ml/min.

Pharmacokinetic studies have also been carried out in special patient groups. In renally impaired subjects, there was evidence of accumulation of stavudine. Dose adjustments proposed by the applicant in line with creatinine clearance rate have been considered as acceptable. Results from a pharmacokinetic study involving end-stage renal disease patients, haemodialysis dependent, who received a single dose of 40 mg of stavudine 2 hours before haemodialysis and on a day between haemodialysis, showed no difference in total exposure between the two arms. Results allowed to conclude that subjects with a CrCl less than 10 ml/min, including those dependent on haemodialysis, can receive Zerit at the same dose as patients with severe renal impairment (CrCl 10-25 ml/min). Exposure was similar to what was observed in patients with CrCl of 10-20 ml/min and who were not on haemodialysis.
Stavudine was shown to be cleared by haemodialysis at an average rate of 120 ml/min. The contribution of this haemodialysis clearance to the total elimination of stavudine in an overdose situation is unknown.
In patients with hepatic impairment and biopsy-proven cirrhosis, the pharmacokinetic profile was not different compared to patients with normal hepatic function.
The pharmacokinetic profile of stavudine was evaluated in 25 HIV-infected children (age ranging from 5 weeks to 15 years, with a median baseline CD4 count of 298 cells/mm^3) following single IV and oral doses of 0.25, 1, 2 and 4 mg/kg and following multiple oral dosing (twice daily) of 0.25, 1, 2 and 4 mg/kg/day. Most of the children had received prior ZDV treatment for a median duration of 104 weeks. The median duration of the therapy for all subjects was 84 weeks. Results from this study showed that the overall mean absolute bioavailability was somewhat lower in children compared to adults (77 % versus 86 % respectively). When normalised for body weight and surface area, the clearance and volume of distribution were age-independent. C_{max} and $AUC_{0-\infty}$ increased linearly with dose. After 12 weeks of oral dosing, the CSF/plasma ratio of stavudine was found to range from 16 % to 125 %, 2 to 3 hours after dose. The terminal half-life after oral and IV administration of stavudine was approximately 1 hour. Given the same dose/kg, children reached about half the C_{max} and AUC of adult patients. On this basis, it was recommended to give to children the double dose/kg compared to adults. The impact of food on the absorption of stavudine has been studied. It has been demonstrated that when stavudine is taken in combination with a high-fat meal, t_{max} increased (from 0.65 to 1.73 hours), C_{max} decreased (from 1.44 to 0.76 µg/ml) but $AUC_{0-\infty}$ remained unaffected. The clinical relevance of these findings is not established. In the study ACTG 240 carried out in children, Zerit was administered without regards to meals. Taking into account the results of this study, the expanded access programme which allowed the mixture of the content of the capsules with food for children who could not swallow and the current clinical practice with regards to drug therapy in HIV disease, the possibility to take Zerit with a light meal, if necessary, was considered to be acceptable. The oral solution of stavudine was shown to be bioequivalent to the 40 mg capsule formulation of stavudine by means of a cross-over study involving 16 healthy adults. Although clinical studies were performed with slightly different capsules in terms of quantitative composition and method of manufacture, the bioavailability is not likely to be affected due to the high solubility of stavudine.

Therapeutic efficacy
A Phase III main therapeutic study (study AI455-019), involving 822 subjects with moderately advanced disease, was designed as a multicentre, randomised, double-blind trial of stavudine (40 mg bid or 30 mg bid if weight < 60 kg) compared to zidovudine (ZDV 200 mg three times daily). Patients included had baseline CD4 counts between 50-500 cells/mm^3 (median 235 cells/mm^3) and had received at least 6 months of ZDV therapy (median 22 months). The median duration of treatment was 79 weeks in the stavudine arm and 53 weeks in the ZDV arm. Fourteen percent of patients recruited for this study had an AIDS diagnosis at baseline, while 50% had symptomatic HIV infection and 36% were asymptomatic. Initially, the primary endpoint included death, occurrence of AIDS defining event and > 50% decline from baseline CD4 count. However as the trial progressed, the follow-up was extended reflecting the current uncertainty surrounding the prognostic significance of the CD4 cells count, such that primary analyses were redefined to include only AIDS events and death. Secondary endpoints included changes in CD4 cells count, p24 antigen levels, quantitative virology, haematological parameters, β-2 microglobulin levels, body weight and Quality of Life measurements.
All randomised patients were included in the intent-to-treat statistical analysis. A statistically significant difference ($p = 0.007$) in favour of stavudine was demonstrated with respect to time to multiple AIDS events and death. However, in a conventional time to first event analysis, a statistically

significant difference was not found (p = 0.11). If results are presented as relative risk, the overall pattern seems, however, rather consistent (see table 1).

