SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Combivir. This scientific discussion has been updated until 30 July 2005. For information on changes after this date please refer to module 8b.

1. Introduction

Current available therapy options for the treatment of Human Immunodeficiency Virus (HIV) infection comprises four different mechanistic classes of compounds: nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and fusion inhibitors. The first category of agents, the NRTIs, acts at an early stage in the HIV life cycle by blocking the activity of reverse transcriptase. This enzyme is essential for the conversion of viral RNA to proviral DNA, thus allowing integration into host cell DNA and subsequent viral replication. Combination therapy, especially triple regimens, is considered to be the standard of care of HIV infected patients. These therapeutic regimens result however in a great number of daily doses of tablets/capsules.

Combivir was the first fixed dose combination containing two known antiretroviral agents belonging to the RT inhibitors class. This medicinal product containing 150 mg of lamivudine and 300 mg zidovudine has been developed as an oral therapy (tablet) for the treatment of HIV-1 infection in adults.

Individual formulations of lamivudine (150 mg tablets) and zidovudine (300 mg tablets) have already been granted a Marketing Authorisation for the treatment of HIV-1 infection. Zidovudine was the first compound to be licensed for the treatment of HIV.

The development of this fixed dose combination aims to reduce the number of daily tablets, and therefore enhance the compliance therapy and thereby minimising the risk of emergence of resistance.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

Combivir is a fixed dose combination formulation presented as a film coated capsule-shaped tablet containing two active substances: 150 mg lamivudine and 300 mg zidovudine. Individual formulations of lamivudine 150 mg and zidovudine 300 mg tablets have already been licensed.

Other ingredients include microcrystalline cellulose, sodium starch glycolate, magnesium stearate, colloidal silicon dioxide and excipients commonly used in film-coatings. The film coating chosen is the same Opadry White, already used for the approved lamivudine 150 mg tablet formulation.

The containers are opaque polyvinyl chloride foil blister units containing 10 tablets per blister card (6 blister cards per carton) and white HDPE bottles with child resistant/tamper evident closures containing 60 tablets.

The composition and shape of the fixed dose combination tablet used in clinical studies are similar to the ones of the medicinal product intended to be marketed. The fixed dose combination tablet has been demonstrated to be bioequivalent to the co-administration of two individual marketed medicinal products as described in section III.4 of this document.

The pharmaceutical development of this formulation was based on the existing experience of the two individual marketed formulation tablets, lamivudine 150 mg and zidovudine 300 mg tablets. The aim for the development of these fixed dose combination tablets was to provide the association of two known active substances, lamivudine and zidovudine, in an easy swallowed formula to help dosing compliance and increase convenience in administration for patients. The choice of the excipients was considered adequate. Lamivudine/zidovudine fixed dose combination tablets were formulated to provide rapid release of the two active substances as confirmed by the dissolution tests. The compatibility between the two active substances as well as the compatibility between both active substances with the excipients has been documented for several conditions.

Method of preparation

Lamivudine/zidovudine tablets are manufactured using traditional methods involving blending, compression and film coating. The in-process controls carried out on tablet cores were considered adequate to ensure batch to batch reproducibility and compliance with standard specifications. Validation data presented on three batches were sufficient to demonstrate the consistency of the process and the quality of the product.

Control of starting materials

Lamivudine and zidovudine are the same active substances as those used in the previously approved marketed medicinal products containing the individual drug substances. The quality of the two active substances is therefore well established.

Lamivudine is (2R, cis)-4-amino-1-(2hydroxymethyl 1,3-oxathiolan-5S-yl)-(1H)-pyrimidin2-one and has not yet been described in any pharmacopoeia. The manufacture of lamivudine involves multistep 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.

Zidovudine (3'azido-3'deoxythimidine) is controlled according to the European Pharmacopoeia (Ph. Eur.) requirements.

All the excipients in the tablet core are described in the monographs of the Ph. Eur. The film-coat is an Opadry, whose components are described in the Ph. Eur.

