SCIENTIFIC DISCUSSION

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

1. Introduction

The Human Immunodeficiency Virus (HIV) is a retrovirus, which replicates by transcribing its viral RNA genome into DNA via the enzyme reverse transcriptase (RT).

The HIV results in a chronic, progressive deterioration in overall cell-mediated immunity with a steady depletion of CD4 T-lymphocytes causing Acquired Immunodeficiency Syndrome (AIDS).

Agents of the family of 2', -3'-dideoxynucleoside analogues are designed to suppress viral replication in two ways: by competitive inhibition with cellular nucleotides for the binding site of RT and, after incorporation into the growing viral DNA strand, by preventing further elongation of the viral DNA (chain termination).

All the currently available nucleoside analogues have dose-limiting toxicities which may limit their long-term use. The development of resistant viruses in patients treated with these nucleosides analogues also demonstrates the pressing need for new agents to widen the choice of therapeutic agents available for treating patients infected with HIV.

Lamivudine is a nucleoside analogue developed as a treatment for HIV infection. It has also activity against hepatitis B virus (HBV). It is metabolised intracellularly to the active moiety, lamivudine 5'-triphosphate. Its main mode of action is as a chain terminator of viral reverse transcription. The triphosphate has selective inhibitory activity against HIV-1 and HIV-2 replication *in vitro*, it is also active against zidovudine-resistant clinical isolates of HIV. Lamivudine in combination with zidovudine exhibits synergistic anti-HIV activity against clinical isolates in cell culture. The demonstration of the benefit of lamivudine is based on bitherapy studies in combination with zidovudine where a significant reduction in the risk of disease progression and mortality has been shown. Moreover, lamivudine has been widely used as a component of triple combination therapies with protease inhibitors, non nucleoside reverse transcriptase inhibitors and with nucleoside reverse transcriptase inhibitors.

Lamivudine is indicated as part of antiretroviral combination therapy for the treatment of HIV infected adults and children. The recommended dose of Epivir is 300 mg (30 ml) daily as either 150 mg twice daily or 300 mg once daily.

2. Chemical, pharmaceutical, and biological aspects

Epivir contains lamivudine as the active substance and is available in two pharmaceutical forms: film coated tablets containing 150 mg or 300 mg lamivudine and an oral solution containing 10 mg/ml lamivudine.

Composition

- **Tablets**

Epivir 300 mg film-coated tablets have the same qualitative core composition as the 150 mg film-coated tablets.

Other ingredients used in the tablet formulations include microcrystalline cellulose, sodium starch glycollate and magnesium stearate and excipients commonly used in film-coatings.

HDPE bottles with child-resistant closures were initially authorised as container. A PVC/Aluminium blister was subsequently authorised through a variation.

The pharmaceutical development of the film-coated tablets, which provide doses of 150 mg and 300 mg of lamivudine in single dosage units, and the choice of the excipients, was adequate.

- **Oral solution**

Other ingredients entering in the composition of the oral solution are methyl hydroxybenzoate, propyl hydroxybenzoate, sucrose, artificial flavours, propylene glycol, citric acid, sodium citrate and sodium hydroxide or hydrochloric acid.

The container is a HDPE bottle, with child resistant / tamper evident closure. Its total volume is 270 ml, but its filling volume is 240 ml.

A suitable dosing device has been developed to allow accurate measurement of low prescribed volumes of solution. This device consists of a 10 ml polypropylene oral-dosing syringe. A polyethylene adapter is provided to facilitate the use of the syringe.

Compared to the original approved formulation, the oral solution has been reformulated to achieve acceptable preservative efficacy in the absence of ethanol. The quality of the new formulation was adequately demonstrated.

Method of preparation

- **Tablets**

Epivir tablets are manufactured according to conventional processes for this pharmaceutical form. The validated in-process controls were considered satisfactory and appropriate to ensure consistent batch to batch quality.

- **Oral solution**

Prior to filling, the bulk solution is filtered (0.5 μm). In-process controls were considered satisfactory. The results of validation procedures showed consistent batch to batch quality.

Control of starting materials

Active substance

Lamivudine is (2R, cis)-4-amino-1-(2hydroxymethyl1, 3-oxathiolan-5-yl)-(1H)-pyrimidin2-one and has not yet been described in any pharmacopoeia. The (-) enantiomer of lamivudine which was shown to be less cytotoxic than the (+) enantiomer or the racemate has been selected for the manufacture of the medicinal product.

Manufacture of lamivudine involves multi-steps synthesis, which includes racemate separation.

Quality specifications of the starting materials and intermediate stages of synthesis were sufficiently validated and adequate to control the quality of the active substance.

The validation of the test methods used (determination of contents for lamivudine, enantiomer and impurities, and lamivudine identification) was considered sufficiently documented.

Other ingredients

- **Tablets**

All the ingredients of the tablet core are specified according to the monographs of the current European Pharmacopoeia (Ph.Eur.). The film coat is a proprietary one, an Opadry, whose components are all described in monographs of the current Ph.Eur, with the exception of the colouring materials.

- **Oral solution**

All the other ingredients included in the oral solution are specified according to the Ph. Eur.

Control tests on the finished medicinal product.

- **Tablets**

Test results of three batches of each strength of tablet were presented. The control tests were considered satisfactory. The specified requirements are adequate to control the quality of the finished product. Test procedures for the control of the finished product are sufficiently validated.

- **Oral solution**

The specified requirements of the oral formulation are considered adequate to control the quality of the finished product and test procedures are sufficiently validated. Results from batch analyses from batches showed that all batches complied with the defined specifications.

Stability

Stability tests on active substance

Lamivudine batches from each variation of synthesis were subject to stability testing. The tests were performed over a period of 24 months and were supplemented with tests on stressed samples. Lamivudine of various origins did not show any physical or chemical changes. The procedures used are suitable for stability testing. Validation of the analytical procedures was documented.

The complete description of the container designed for storage of the active substance is part of the additional information the company agreed to provide.

Stability tests on the finished medicinal product

- **Tablets**

HPDE bottle

Stability tests were carried out on batches of the tablets stored for up to 36 months, at 30°C /60% relative humidity. In addition, results of stress tests were documented. The minor deviations of the container, used in stability testing, from the one designed for marketing of the finished product, were considered acceptable. Test results showed no changes in finished product, in the chosen conditions and time. Based on the total data available, shelf- lives of 36 months, for both strengths of tablets, were considered acceptable at the time of the initial authorisation, when the tablets are stored at or below 30°C. The shelf life was extended to 5 years through a type I variation for the 150 mg strength.