Table 1: Main results (study AI455-019)

	Relative Risk (RR Stavudine/ZDV)	Confidence Intervals 95%	RR after stratified adjusted analyses*
Death	0.74	0.54 - 1.03	0.78
Clinical progression (first AIDS event, death)	0.82	0.64 - 1.05	0.77
Clinical progression (AIDS events, death)	0.78	0.65 - 0.94	0.77
Treatment failure (combined CD4↓, AIDS events, death)	0.81	0.71 - 0.93	0.80
Treatment failure (first CD4↓, AIDS event, death)	0.71	0.59 - 0.85	0.69
Premature discontinuation of assigned therapy	0.69	0.58 - 0.81	0.68

- Adjusted for covariates predictive of outcome of HIV disease

With regard to the statistical analysis, the use of a multiple event analysis for the primary endpoint clinical progression was specified prior to any data analysis or unblinding. The method (Andersen-Gill) used in the original submission requires an assumption of independence between multiple endpoints within patients. The validity of this assumption must be questioned. However, an alternative analysis (Wei-Lin-Weissfeld) in which no assumption of independence is necessary confirms the results of analysis according to Andersen-Gill (p = 0.03).

Subgroup efficacy analyses for the following groups identifiable at baseline (CD4 cells count < 100, between 100 - 300, > 300 cells/µl; AIDS or symptomatic/asymptomatic patients; time of prior ZDV therapy < 24 months, > 24 months, < 9 months) also revealed consistent results.

Recognising the consistency of the results irrespective of designated endpoints, subgroup of patients analysed and statistical method, the efficacy of stavudine compared to ZDV was considered as being demonstrated even if the primary outcome analysis (Andersen-Gill) time to multiple events, may be statistically questionable. This conclusion was further supported by CD4 counts improvement (sustained difference in CD4 count was about 40-50 cells/µl between stavudine and zidovudine), p24 antigen level reduction, change in body weight and haematological parameters. Only preliminary data on viral load (PBMC HIV titres) are available, indicating an approximately 50% decrease during the first months of therapy.

In summary, the study is considered well designed and well conducted. Results appear to be robust and consistent and demonstrate a clinical benefit, about 20% risk reduction for progression, corresponding to a delay of approximately 16 weeks.

With respect to pneumocystis, results indicate that more *Pneumocystis carinii* pneumonia (PCP) events were encountered while on stavudine therapy. In order to define whether failure of a specific agent was responsible for the difference between stavudine and ZDV, the data were further tabulated according to the prophylactic agent administered immediately prior to the PCP episode (sulfamethoxazole-trimethoprim, aerosolised pentamidine, dapsone or no prophylactic agent). PCP seemed less effectively prevented among stavudine treated patients as compared to zidovudine treated group when patients received aerosolised pentamidine, dapsone or no prophylactic agent. Although several methodological limitations precluded assessing the relationship between stavudine and PCP prophylaxis, the use of sulfamethoxazole/trimethoprim was recommended as the agent of choice when PCP prophylaxis is warranted.

The stavudine Parallel Track Program (study AI455-900) was an expanded access program which was conducted as a multicentre, randomised, double-blinded comparative trial of two doses of stavudine, 20 and 40 mg bid (15 and 30 mg bid if body weight < 60 kg; 10 and 20 mg bid if < 40 kg).

The trial was initiated to assess the safety and efficacy, using biological markers and survival, of stavudine when used in a community setting for the treatment of HIV-infected subjects throughout the United States and Puerto Rico. The study was carried out in 13299 subjects who had either failed therapy or were intolerant to alternative anti-retroviral therapy (ZDV, ddI and ddC). Amongst the enrolled subjects aged from 12 to 85 there was a definite dominance of males (95%) and 15% of recruited subjects were non-white. The median duration of treatment was respectively 22 weeks for high dose and 23 weeks for low dose. With respect to efficacy as measured by survival, no difference was found between treatment groups. Survival curves were almost identical, also in patients with baseline CD4 count below and above 50 cells/mm^3. However, a tendency towards shortened survival was observed in women treated with 40 mg bid (RR 1.36; 95% CI 0.93 - 2.00) as well as in non-white subjects (RR 1.16; 95% CI 0.94 - 1.43). This finding justified the performance of an additional safety analysis with respect to severe events in women treated with 40 mg stavudine.

More recent data on the efficacy of stavudine in combination antiretroviral therapy is provided from the studies of immediate release (IR) versus prolonged release (PR) formulations of stavudine, AI455-099 and AI455-096. Both these studies were 48 weeks, randomised and double blind, comparing stavudine IR with PR in combination with lamivudine and efavirenz in 783 treatment naive patients (median CD4 cell count of 277 cells/mm^3 and median plasma HIV-1 RNA of 4.80 $\log_{10}$ copies/ml at baseline) in AI455-099 and in 150 treatment-naive patients (median CD4 cell count of 285 cells/mm^3 and a median plasma HIV-1 RNA of 4.65 $\log_{10}$ copies/ml at baseline) in AI455-096. The results of these two studies are presented in table 2.