Standard packaging materials, e.g. HDPE and PVC, were shown to comply either with the Ph. Eur. requirements or the requirements for materials used in contact with food.

Control tests on the finished medicinal product

Tablets are tested according to standard methods. The specifications and routine tests at release and at the end of shelf life for the finished product are acceptable. Test procedures for the control of the finished product are sufficiently validated.

Stability

Stability data of lamivudine up to 18 months met specifications at all storage conditions, and no degradation was observed.

Stability tests for up to 36 months were presented for two batches of zidovudine. No significant increase in drug-related substances was observed. The samples that show signs of deterioration were those exposed to light, indicating the need for protection from light.

Finished product stability tests were carried out on batches packed in the proposed commercial containers. The stability data submitted by the applicant support the proposed shelf life and storage conditions defined in the SPC.

Overall, apart from clarifications to be submitted by the applicant, the chemical and pharmaceutical data submitted were found acceptable to ensure the quality of Combivir film coated tablets.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

Both lamivudine and zidovudine are pyrimidine nucleoside analogues. After intracellular uptake, both compounds are sequentially phosphorylated by host cell intracellular kinases to their respective 5'-triphosphates (TP). Thereafter, the monophosphate of respective 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. Both compounds are also competitive inhibitors of the viral RT. Their specific activity against HIV is mainly related to their selectivity for dividing cells and their high affinity for viral RT. Furthermore, mammalian DNA-dependent DNA polymerases are hardly inhibited by zidovudine-TP. 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 2 nM to 15 μM. In addition, lamivudine-TP inhibited viral RT with a Ki value of 10-12 μM. Depending on the host cell lines and wild-type virus strains used, IC50s for zidovudine ranged from 1-350 nM. Zidovudine-TP was also a potent inhibitor of HIV RT, with a Ki of 40 nM. For both compounds, antiviral activity was seen at lower concentrations than those required for RT inhibition, suggesting that chain termination is the main mechanism of action.

Antiviral activity of the lamivudine and zidovudine combination 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 to synergistic effects of the combination.

The *in vitro* intracellular half-lives of lamivudine TP and zidovudine TP were 10-15 h and 3 h, respectively. Antiviral effects have been demonstrated at extracellular concentrations <0.5 μM for zidovudine and 10 nM for lamivudine. 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 either compound 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%) for lamivudine and zidovudine were >30 μM and >5 μM respectively. Depending on the test systems used, the therapeutic index (i.e. the ratio between LC50 and IC50) was in general large for both compounds. In various studies the cytotoxicity was in general additive.

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. Zidovudine was also well tolerated in studies addressing Central Nervous System, cardiovascular, respiratory and diuretic parameters. Safety pharmacology studies with the combination have not been performed. This was considered acceptable since there were no indications of pharmacodynamic or pharmacokinetic interactions

Pharmacokinetics

The pharmacokinetic profiles of both compounds have been studied separately in the main species used in the preclinical testing programmes. In both cases, protein binding was moderate to low in all species including humans (25-35% for zidovudine; 35-50% (at 0.1 μg/ml) to <10% (at 100 μg/ml) for lamivudine). In distribution studies with radioactively labelled lamivudine or zidovudine, rapid and wide tissue distribution of drug-related radioactivity was seen for both compounds. There were no signs of tissue accumulation. Placental transfer of drug-related material has also been demonstrated with both compounds. Studies in lactating rats have shown that both compounds, after oral administration, are 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 oral administration of zidovudine to rats, up to 98% of the drug-related material was excreted in urine of which about 85% was unchanged, indicating high absorption and minor metabolism. Four minor metabolites were present, and one of them corresponded to the main metabolite in human, 5'-glucuronylazidothymidine (GAZT), which lacks anti-HIV activity. In dogs, drug-related material was mainly excreted via the kidney. Three metabolites were identified, one of them being GAZT. Studies in cynomolgus monkeys indicated extensive metabolism to GAZT. These studies showed that the pharmacokinetic profile of zidovudine in cynomolgus monkeys most closely resembled that observed in humans.