PVC/Aluminium blister

The stability data provided support the proposed shelf life of 2 years and storage conditions for the tablets packed in PVC/Aluminium blister.

- **Oral solution**

The provided data obtained with the ethanol-free formulation support a shelf-life of 24 months when stored at or below 25°C. The simulated patient-use testing of the oral formulation demonstrated a shelf-life after opening of 30 days which is considered acceptable.

The chemical and pharmaceutical data submitted, together with the additional information provided as requested by the CPMP and as part of the obligations to be fulfilled by the applicant, are acceptable to ensure the quality and the consistency of both the strengths of the tablets and the oral solution.

3. Toxico-pharmacological aspects

Lamivudine is a pyrimidine nucleoside analogue. After intracellular uptake, it is sequentially phosphorylated by host cell intracellular kinases to its respective 5'-triphosophates (TP). Thereafter, the monophosphate compound is inserted into the DNA transcript by the viral enzyme reverse transcriptase (RT). However, due to lack of a 3'-OH group, the nucleic acid strand extension is terminated. Lamivudine is also a competitive inhibitor of the viral RT. Its specific activity against HIV is mainly related to its selectivity for dividing cells and its high affinity for viral RT. In the case of lamivudine-TP, the eukaryotic DNA polymerases can repair a falsely inserted nucleoside through their simultaneously expressed 3', 5'-exonuclease function, but the insertion of the defective base in the RT-DNA transcript is virtually irreversible.

Lamivudine inhibited viral replication of several laboratory strains and clinical isolates of HIV-1 and HIV-2 in different monocyte or lymphocyte cell lines or fresh human peripheral blood lymphocytes. The IC50 (concentration leading to 50% inhibition of viral replication) ranged from 2nM to 15 μM. In addition, lamivudine-TP inhibited viral RT with a Ki value of 10-12 μM.

The *in vitro* intracellular half-life of lamivudine TP was 10-15 h. Antiviral effects have been demonstrated at extracellular concentrations of 10 nM. The extent of lamivudine triphosphorylation was not impaired by the presence of zidovudine concentrations of 5 to 50 μM. Effects of lamivudine on zidovudine triphosphorylation have not been reported.

Lamivudine had no activity against a number of other pathogens [RNA and DNA viruses (except hepatitis) bacteria and fungi] normally occurring during HIV disease, indicating anti-HIV specificity. *In vitro* studies of lamivudine given in combination with other antimicrobial agents showed that ganciclovir reduced the antiviral activity (IC50) of lamivudine by a factor of 2-3, which is within experimental variation.

Data with lamivudine from *in vivo* animal models of HIV infections were limited and of doubtful validity.

Cytotoxicity

Using different *in vitro* cell systems (e.g. human erythroid precursors, human bone marrow progenitor cells), LC50s (concentration reducing cell viability by 50%) was >30 μM. Depending on the test systems used, the therapeutic index (i.e. the ratio between LC50 and IC50) was in general large.

Antiviral activity of lamivudine in combination with other antiviral compounds was studied in a number of HIV-1 and HIV-2 sub-strains in different host cell lines to investigate synergistic, additive or antagonistic effects as well as cytotoxic activity.

These studies indicated additive effects of lamivudine with didanosine (ddI) and zalcitalbine (ddC) and synergistic effects of the lamivudine/zidovudine (ZDV) combination.

Resistance

HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral reverse transcriptase (RT). This variant arises both *in vitro* and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity *in vitro*. *In vitro* studies indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.

Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation. The M184V RT mutant shows a <4-fold decrease in susceptibility to didanosine and zalcitabine; the clinical significance of these findings is unknown. *In vitro* susceptibility testing has not been standardised and results may vary according to methodological factors.

Secondary pharmacology

Safety pharmacology studies with lamivudine showed no major effects on cardiovascular or respiratory parameters or on intestinal transport.

Pharmacokinetics

The pharmacokinetic profile of lamivudine has been studied separately in the main species used in the preclinical testing programmes. Protein binding was moderate to low in all species including humans (35-50% (at 0.1 μg/ml) to <10% (at 100 μg/ml)). In distribution studies with radioactively labelled lamivudine, rapid and wide tissue distribution of drug-related radioactivity was seen. There were no signs of tissue accumulation. Placental transfer of drug-related material has also been demonstrated with lamivudine. Studies in lactating rats have shown that lamivudine, after oral administration, is excreted in milk.

Following oral administration of lamivudine to rats, about 60% of the drug related material was excreted in urine within 24 h, predominantly as unchanged drug and the data indicated active tubular renal excretion. Two minor metabolites (<5%) were detected. The remaining drug-related radioactivity was recovered as unchanged drug in faeces, indicating incomplete absorption. In dogs, about 97% of

the radioactivity were recovered in urine after oral administration, of which 2 metabolites accounted for 52% of the dose. Of the species studied, the pharmacokinetic profile of lamivudine in rats most closely resembled that observed in humans.

After administration of lamivudine, toxicokinetic data obtained in the species used in the toxicity studies showed that the systemic exposure of animals exceeded the systemic exposure of humans given therapeutic doses.

Animal studies or *in vitro* data suggested the lack of interactions between lamivudine and a number of concomitantly administered drugs. Lamivudine was shown not to interact with the cytochrome P450. Interactions only occurred with ganciclovir (weakening of the anti-HIV activity) and trimethoprim (impeding elimination).

Toxicology

The preclinical toxicity profile of lamivudine has been characterised separately in a number of different species in studies of up to 2 years duration. The haematopoetic system was the most commonly affected target organ. Furthermore, lamivudine showed a potential to induce embryotoxicity after administration to pregnant animals.

Single dose toxicity of lamivudine after intravenous (i.v.) or oral administration was studied in rodents. The acute toxicity was low, where doses up to 2000 mg/kg i.v. (both species) or 2x2000 mg/kg orally (mice only) were well tolerated without signs of target organ toxicity.

Repeated dose toxicity of lamivudine after oral administration was studied in rats (up to 6 months) and dogs (up to 12 months). The target organ of toxicity was the haematopoietic system (anaemia, decreased platelet count, leukopenia and splenic hemosiderosis). Furthermore, following high doses and extended exposure periods, impaired liver function (raised ALT and AST without major histological effects), and gastrointestinal effects (ulcers, inflammation) were observed. Non observable effect level (NOEL) was 300-425 mg/kg/day b.i.d. in rats and <45 mg/kg/day b.i.d. in dogs.