Table 2: Results of the studies AI455-099 and AI455-096

Study	Percent of patients with HIV RNA < 400 copies/ml Treatment response (%)[a]	Percent of patients with HIV RNA < 50 copies/ml Treatment response (%)[a]	HIV RNA Mean Change from Baseline ($\log_{10}$ copies/ml)	CD4 Mean change from Baseline (cells/mm^3)
AI455-099 (48 weeks)				
Zerit prolonged-release capsule + lamivudine + efavirenz (n = 392)	78	54	-2.86	+202
Zerit immediate-release + lamivudine + efavirenz (n = 391)	77	55	-2.83	+182
AI455-096 (48 weeks)				
Zerit prolonged-release capsule + lamivudine + efavirenz (n = 74)	70	41	-2.74	+232
Zerit immediate-release + lamivudine + efavirenz (n = 76)	66	38	-2.64	+195

[a] Percent of patients who have HIV RNA < 400 c/ml or < 50 c/ml and do not meet any criteria for treatment failure including the occurrence of a new AIDS-defining diagnosis.

In February 2005, the Marketing Authorisation Holder requested to withdraw the marketing authorisation of Zerit prolonged-release hard capsules for manufactoring reasons.

Safety

The initial safety profile of stavudine was established based on experience with over 13,000 subjects in clinical trials, with a median therapy duration of about 23 weeks.

In all clinical trials, the majority of clinical adverse events reported represented symptoms and complications of the underlying disease of HIV infection.

The major clinical toxicity observed with stavudine is dose-related reversible peripheral neuropathy. It is more commonly encountered in patients with advanced disease or in those with pre-existing signs of

neuropathy. Due to this risk, for some patients involved in the trials stavudine therapy had to be discontinued or modified in terms of dose.
Asymptomatic elevations of hepatic transaminases which did not interfere with dosing were also observed.
Pancreatitis, a well-known common side-effect associated with the other nucleoside analogues, appeared with an overall low frequency. In the main efficacy study, the same incidence (1 %) was found in the stavudine and zidovudine groups. In the expanded access study, the incidence was higher (2 %), and so especially in patients with a prior history of pancreatitis (5 %, n = 1500). No overall dose/event relationship was observable.
In women, however, slightly more events were reported in the 40 mg bid stavudine group than in the 20 mg bid stavudine group (3.7 % versus 2 %, p = 0.24). There were no other notable findings in the safety analysis in women.
Other common adverse events are diarrhea, nausea, abdominal pain, dyspepsia, fatigue, headache, insomnia, depression, rash and pruritus. Most adverse events were reported with similar frequencies in both treatment groups. However anaemia, leucopenia and neutropenia were less frequent with stavudine when compared to ZDV.
In the original submission, safety data were reported from 38 HIV paediatric patients with doses ranging from 0.125 mg/kg/day to 1.0 mg/kg/day. Additional results obtained from 51 children, including 6 under 24 months and 7 above 12 years, with median treatment of 4 months with stavudine (most at a dose of 2 mg/kg) in an open-label compassionate use protocol in the U.S. have been presented.
Serious adverse events observed in children included ASAT/ALAT elevations, infections, lymphadenopathy, hepatosplenomegaly, chills/fever, neuropathy and other disease-related complications. "Dose limiting" liver enzyme elevation (higher than 5 x Upper Limit Normal) was observed in a substantial number of patients (40-50 %), but peripheral neuropathy was seemingly less of a clinical problem. Given the limited documentation on the use of stavudine in children, licensing of stavudine for children below the age of 12 years was not considered justified at the time of the original CPMP opinion.
It is noted also that there were no safety data available from elderly patients.
Rare cases of hepatic steatosis and lactic acidosis, some of which have been fatal, have been reported during the post-marketing phase. Considering that similar cases have been reported with other antiretroviral nucleosides, as monotherapy or combination therapy, it was agreed to include a harmonised statement into their SPC to reflect this potential class effect. The statement mentions the most common risk factors identified which include obesity, treatment with combination antiretroviral nucleoside therapy and female gender. A further revision of the class labelling in September 2000 included respiratory and neurological symptoms which might be indicative of lactic acidosis development. In addition, it informs that severe cases of lactic acidosis, sometimes with fatal outcome, were associated with pancreatitis, liver failure/hepatic steatosis, renal failure and higher levels of serum lactate. It also states that lactic acidosis generally occurred after a few months of treatment. Further revisions introduced a "box warning" and restructured the paragraph in order to improve readability and to inform the reader on early symptoms. The main reason for this change was severity of the condition and a frequent delay between early symptoms and diagnosis.
Treatment with a combination of at least three antiretroviral drugs can induce a characteristic syndrome termed lipodystrophy or fat redistribution syndrome containing peripheral fat wasting (including accentuation of facial folds) and central adiposity. Metabolic disturbances such as hyperlipidaemia and insulin resistance also often appear. PIs were originally believed to be the causal agents. NRTIs have also been implicated. In addition, lipodystrophy has also been observed with protease-inhibitor-sparing regimens. The emerging picture is that of a connection between visceral lipomatosis and protease inhibitors and lipoatrophy and NRTIs correlating with different possible mechanisms e.g. effects on lipoprotein production and adipocyte differentiation. Non-drug factors are also of importance e.g. increasing age, duration and severity of HIV infection.
Following evaluation of data submitted by all MAHs of antiretroviral medicinal products, a class labelling, which harmonises the information on lipodystrophy for all three classes of antiretroviral products, has been agreed and implemented in the product information for all antiretroviral medicinal products. The wording presents as much as possible of the presently available knowledge; it gives a description of the condition (although there is at present no clear definition of lipodystrophy), information about causality and surveillance measures. The higher risk of developing lipodystrophy