Using *in vitro* models, there was no evidence of interactions between lamivudine and zidovudine at the absorption or elimination levels. Based on different metabolic pathways, the potential for metabolic interactions is considered to be low.

After administration of either lamivudine or zidovudine, 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 of either compound. A combination toxicity study demonstrated that there was no indication of changes in plasma levels of either compound when given separately or in combination.

Toxicology

The preclinical toxicity profiles of lamivudine and zidovudine have been characterised separately in a number of different species in studies of up to 2 years duration (see more detail below). With both drugs, the haematopoetic system was the most commonly affected target organ. Furthermore, both compounds showed a potential to induce embryotoxicity after administration to pregnant animals. One toxicity study has been undertaken with the combination (see below).

Single dose toxicity of lamivudine or zidovudine after intravenous (i.v.) or oral administration was studied in rodents. The acute toxicity of lamivudine 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. In the case of zidovudine, the median lethal doses were > 750 mg/kg (i.v.) and > 3000 mg/kg (oral) in both species.

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. The oral repeated dose toxicity of zidovudine was studied in rats (up to 12 months) and monkeys (up to 12 months). Anaemia was observed in both species. In monkeys, also white blood cell counts were decreased and bone marrow examinations revealed progressive retardation of the maturation of all cell lines. One toxicity study has been undertaken with the combination. The study focussed on haematoxicity and was conducted in mice since it is the most sensitive species for zidovudine-induced haematoxicity. Following 36 days administration of various doses of lamivudine together with a weakly hematotoxic dose of zidovudine, anaemia that was most likely related to zidovudine, was observed. There was no evidence of synergistic toxicity.

Reproductive function: Lamivudine did not impair the overall reproductive performance in rats. Embryonic deaths occurred in rabbits (lamivudine) or in rats and rabbits (zidovudine). Lamivudine showed no teratogenic potential in either species. After administration of zidovudine to rats during the organogenetic period, malformations were evident after doses that also caused maternal toxicity (3000 mg/kg/d). Studies in rabbits revealed no teratogenic effects up to 500 mg/kg/d. Peri-post natal studies in rats with either compound 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.

Zidovudine induced both gene mutations and chromosomal aberrations in a number of *in vivo* and *in vitro* test systems. In relation to lamivudine, zidovudine showed a greater genotoxic potential both *in vitro* and *in vivo*.

The carcinogenic potential of lamivudine was studied in conventional 24-month 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.

With zidovudine, carcinogenicity was studied in mice and rats in 22-24 month studies. In female mice, a dose dependent increase of vaginal tumors was observed. Also rats developed vaginal tumours at the highest dose tested. These may be related to local effect of unmetabolised zidovudine. In addition, a transplacental carcinogenicity study has been performed in mice. Also this study indicated increased incidence of vaginal tumours after life time treatment, possibly due to a local effect as above. Based on these data, zidovudine is considered to be a rodent carcinogen. However, due to metabolic differences between rodents and humans, the relevance of these findings for humans is uncertain.

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. Neither lamivudine nor zidovudine appeared to affect the immune system.

4. Part IV: Clinical aspects

The use of lamivudine and zidovudine as either monotherapy or in combination for the treatment of HIV-1 infection has been extensively studied. For the development of the fixed dose formulation, the properties of each substance, the administration of lamivudine with zidovudine and the bioequivalence of the compounds were reviewed. The development of the fixed dose combination tablet was based on the recommendations of the existing CPMP Guideline on fixed combination medicinal products.

Pharmacokinetics

Co-administration of lamivudine with zidovudine has been evaluated in several studies and no pharmacokinetic interaction between both substances was found as described below.