Reproductive function: Lamivudine did not impair the overall reproductive performance in rats. Embryonic deaths occurred in rabbits. Lamivudine showed no teratogenic potential in either species. Peri-post natal studies in rats did not reveal any cause of concern.

Genotoxicity: Lamivudine induced gene mutations in the mouse lymphoma assay (at 1000 μg/ml and above). It was also clastogenic in an *in vitro* cytogenicity test in human lymphocytes at 300 μg/ml which is 150 times higher than the concentrations observed at clinical use. However, no chromosomal damage was seen in *in vivo* tests in rats. Other *in vitro* and *in vivo* tests were also negative. Since these genotoxic effects were observed only at concentrations considerably higher than those observed at clinical use, the genotoxic potential of lamivudine was considered to be acceptable.

The carcinogenic potential of lamivudine was studied in conventional 24 months studies in rats and mice. No signs of carcinogenic effects were seen. In these studies, the systemic exposure of animals was 10 - 58 higher than the systemic exposure of humans at clinical use.

In local tolerance studies, lamivudine did not cause ocular or cutaneous irritation. Furthermore, the potential for hypersensitivity reactions was considered to be low and there was no indication of IgE mediating properties.

Environmental risk: An environmental risk assessment for lamivudine tablets and oral solution has been undertaken. Although lamivudine is not biodegradable and its predictive residual concentration in water was more than allowed by norms, no adverse environmental effects are expected to occur because there is no toxic effect on aquatic species. No further investigations are required.

4. Clinical aspects

Clinical pharmacology

Pharmacodynamics

The starting dose of 0.25 mg/kg/day was chosen based on the inhibitory concentrations (IC) for different HIV strains *in vitro*.

The administration of a single dose of lamivudine in the 8 phase I trials did not reveal any clinically relevant side effects in the dose range investigated (0.25-8 mg/kg/day). The most frequently observed adverse event with a single dose was headache. This event was not dose-dependent.

Absorption

Lamivudine is well absorbed from the gastrointestinal tract, and the bioavailability of oral lamivudine in adults is normally between 80 and 85 %. Following oral administration, the mean time (t_{max}) to maximal serum concentrations (C_{max}) is about an hour. Based on data derived from a study in healthy volunteers, at a therapeutic dose of 150mg twice daily, mean (CV) steady-state C_{max} and C_{min} of lamivudine in plasma are 1.2 µg/ml (24%) and 0.09 µg/ml (27%), respectively. The mean (CV) AUC over a dosing interval of 12 hours is 4.7 µg.h/ml (18%). At a therapeutic dose of 300mg once daily, the mean (CV) steady-state C_{max}, C_{min} and 24h AUC are 2.0 µg/ml (26%), 0.04 µg/ml (34%) and 8.9 µg.h/ml (21%), respectively.

The 150 mg tablet is bioequivalent and dose proportional to the 300 mg tablet with respect to AUC_{∞}, C_{max}, and t_{max}.

Co-administration of lamivudine with food results in a delay of t_{max} and a lower C_{max} (decreased by 47 %). However, the extent (based on the AUC) of lamivudine absorbed is not influenced. Co-administration of zidovudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary.

Distribution

From intravenous studies, the mean volume of distribution is 1.3 l/kg. The observed half-life of elimination is 5 to 7 hours.The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (> 70 %) via the organic cationic transport system.
Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (< 16 % - 36 % to serum albumin in *in vitro* studies). Limited data show that lamivudine penetrates the central nervous system and reaches the cerebro-spinal fluid (CSF). The mean ratio CSF/serum lamivudine concentration 2-4 hours after oral administration was approximately 0.12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Metabolism

The active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16 to 19 hours) compared to the plasma lamivudine half-life (5 to 7 hours). In 60 healthy adult volunteers, Epivir 300 mg once daily has been demonstrated to be pharmacokinetically equivalent at steady-state to Epivir 150 mg twice daily with respect to intracellular triphosphate AUC_{24} and C_{max}. Lamivudine is predominately cleared unchanged by renal excretion. The likelihood of metabolic interactions of lamivudine with other medicinal products is low due to the small extent of hepatic metabolism (5-10 %) and low plasma protein binding.

Elimination

Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. A recommended dosage regimen is presented for patients with creatinine clearance below 50 ml/min.

Pharmacokinetic interactions

The administration of trimethoprim/sulphamethoxazole, at the dose 160 mg/800 mg, has been shown to increase the AUC of lamivudine by 40%. This interaction, which is explained by a reduced renal elimination, has been adequately addressed in the SPC.

The pharmacokinetic of lamivudine was unchanged whether administered alone or in combination with ZDV as demonstrated by similar AUC or C_{max}.

Further pharmacokinetic interactions were studied *in vitro* but not investigated in clinical trials.

Special population

The pharmacokinetic behaviour of lamivudine has been evaluated in patients with renal and hepatic impaired function.

Study NUCB 1003

This single dose open study was designed to investigate the pharmacokinetics of single oral dose of lamivudine to patients with various degrees of renal impairment compared to a control group with normal renal function and to determine whether lamivudine was dialysable in patients with severe renal impairment. This study involved 9 subjects with normal renal function (Clcr > 60 ml/mn) and 20 patients with renal impairment. Final results confirmed that there is a linear relationship between lamivudine clearance and renal function (assessed as creatinine clearance) i.e. a reduction in renal clearance will produce a higher exposure to lamivudine. In case of creatinine clearance reduction between 20 and 50 ml/min, the AUC average increase is 3 fold. In study NUCB 1004, detailed below, the AUC average increase was determined to be 4 fold. The current dosage recommendations in renally impaired patients proposed by the MAH are consistent with the results of the two studies and no modifications are therefore necessary.

Study **NUCB 1004**, an open single dose study, was designed to evaluate the effects of hepatic impairment on the pharmacokinetics of lamivudine. The study involved 24 non-HBV infected patients divided in three groups according to their hepatic impairment function: normal, moderate or severe. Single 300 mg doses of lamivudine (as 3 x 100 mg tablets) were administered to all subjects. The severity of the hepatic impairment was assessed according to the Child-Pugh classification, 14C aminopyrine breast test, measurement of hepatic blood flow by sonography and caffeine clearance.