with long-term therapy as well as importance of factors such as age and disease related factors is mentioned.
Further to the discussions held by the Ad-hoc Group of Experts on Anti-HIV medicinal products in November 2001, the CPMP agreed that liver impairment was of increasing concern in HIV positive patients both in the form of adverse hepatic effects in patients with normal liver function prior ART and as regards patients with chronic liver disease treated with ART.
In January 2002 the CPMP requested the MAH for all authorised anti-retroviral medicinal products to conduct a retrospective review of clinical trials and post-marketing data relating to the use of their product(s) in patients with hepatic impairment and/or HBV/HCV co-infection. Following review of the submitted responses and discussions held during the CPMP meeting and the Pharmacovigilance Working Party meeting in October 2002, the CPMP adopted a list of questions (including general, product specific and SPC wording recommendations). The review of the MAHs' responses has essentially confirmed that co-infected patients and patients with underlying liver disorders are at increased risk for adverse events, essentially confined to liver events.
Following the review of responses submitted by all MAHs of antiretroviral medicinal products, a class labelling on "liver disease" has been agreed and implemented in the product information for all antiretroviral medicinal products.
To further support the safe use of NRTIs the CPMP adopted a class labelling on mitochondrial toxicity in children with in utero/ post-natal exposure to Nucleotide/Nucleoside Reverse Transcriptase Inhibitors. The main adverse events 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.
The CHMP adopted in November 2004 a class labelling on 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.
With regard to all the available data, it was considered that stavudine was rather well tolerated and that the principal dose-limiting toxicity, peripheral neuropathy, was reversible after discontinuation of treatment. If symptoms of peripheral neuropathy develop (usually characterised by persistent numbness, tingling, or pain in the feet and/or hands), switching the patient to an alternate treatment regimen should be considered. In the rare cases when this is inappropriate, treatment with Zerit may be continued at 50% of the previous dosage while the symptoms of peripheral neuropathy are under close monitoring.
The safety profile of stavudine in adolescents, children and infants was established based on different studies. Undesirable effects 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 aged 3 month 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 (performed in South-Africa, 362 mother-infant pairs were included in a prevention of mother-to-child-transmission study), 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. 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.

Benefit/risk assessment

Stavudine is a well established component of various combination antiretroviral therapy regimes and has been used in a large number of patients since it became available. There is good evidence supporting the effectiveness of stavudine in combination therapy in the treatment of antiretroviral-naïve adults with HIV infection as assessed by viral load and CD4 counts, the standard efficacy endpoints for antiretroviral treatment. Stavudine has also been beneficial as part of triple (or quadruple) therapy in antiretroviral-experienced patients. There are limited but positive data regarding its use in antiretroviral-naïve and resistant or experienced children with HIV infection. High level resistance to stavudine is uncommon, making it a useful agent in combination therapy, although resistance mutations conferring resistance to multiple NRTIs (including stavudine) have been described. The safety profile of stavudine is quite well established.

5. Conclusion

The chemical and pharmaceutical data of both stavudine oral formulations, capsules and oral solution, were adequate to support the quality and the shelf life of Zerit. The preclinical data showed that stavudine has a genotoxic potential similar to the other nucleoside analogues. In overall the toxicological profile of this anti-retroviral has been considered well characterised. The clinical efficacy and safety of stavudine has been established on the basis of changes in biological markers and clinical endpoints in proper randomised, controlled clinical trials.

The CHMP considered during the initial review process and the subsequent variations post-authorisation that, with regards to the data provided, the overall benefit/risk ratio for Zerit is favourable in combination with other antiretroviral medicinal products for the treatment of HIV infected patients