Absorption and distribution

Administered by the oral route the extent of absorption of lamivudine in adults is normally between 80 and 85%. Food intake results in a delay of T_{max} (0.75 hours) and a lower C_{max} (decrease by 15%) but did not significantly affect the AUC.

With respect to zidovudine, the bioavailability is normally between 60 and 70%. Food intake results in a delay of T_{max} (0.5 hours) and a lower C_{max} (decrease by 45 %) but did not significantly affect the AUC.

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range. Binding to human plasma proteins was low for both substances with less than 36% for lamivudine and 34% to 38% for zidovudine. The mean apparent volumes of distribution (Vdss) determined after intravenous administration was 1.3 l/kg and 1.6 l/kg for lamivudine and zidovudine respectively, suggesting a wide tissue distribution. Lamivudine and zidovudine were shown to penetrate the blood-brain barrier at moderate amounts. The mean ratios of CSF/serum lamivudine and zidovudine concentrations 2-4 hours after oral administration were approximately 0.12 and 0.5 respectively.

No change in absorption of lamivudine was observed when zidovudine was co-administered. Although a small increase in C_{max} (28%) was observed for zidovudine when lamivudine is co-administered, no statistical difference was found on the overall exposure as defined by the AUC.

Biotransformation

Lamivudine is not extensively eliminated by hepatic metabolism (5-10%). The amount of urinary trans-sulfoxide metabolite recovered in urine was minor. Lamivudine is predominantly cleared by renal excretion of unchanged drug.

On the contrary zidovudine was found to be extensively metabolised. The major inactive metabolite found in both plasma and urine is 5'-glucuronide of zidovudine accounting for approximately 50-80% of the administered dose eliminated by renal excretion. Following intravenous administration of zidovudine, the metabolite 3'-amino-3'deoxythymidine (AMT) has been identified.

Considering the different metabolism pathway between lamivudine and zidovudine no interaction is expected or observed.

Elimination

Lamivudine is excreted through renal route via glomerular filtration and active tubular secretion (most likely the organic cationic transport system) mainly as unchanged drug (>70% of unchanged drug) with a mean systemic clearance of approximately 0.32 l/h/kg. The observed half-life of elimination is 5 to 7 hours.

Zidovudine is eliminated through renal and metabolic routes. Following intravenous administration, the mean terminal half-life was 1.1 hours and the mean systemic clearance accounted for 1.6 l/h/kg. The estimated renal clearance of 0.34 l/h/kg indicated glomerular filtration and active tubular secretion by the kidneys.

Since zidovudine is only partially eliminated by active renal secretion, no potential interaction with lamivudine was expected.

Special population

Since data are available in patients with renal or hepatic impaired function with the separate formulations of lamivudine and zidovudine, no study was performed with the fixed formulation.

The pharmacokinetic behaviour of lamivudine has been evaluated in patients with renal impaired function. Lamivudine elimination was shown to be affected by renal dysfunction. A dosage reduction for patients with creatinine clearance below 50 ml/min was therefore recommended. With respect to zidovudine, a higher plasma concentration of zidovudine and its metabolites was found in patients with advanced renal failure suggesting the need for dosage reduction in this population.

Data obtained in patients with moderate to severe hepatic impairment showed that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction. Limited data in patients with

cirrhosis showed that accumulation of zidovudine might occur in patients with hepatic impairment because of decreased glucuronidation. A dosage reduction of zidovudine in severe hepatic impaired population is therefore warranted.

Based on this information, the administration of the separated preparations of lamivudine and zidovudine is therefore warranted in hepatic or renal impairment populations.

Since there are insufficient data on the use of the fixed dose combination in children, the use of the fixed dose tablet is not recommended. Similarly the use of the fixed dose tablet is not recommended since the safety of lamivudine has not been established in pregnancy.