Results indicated that there was little difference in overall lamivudine exposure (AUC or C_{max}) or other pharmacokinetic parameters such as Clr, t_{max}, $t_{1/2}$ between healthy control subjects and patients with hepatic impairment. Patients involved in the study had however mild to moderate liver dysfunction. No patients with real severe hepatic impairment were included.

The results observed are coherent since lamivudine is mainly eliminated through the renal excretion. No dose adjustment in patients with impaired hepatic function is therefore warranted.

Study NUCB 1002

This phase I study specifically designed and statistically powered to evaluate the influence of hepatic function on lamivudine disposition revealed no significant parameters between healthy controls and patients with moderate-severe hepatic impairment. These results support the use of lamivudine in patients with hepatic impairment without any dose adjustment unless accompanied by renal impairment. This is consistent since the primary route of excretion of lamivudine is renal. An amendment to the hepatic impairment statement was introduced in the SPC to reflect these results.

Patients with diarrhoea

The effect of diarrhoea on lamivudine bioavailability has not been investigated.

Children

Four pharmacokinetic studies were conducted in neonatal, paediatric and pregnant patients receiving lamivudine alone or in combination with ZDV and/or didanosine (ddI) (NUCA 2002, NUCA 2005, NUCA 2018 and ZDVB 1003). Pharmacokinetic data are therefore available in neonates (n = 36), in children from 3 months to 2 years (n=7), from 2 to 12 years (n=68) and 12 to 18 years (n=25).

NUCA 2002 is an open-label, non comparative, dose-escalating study (0.5; 1.0; 2.0; 4.0; 6.0 and 10.0 mg/kg bid) to establish the pharmacokinetic profile of lamivudine in 89 HIV infected children aged 3 months to 17 years. Patients received a single intravenous administration of lamivudine 48-72 hours prior to the initiation of oral dosing. Results from 60 and 58 patients for oral and intravenous route respectively showed that lamivudine exhibited linear pharmacokinetics and dose proportionality throughout given dose range (1-20 mg/kg/day) in paediatric patients, as it was observed in adults. The overall exposure is lower in children than in adults for a given dose as a consequence of lower

absolute bioavailability (57 ± 22% versus 80-85% in adults) and higher systemic clearance. No change in apparent volume of distribution was observed between paediatric and adult patients (1.3 l/kg after intravenous administration). The observed half-life was shorter (1.5-2.5 hours in paediatric versus 2.5-3.5 hours in adults), but this difference could be the result of an underestimation as a consequence of samples timing (up to 12 hours). It was also observed that body weight was a significant co-variate in these parameter differences.

Lamivudine CSF penetration that was assessed on day 4 and week 12 was moderate. Average CSF lamivudine concentrations ranged from 18 ng/ml to 288 ng/ml for the dose ranges 1 to 20 mg/kg/day respectively. In adults, CSF lamivudine concentrations ranged from 94 to 328 ng/ml for the dose ranges 8 mg/kg/day up to 20 mg/kg/day.

NUCA 2005 is an open label phase II to investigate the safety, efficacy, tolerance and pharmacokinetic profiles of the combination lamivudine, ZDV and ddI in HIV infected children. The study involved 65 children aged 3 months to 18 years who had received no or minimal prior antiretroviral therapy, or who had experienced toxicity or become refractory to prior treatment. Pharmacokinetics parameters were estimated following either single or repeated administration of 4 mg/kg bid of lamivudine co-administered with ZDV (180 or 90 mg/m2 every 6 hours) or ddI (135 mg/m2 bid) and data are available from 39 patients.

Results showed that AUC values differ significantly between the age groups 2-12 years and 12-18 years ($p < 0.05$). The pharmacokinetics of lamivudine assessed by AUC at day 2 or at steady state (week 4) was unchanged whether administered alone or with concomitant administration of ZDV, ddI or both. Similarly AUC of ZDV and ddI remained unchanged when co-administered with lamivudine. It was therefore demonstrated that, as in adults, no dosing adjustment based on pharmacokinetics was needed when these products were combined. Based on differences in exposure due to a decrease in absolute bioavailability and systemic clearance, 4 mg/kg bid dose (up to a total dose of 150 mg twice daily) for paediatric patients was estimated to provide similar daily exposure as in adults receiving 150 mg x 2.

NUCB 2018, a phase II open-label study was designed to evaluate the safety and pharmacokinetics of lamivudine administrated alone and in combination with ZDV to HIV-1 infected pregnant women and their offspring.

Twenty infected pregnant women received either lamivudine alone (300 mg bid) or lamivudine (150 mg bid) in combination with ZDV (300 bid) starting at 38 weeks gestation during and after birth (1 week). All neonates received lamivudine (4 mg/kg bid) either alone or in combination with ZDV (2 mg/kg qid) for one week and were followed for 12 weeks. Results in 20 neonates showed differences in pharmacokinetics parameters between neonates and paediatrics. It was suggested that these differences were likely due to immature renal function and variable absorption because of irregular gastrointestinal function and irregular feedings. From a safety perspective the overall exposure was consistent with that observed in paediatrics and therefore data support the dosage recommendation of 2 mg/kg bid from 12 hours to 1 week.

After the Commission Decision, the Marketing Authorisation Holder submitted the results of a phase I open label study (ZDVB 1003) designed to evaluate the pharmacokinetics of ZDV and lamivudine when administered in combination to HIV-1 infected pregnant women and their offspring.

Sixteen infected pregnant women received ZDV (300 mg bid) in combination with lamivudine (150 bid) starting at 36 weeks gestation, during and after birth (1 week). Intrapartum the dose of ZDV increased to (300 mg/ 3 hourly). All neonates received ZDV (4 mg/kg bid) in combination with lamivudine (2 mg/kg bid) for one week and were followed for 12 weeks. Results in 16 neonates are consistent with pharmacokinetics parameter contained in study NUCB 2018, and confirm the current recommendation for lamivudine in neonates (4mg/kg BID).

Glomerular filtration estimates suggests that to achieve similar adult and paediatric exposure, the recommended dose for children aged six weeks and older could be 8mg/kg/day.

With regard to paediatric patients with renal dysfunction, no pharmacokinetics data are available. However based on the gained experience, it is foreseen that renal clearance will decrease in direct proportion to creatinine clearance. Percent reductions in daily dose, in a similar way as in adults with the same level of renal impairment, are therefore considered acceptable.

Pregnancy

Following oral administration, lamivudine pharmacokinetics in late pregnancy were similar to non-pregnant woman.

Elderly patients

No pharmacokinetic data are available in the elderly.

Conclusions on pharmacokinetics

As with other nucleoside analogues, the active moiety is the intra-lymphocyte triphosphate metabolite. . Pharmacokinetics of lamivudine, in adults, was considered to have been well covered. The methodology, design of studies and statistics were appropriate.

Studies performed in healthy volunteers demonstrate that 1x300mg per day provides an equivalente lamivudine exposure as the 2x150 mg per day regimen.

Final analysis of the population pharmacokinetics of trials NUCA3001 and NUCA3002 confirmed the absence of interaction between lamivudine and ZDV.

Pharmacokinetics profile of lamivudine in children aged 2-12 years was well defined. Data support the dosage recommendation of 4 mg/kg twice daily of lamivudine which give overall exposure (expressed in plasma lamivudine AUC) close to that reported in adults receiving 150 mg x2.

Although data are limited in children from 3 months to 2 years (n=7), it was shown that oral clearance was in the range of that observed in older children (0.81 – 1.53 l/h/kg versus 0.77 – 1.23 l/h/kg) and therefore the same dosage recommendation is warranted. . There are limited pharmacokinetic data for patients less than three months of age. In neonates one week of age, lamivudine oral clearance was reduced when compared to paediatric patients and is likely to be due to immature renal function and variable absorption. Therefore, to achieve similar adult and paediatric exposure, the recommended dose for neonates is 4 mg/kg/day. Glomerular filtration estimates suggests that to achieve similar adult and paediatric exposure, the recommended dose for children aged six weeks and older could be 8mg/kg/day.

Clinical experience

Clinical trials

A total number of 1317 (1173 adults, 144 children) patients were included in the clinical program. Eight studies were performed, six in adults and two in children.

Criteria for evaluation of efficacy were the following:

Immunological markers and viral load: the principal criteria were the CD4 lymphocyte count and HIV-1 RNA levels in peripheral blood by polymerase chain reaction (PCR) assays. The methods of quantification of these parameters were well validated.

Clinical manifestations of HIV-1 disease: progression to CDC class B or class C (AIDS events)

Resistance: The methods of resistance evaluation were well standardised.

Open label phase II trials in adults

NUCA2001 was a monotherapeutic dose escalation trial of lamivudine 0.5-20 mg/kg/day, in 97 adults with advanced ARC (AIDS Related Complex) or AIDS and CD4 cell count = 300/mm3. After 24 weeks the patients had the option to change to 2x4 mg/kg/day.

Efficacy was evaluated over 24 weeks.

Twenty-eight percent (28%) of the patients were withdrawn from the study within 24 weeks.

NUCB2001 was a monotherapeutic dose escalation trial of lamivudine 0.5-2.0 mg/kg/day in 104 adults asymptomatic or with symptoms of mild ARC and CD4 cell count <400 mm3. After 52 weeks the patients had the option to change to 2x300 mg/day.

Efficacy was evaluated over 52 weeks.

Eighteen percent (18%) of patients were withdrawn from the study within 52 weeks.

Randomised, double-blind studies in therapy-naive adults

NUCA3001 included 366 ZDV-naive patients, or patients who had received less than four weeks previous ZDV therapy, and with CD4 counts of 200-500 cells/mm3. They were randomly assigned to receive zidovudine (3x200 mg/day) or lamivudine (2x300 mg/day) or ZDV (3x200 mg/day) + lamivudine (2x150 mg/day) or ZDV (3x200 mg/day) + lamivudine (2x300 mg/day), for 24 weeks.

Ninety-one patients (25%) were withdrawn from the study within 24 weeks and 275 were defined as completers.

NUCB3001 included 129 ZDV-naive patients with CD4 counts of 100-400 cells/mm3.

They were randomly assigned to receive ZDV (3x200 mg/day) or ZDV (3x200 mg/day) + lamivudine (2x300 mg/day), for 24 weeks. After the blinded period the patients were offered the option to receive open-label lamivudine to which ZDV could be added.

Sixteen patients (12%) were withdrawn from the study within 24 weeks.

Studies in adults previously treated with zidovudine

NUCA3002 included 254 patients who had received prior ZDV therapy for = 24 weeks and with CD4 counts of 100-300 cells/mm3. They were randomly assigned to receive ZDV (3x200 mg/day) + ddC (3x0.375 mg/day) or ZDV (3x200 mg/day) + lamivudine (2x150 mg/day) or ZDV (3x200 mg/day) + lamivudine (2x300 mg/day, for 24 weeks. Surrogate markers were evaluated over 24 weeks.

Fifty-seven patients (22%) were withdrawn from the study within 24 weeks.

NUCB3002 included 223 patients who had received prior ZDV therapy and with CD4 counts of 100-400 cells/mm3. They were randomly assigned to receive ZDV (3x200 mg/day) or ZDV (3x200 mg/day) + lamivudine (2x150 mg/day) or ZDV (3x200 mg/day) + lamivudine (2x300 mg/day), for 24 weeks.

Surrogate markers were evaluated over 24 weeks.

Twenty-seven patients (12%) were withdrawn from the study within 24 weeks.

Efficacy in controlled studies in adults:

Efficacy on immunological markers and viral load

CD4 cell count: a noteworthy beneficial effect on CD4 count of the combination ZDV-lamivudine (2x150 and 2x300 mg) compared with monotherapy (ZDV or lamivudine) or bitherapy (ZDV-ddC), both in naive and previously treated patients, was shown. However, given the large number of undocumented patients at week 24, it was difficult to consider this effect sustained over 24 weeks.

Viral load (HIV-1 RNA by PCR): in all the studies patients in the ZDV-lamivudine (2x150 and 2x300 mg) groups exhibited substantial drop in HIV-RNA at weeks 2 to 4, followed by a rebound effect. The mean peak of decrease from baseline was around -1.5 log10 HIV-1 RNA. Such a dramatic effect on viral load has not been observed with ZDV or other nucleosides.

On request of the CPMP, the company submitted additional data on CD4 count and HIV-1 RNA from NUCA3001 and NUCA3002. The efficacy of ZDV-lamivudine was analysed at 52 weeks, instead of 24 weeks as used previously. The treatment effect of the ZDV-lamivudine combination on CD4 and viral load was sustained over the 52 weeks period and remained superior to the control group.

With regard to the GCP inspection of biological data (CD4 and HIV1 RNA) of European trials, carried out by the French Inspectorate, the company has provided results of the reanalyses, which are consistent with the results of the original study reports.