Interactions

As Combivir contains lamivudine and zidovudine, any interactions that have been identified with these agents individually may occur as detailed in the individual SPCs for Epivir and Retrovir. The likelihood of metabolic interactions with lamivudine is low due to limited metabolism and plasma protein binding, and almost complete renal clearance. Zidovudine is primarily eliminated by hepatic conjugation to an inactive glucuronidated metabolite. Medicinal products which are primarily eliminated by hepatic metabolism especially via glucuronidation may have the potential to inhibit metabolism of zidovudine.

Bioequivalence testing

A study was carried out to assess the bioequivalence between the fixed dose combination tablet to the two marketed formulations being lamivudine 150 mg tablets and zidovudine 300 mg tablets. This open-label, three-way crossover study involved 24 healthy volunteers. The three treatments were as follows:

- fixed dose combination tablet (lamivudine 150 mg/zidovudine 300 mg) after an overnight fast
- separate lamivudine 150 mg tablets and zidovudine 300 mg tablets swallowed simultaneously after an overnight fast
- fixed dose combination tablet (lamivudine 150 mg/zidovudine 300 mg) after a standardised breakfast.

Results from this study confirmed the lack of pharmacokinetic interaction between zidovudine and lamivudine since the properties of both substances in combination are in the range of the respective administration of monotherapy. In addition, the fixed dose combination tablet was shown to be bioequivalent to the two marketed formulations, lamivudine 150 mg tablets and zidovudine 300 mg tablets, when co-administered under fasting conditions. The influence of food was also evaluated. When the combined lamivudine/zidovudine fixed dose tablet was administered with food the extent of the absorption of either lamivudine or zidovudine was unchanged in comparison to administration under fasting conditions. The effect of food to slow the rate of absorption was previously demonstrated with current available separated formulations and was not expected to have clinical consequence. Therefore the combined lamivudine/zidovudine fixed tablet may be administered without regard to meal since there was no significant difference in extent of absorption following a meal and no clinical consequence of slowed absorption is expected.

Clinical experience

Efficacy

Zidovudine was the first antiviral agent to be licensed for the treatment of HIV. It has been extensively used and studied. Lamivudine 150 mg tablet was authorised in 1996 for the treatment in HIV-infected patients in combination with other antiretroviral agents including zidovudine. The dosing regimen in clinical trials conducted with the combination of both substances was 200 mg tid zidovudine with 150 mg lamivudine bid. The proposed dosing regimen for the fixed dose formulation, which contains 300 mg zidovudine and 150 mg lamivudine, is one tablet twice daily.

During the development of lamivudine, the co-administration with zidovudine has been extensively studied and the favourable risk/benefit of lamivudine in combination with zidovudine has already been established. Since then the combination of lamivudine with zidovudine has been widely used. The

fixed dose combination corresponds closely to combinations that are already used in practice. The results of a study (NUCB 3027) demonstrated therapeutic equivalence between the fixed dose combination and dosage regimens used in the efficacy studies.

The efficacy and safety of lamivudine in combination with zidovudine was established on the basis of 4 phase II/III (NUCA 3001, NUCA 3002, NUCB 3001 and NUCB 3001) comparative biological markers studies, a meta-analysis of clinical events and safety data from a large open label programme. In the 4 above-mentioned studies, patients received 150 mg bid in combination with 200 mg zidovudine tid. These studies involving zidovudine naive patients (NUCA 3001 and NUCB 3002) and experienced patients (NUCA 3002 and NUCB 3002) compared double combination of lamivudine/zidovudine with lamivudine or zidovudine monotherapy. The overall results showed that combination of zidovudine and lamivudine was associated with significant increases in CD4 cell counts and reduction in viral load as measured by PCR compared with zidovudine monotherapy or zidovudine + zalcitalbine in naïve and pre-treated patients. Patients in the zidovudine/lamivudine groups exhibited substantial drop in viral load at weeks 2 and 4 followed by a rebound effect with a mean peak decrease from baseline of around -1.5 $\log_{10}$ copies/ml. Over 24 weeks, results did show significant advantage of the combination over each treatment monotherapies.