Drug susceptibility

A high level of phenotypic or genotypic resistance to lamivudine developed rapidly, in the majority of the therapy-naive or ZDV-previously treated patients. In therapy naive patients treated with a combination of lamivudine and ZDV, the emergence of resistance to ZDV is delayed.

Efficacy on clinical end-points

The company performed a meta-analysis of the progression to CDC B/C end-points, using combined data from the four double-blind randomised controlled trials of ZDV-lamivudine in adult patients **(NUCA3001, NUCA3002, NUCB3001 and NUCB3002).**

The main findings were:

- A statistically significant 66% reduction in the rate of progression to new AIDS defining (CDC C) endpoints for combination ZDV-lamivudine treatment compared to control treatments, when results from the four trials were combined.
- A statistically significant reduction of 49% in the rate of progression to new ARC/AIDS defining (CDC B/C) endpoints for combination ZDV-lamivudine treatment compared to control treatments, when results from the four trials were combined.
- Consistent reductions in progression to CDC C and CDC B/C endpoints of similar magnitude across the four clinical trials and for different subgroups of patients. However it was decided that these data could only be considered as supportive data, because the assessment of clinical events was not a primary efficacy parameter planned in the protocol. Thus, confirmation of the clinical benefit has to be provided with the results of phase III trials.

Study **NUCB 3007** (the CAESAR TRIAL) was designed to compare the efficacy and the safety of lamivudine versus lamivudine/loviride versus placebo in the treatment of HIV-1 infected patients, with CD4 cell counts between 25-250 cells/mm3, who were taking concurrent ZDV containing treatment regimens. This double-blind, randomised, multicentre, comparative trial involved 1895 antiretroviral naive or experienced patients, from both sex and over 18 years old. 83 % patients were antiretroviral experienced at baseline (>4 weeks of prior antiretroviral treatment) with a median duration of prior therapy of approximately 28 months. The primary endpoint was clinical progression of HIV disease defined as death or new AIDS defining events. The final analysis was conducted on an intent-to-treat population of 1840 patients who were assigned to treatment in a ratio of 1:2:1 as follows:

- current treatment (n=483)
- current treatment/lamivudine 150 mg bid (n=937)
- current treatment/lamivudine 150 mg bid/loviride 100 mg tid (n=475)

The current therapy consisted of ZDV monotherapy for 62 %, ZDV/ddC for 23 % or ZDV/ddI for15%. Patients in all treatment groups presented consistent baseline characteristics, in particular with respect to disease stage at baseline, current therapy or antiretroviral experience at baseline: 26 % were CDC stage C, median CD4 cell counts was 126 cells/mm^3.
Two interim analyses were planned and an independent body (Data and Safety Monitoring Board) reviewed data. Based on the available results from the second interim analysis which demonstrated a significant delay in time to progression to new AIDS event or death in the lamivudine arms compared to placebo and a delay in time to progression alone, it was recommended to end the study. A large number of patients did not complete the 52 weeks of blinded study medication (59 % in placebo group, 45 % in lamivudine group and 44 % in lamivudine/loviride group) mainly due to premature termination of the trial or occurrence of a clinical endpoint. The medium duration on study medication was approximately 9 months.

The final results over 12 months confirmed the preliminary data, which demonstrated the clinical benefit of lamivudine in combination with ZDV-containing regimens, compared to ZDV-containing regimens alone. A statistically significant difference in favour of lamivudine in combination with ZDV-containing regimens was demonstrated in reduction of risk of death or disease progression ($p < 0.0001$).

Clinical endpoints	Current treatment + placebo	Current treatment + lamivudine	Current treatment + lamivudine + loviride
Progression to new AIDS event or death	95/471 (20 %)	86/907 (9 %)	42/462 (9 %)
Progression to death	28/471 (6 %)	23/907 (3 %)	14/462 (3 %)

The relative hazard for progression to the combined endpoints of disease progression or death was 0.427 (95 % confidence interval 0.318 - 0.572) which represents a relative reduction in disease progression and death of 57 % for patients on lamivudine compared to the placebo arm.

There was also a significant benefit in survival with a 60 % relative reduction in risk of mortality (p=0.0007) in the lamivudine groups compared to placebo. The relative hazard for reduction in risk of death was 0.399 (95 % confidence interval 0.230 - 0.693).

The results showed that the addition of loviride to lamivudine did not confer any additional clinical benefit.

The provided sub-group analyses according to CD4 cell counts, CDC disease stage, gender, prior antiretroviral therapy, current antiretroviral therapy at baseline confirm the clinical benefit of Epivir in addition to current therapy.

The primary treatment comparison was based on staged endpoint, which excluded a number of CDC events as endpoints in patients who entered the study with any previous AIDS defining event. Three secondary analysis were therefore performed to investigate the effect of these events on the robustness of the primary analysis:

- total number of CDC events or deaths as endpoints regardless of the patient's disease stage at baseline
- total number of new or recurrent CDC events or death as endpoint
- total number of new or recurrent CDC events or death including all disease progression events where the diagnosis was rejected by the endpoint review committee

Since results were consistent with the primary analysis, the robustness of the primary analysis was confirmed.

The analysis of biological markers CD4 cell counts and HIV RNA was performed in a subset of patients. Results were not in favour of a close correlation between clinical endpoints and biological markers.

However, the lamivudine and lamivudine + loviride arms were associated with higher CD4 counts (31 and 40 cells/mm3 respectively over 52 weeks) than the control arm (1.8 cells/mm3). There was a low effect on viral load inferior to variability of the assay (time-weighted difference average over 28 weeks or DAVGT: -0.37 to 0.49 log10).

The study was however not designed to address the surrogacy of biological markers.

Validation of surrogate markers

The company was requested by the CPMP to provide data to validate that changes in CD4 count and viral load related to anti-HIV drug treatments are predictive for disease progression. The company provided data based on studies NUCA3001, NUCA3002 and VA298. The clinical events were not assessed as primary efficacy endpoints in studies NUCA3001 and NUCA3002. In study VA298 the predictability in terms of clinical progression of a combined fall in plasma HIV-RNA and rise in CD4 count appeared after 48 months of follow-up, but not at 6 or 13 months, which was the duration of the lamivudine studies.

Clinical efficacy - once daily use dosage regimen

Three studies were submitted aiming at demonstrating non inferiority between lamivudine OAD and BID containing regimen. However, only the pivotal study EPV 20001 is detailed hereafter.

STUDY EPV20001

This randomised, double-blind, controlled, multicenter international Phase II/III study, was designed to evaluate the antiviral effect and safety profile of lamivudine administered 300 mg OAD versus lamivudine 150mg BID, as a component of triple drug therapy, in antiretroviral-naïve patients with HIV-1 infection during 48 weeks.

A central randomisation was performed to assign patients in the group A or group B treatment:

-Treatment Group A: 3TC 300mg OAD / 3TC placebo BID / ZDV 300mg BID / EFV 600mg OAD

-Treatment Group B: 3TC placebo OAD / 3TC 150mg BID / ZDV 300mg BID / EFV 600mg OAD

Patients were to be given combination therapy with lamivudine, zidovudine and efavirenz for at least 48 weeks (study medications received until either the patients met a treatment discontinuation criterion (protocol defined virologic failure, AE, clinical progression, insufficient viral load response, consent withdrawn, lost to follow-up, protocol violation) or end of the study. Real time plasma HIV-1 RNA measurements were performed at weeks 4, 8, 12, 16, 20, 24 and then every 8 weeks. Only plasma HIV-1 RNA levels were used to assess treatment success or failure.

48-week data from study EPV20001 are further reassuring with regard to the similar efficacy and safety profile of Epivir once and twice a day regimen.

Studies in children

ACTG 300, a Phase III study was designed to determine the comparative effectiveness of the combination lamivudine/ZDV versus the better of ddI versus ZDV/ddI therapy in symptomatic HIV-infected children aged between 42 weeks and 15 years, who had received less than 56 days of prior antiretroviral therapy. Paediatric patients were stratified according to age (<3 years and = 3 years). The efficacy was evaluated in terms of time to disease progression and/or death. Secondary endpoints include safety and tolerance parameters. The dose of lamivudine administered was 4 mg/kg bid. Considering the results of ACTG 152 that showed the equivalence between ddI and ZDV/ddI in the rate of disease progression endpoints, the randomisation to the ZDV/ddI group ended. On the basis of the interim analysis an independent body (Data and Safety Monitoring Board) recommended the termination of the study. Of a total of 615 children enrolled, 596 were included in the analysis divided as follows: 236 in the lamivudine/ZDV group, 235 in ddI group and 125 in ZDV/ddI group. The median time on study medication was 9.3 months and 8.3 months for the lamivudine/ZDV group and ddI treatment arms respectively. Characteristics of the population at baseline were similar in all treatment groups.

Results showed a statistically significant difference in time to disease progression in favour of lamivudine in combination with ZDV as compared to ddI alone for children less than 3 years old but not in the older group. This represents a relative reduction in the risk of disease progression of 76% for this strata group. Due to early termination in the enrolment in the ZDV/ddI arm, no conclusion can be drawn on the clinical efficacy of ZDV/lamivudine compared to ZDV/ddI. Data related to clinical progression only in patients enrolled until the date when inclusions in ZDV/ddI arm have stopped will be submitted once available in order to have similar treatment exposure and follow-up.

In terms of biological markers (HIV-RNA and CD4 cell counts) results showed a significant reduction of viral load and a significant increase of CD4 cell counts in the ZDV/lamivudine arm compared to ddI group except at week 48 for both age strata.

PENTA-4, a placebo controlled phase II study was designed to evaluate the safety and tolerability of 4 mg/kg bid of lamivudine added to the current antiretroviral therapy with ZDV, ddI, ZDV + ddI or ZDV + ddC compared with these therapies alone in antiretroviral experienced children (current therapy for at least 3 months). Of 172 children randomised aged between 5 months and 15 years, 162

were analysed (81 per group). The primary endpoint was defined as serious laboratory or clinical events.

Results showed that lamivudine is safe and well tolerated with no increase of serious adverse events when compared with placebo. During the double-blind phase, in total eleven serious adverse events were possible or probably related to the drug trial, 5 (in 4 children) were in the lamivudine group and 6 (in 5 children) in the placebo group.

The analysis of biological markers showed that the addition of lamivudine to current therapy resulted in a significant reduction in viral load a significant increase of CD4 cell counts. At week 24, the reduction in viral load was in average -0.37 log10 copies/ml in the lamivudine group versus-0.01 log10 copies/ml in the placebo group (p=0.0007). Provision of an analysis of viral load according to antiretroviral therapy at inclusion were submitted as part of the follow-up measures to define if benefit in favour to lamivudine is greater in children treated at baseline by only one antiretroviral. The CPMP concluded that the multivariate analysis showed that there was no evidence of any difference in the effect of lamivudine on HIV RNA between children entering the trial on monotherapy (ZDV or ddI) and those entering on combination therapy (ZDV + ddI or ZDV +ddC), after adjusting for baseline CD4 count, HIV RNA, disease stages and total time spent on antiretroviral (p=0.143). The median change in CD4 cells count from baseline was significantly in favours of lamivudine group at week 24 (+ 24 cells/mm3 versus -0.11 cells/mm3, p=0.02).

On the basis of these trials, the efficacy of lamivudine in combination with ZDV and ZDV containing regimens was demonstrated in antiretroviral naive and experienced children in terms of changes in biological markers and clinical efficacy (disease progression and death).

Safety

Analysis of adverse events and laboratory data is based on the clinical program (1,173 adults and 144 children) and on the open-label program (17,572 patients). Lamivudine was well tolerated. The combination of lamivudine and ZDV was as well tolerated as ZDV alone, with no clinically important increases in adverse events or laboratory abnormalities.

The ZDV-lamivudine (2x300 mg/day) group had a slightly increased incidence of serious adverse events (14%) compared with ZDV-lamivudine (2x150 mg/day) (10%), particularly for haematological parameters (anaemia, decrease of neutrophil count).

In adults the incidence of serious adverse events, usually associated with other nucleosides, was low.

The incidence of anaemia and decrease of white blood cells count was higher in the lamivudine (2x300-mg/day) group compared with the lamivudine (2x150-mg/day) group (open-label study). The incidence of neuropathy was not dose related; 12% with ZDV-lamivudine (2 x 150mg/day) compared to 8% with ZDV-lamivudine (2 x 300mg/day).

On request of the CPMP the company performed a meta-analysis on safety data of the four double-blind randomised controlled clinical trials (NUCA3001, NUCA3002, NUCB3001 and NUCB3002). Lamivudine and ZDV combination treatment showed a similar safety profile to control therapy. With respect to study NUCB 3007, no unexpected clinical or laboratory adverse events were reported.

Skin rashes and fever or chills occurred in four surrogate markers studies with a frequency of 9% and 10 % respectively. During the period November 1995 - June 1997, 15 spontaneous post-marketed cases of fever and or chills have been reported which represent 3.2% of the total number of events reported. Similarly 33 cases of rash, allergic rash, pruritic rash, erythematous macular rash, maculopapular rash and acne-like rash were reported which represent 7.1 % of the total number of events reported. Following the assessment of the report, the CPMP therefore recommended to add “fever” and “rash” as undesirable effects.

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 enunciating symptoms, i.e. benign digestive symptoms such as nausea, vomiting and abdominal pain and 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. During their meeting in February 2002 the CPMP adopted a further revision of the class labelling as agreed by the Pharmacovigilance Working Party in January 2002. This revision introduced a "box warning" and restructured the paragraph in order to improve readability and to focus 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.

Following the spontaneous report of 41 cases of alopecia, it was felt necessary to include this adverse event in the SPC considering the possible causal relationship to lamivudine in some cases. Following reports of muscle disorders including rarely rhabdomyolysis, it was decided to include them in the SPC.

Following reports of arthralgia in the post marketing phase including 30 cases with a possible relationship with lamivudine, the company added this adverse event in the SPC.

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. During clinical trials and practice with lamivudine, it has been observed that discontinuation of lamivudine in patients co-infected with hepatitis B has resulted in clinical or laboratory evidence of recurrent hepatitis in some patients. An adequate statement was therefore introduced into the SPC to recommend appropriate monitoring of both liver function tests and markers of HBV replication**.**

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. In response to the request for supplementary information, the applicant introduced pharmacokinetic parameters for lamivudine which are derived from study EPV10001 in 60 healthy volunteers receiving lamivudine 150 mg twice daily or one 300 mg tablet. Of a total of 821 children included in the five clinical studies, 504 were treated with lamivudine either alone or in combination with other antiretrovirals and 317 were treated with control treatments. In

summary, lamivudine appeared to be well tolerated in therapy naive and experienced children and no major safety concerns were identified.

A retrospective safety study provided information on 102 therapy experienced children who received lamivudine in clinical practice. Children of both sexes (55 male and 47 female), aged from less than 1 year to 18 years received lamivudine either alone or in combination with other antiretroviral therapies being ZDV (60%) stavudine (51%), indinavir (38%) ddI (16%) ddC (11%) ritonavir (8%), saquinavir (3%) and nelfinavir (1%). The median daily dose of lamivudine administered was 150 mg (range between 8 and 482) with a median exposure of approximately 8 mg/kg/day. The median duration treatment was 252 days with a range from 15 to 1187 days. In overall no unexpected adverse events were reported. The most commonly reported events included gastro-intestinal events (11%), metabolic events (7%), fever (6%) infections and respiratory problems (5%). The results confirm the good safety profile of lamivudine in children, similar to that in adults. Serious adverse events were reported in 23 patients (23%) but only one (pancreatitis) was considered to be possibly related to treatment with lamivudine.

To further support the safe use of Epivir 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.**Bioavailability and bioequivalence**

Several formulations have been used throughout the clinical development of lamivudine: intravenous solution, oral solution (1 mg/ml without ethanol, 10 mg/ml with ethanol) tablets, capsules.

Bioequivalence of 1x300 mg tablets with 2x150 mg tablets was shown.

Bioequivalence of 4x75 mg, 3x100 mg and 1x300 mg tablets was shown.

Bioequivalence of tablets, oral solution (1 mg/ml) and capsules at a dose level of 100 mg was shown.

The bioequivalence of the oral solution 10 mg/ml was not directly compared with tablets, but the company has provided evidence that the 10 mg/ml oral solution has comparable bioavailability to the tablet.

Bioequivalence studies performed comparing lamivudine 1 mg/ml alcohol-free, 10 mg/ml (6% v/v ethanol) and 10 mg/ml (10% v/v ethanol) oral solutions previously demonstrated comparable bioequivalence between formulations. However the alcohol-free formulation differs from the proposed ethanol-free Epivir formulation, the concentration of the active substance is not identical and alcohol may theoretically have an impact on the absorption of the active substance by a vasodilator effect. Taking into account the good bioavailability of the active substance (approximately 82%) and the pharmaceutical form of the finished product (oral solution) further bioequivalence studies would not seem to be necessary.

5. Overall conclusions and benefit/risk assessment

The data provided related to chemical and pharmaceutical aspects were considered acceptable to ensure the quality and the consistency of Epivir tablets and oral solution.

The preclinical data were extensive and demonstrated the antiviral activity of lamivudine and relevant for the indication claimed.

On the basis of the surrogate markers data, the preliminary evidence of clinical benefit from the meta-analysis of clinical events, and a favourable safety profile, the CPMP issued on 18 April 1996 a favourable Opinion for Epivir for granting a Marketing Authorisation under exceptional circumstances. As part of the specific obligations to be fulfilled as set out in Annex IIC of CPMP Opinion and Annex IIC of Commission Decision dated 8 August 1996 the company was requested to submit the final report of study NUCB 3007 to confirm the clinical benefit of lamivudine.

Clinical end-point data indicate that lamivudine in combination with ZDV, and lamivudine/ZDV containing treatment regimens result in a significant reduction in the risk of disease progression and mortality.

On the basis of the additional efficacy and safety data available, the CPMP considered that the risk benefit ratio of lamivudine in adults remained favourable. Since all the specific obligations were fulfilled the CPMP agreed that there were no remaining grounds to maintain the Marketing Authorisation under exceptional circumstances.

ACTG 300 and PENTA-4 support the immuno-virological and clinical efficacy of lamivudine in antiretroviral naive and experienced paediatric population (including 127 children less than 3 years in ACTG 300, 20 children less than 2 years in PENTA-4 and 20 children less than 3 years in the retrospective study) at the recommended dose of 4 mg/kg bid.

Based on the data from all the studies, the safety profile of lamivudine in children appears to that observed in HIV infected adults. The number of children aged less than 2-3 years was considered sufficient to confirm the proposed dose recommendation based on pharmacokinetic data in few children less than 2 years. The overall risk/benefit ratio of lamivudine in children was therefore considered acceptable. As a consequence, Epivir was recommended for the treatment of HIV infected children.

In conclusion, Epivir is approved for the following therapeutic indication:

Epivir is indicated as part of antiretroviral combination therapy for the treatment of HIV-infected adults and children.