On the basis of the results from these studies a meta-analysis of the progression to CDC B/C clinical endpoints was performed. Zidovudine in combination with lamivudine was associated with a 49% reduction in disease progression. This benefit was found to be consistent in different sub-populations.

A large randomised controlled double blind clinical endpoint trial (NUCB 3007) was designed to compare the efficacy and safety of lamivudine and lamivudine + loviride against placebo in the treatment of HIV-1 infected patients taking concurrent zidovudine-containing regimens with CD4 cell counts between 25-250 cells/ mm^3. This well conducted trial involved 1895 antiretroviral naïve or experienced patients, from both sex and over 18 years old. Patients were antiretroviral experienced for 83% with a median duration of prior therapy of approximately 28 months. The concurrent zidovudine-containing regimens consisted of zidovudine/zalcitalbine for 23% and zidovudine/didanosine for 15%, the rest being zidovudine alone. Based on the results from the second interim report which demonstrated a significant delay in time to progression to new AIDS event or death in the lamivudine arms compared to placebo, it was recommended to end the study. Due to premature termination of the study, the median duration on study medication was approximately 9 months.

Final results over 12 months from this study confirmed and extended the clinical data described in the meta-analyis of the 4 biological markers studies. The addition of lamivudine to zidovudine containing regimens was associated with a highly significant relative reduction in risk of disease progression to AIDS/death (57%). The combination lamivudine with zidovudine-containing regimen was also associated with a significant benefit in survival alone with 60% relative reduction in mortality (p=0.0007). The results showed that the addition of loviride to lamivudine did not add any additional clinical benefit.

Study (NUCB 3027) aimed to compare the antiviral activity between two regimens of the combination lamivudine/zidovudine. The first regimen consisted of the fixed dose combination formulation (lamivudine 150mg/zidovudine 300 mg) administered twice daily whereas the second consisted of the separate formulations (zidovudine 2x100 mg capsules tid plus lamivudine 150 mg tablet bid). This open-label, randomised study involved 75 antiretroviral naive patients of both sex, with CD4 cell counts (200 cells/ mm^3 and viral load (10,000 copies/ml. Primary endpoint was changes from baseline in viral load as measured by PCR at week 12.

Results showed that, at week 12, change from baseline in HIV-RNA was -1.36 $\log_{10}$ copies/ml in both treatment groups. No statistically significant difference on the CD4 cell counts was observed at week 12 between the fixed dose combination tablets and the separate formulations. Both treatments seemed to be well tolerated. Based on these results, both treatment regimens can be considered as equivalent with respect to antiviral activity.

The potential clinical benefit of the fixed combination has not yet been established in children. Therefore the administration of the fixed dose formulation is only recommended in adolescents over 12 years of age.

Resistance

Individually lamivudine and zidovudine therapy has resulted in HIV clinical isolates, which show reduced sensitivity *in vitro* to the nucleoside analogue to which they have been exposed. However *in vitro* studies indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. In therapy naïve patients treated with a combination of lamivudine and zidovudine, the emergence of zidovudine phenotypic resistance was delayed without influencing development of lamivudine phenotypic resistance (9% versus 39% in patients treated with zidovudine monotherapy after 24 weeks).

Considering that the combined lamivudine/zidovudine fixed dose tablet may allow a simplification of therapy and therefore improves patients compliance, which is the limiting factor in therapeutic success leading to drug resistance, the fixed combination tablet may offer an interest in minimising the risk of emergence of resistance.

Safety

Safety data with the fixed dose tablet are limited to data derived from the bioequivalence study, which showed that Combivir was well tolerated. Extended data on the combination of zidovudine/lamivudine shows it to be well tolerated and with a safety profile, which indicated that the magnitude and frequency of adverse events or laboratory abnormalities are similar to that observed with zidovudine alone. In addition based on the results from study NUCB 3007, there was no evidence that lamivudine increases the incidence or the severity of clinical and laboratory toxicities observed with zidovudine-containing regimen alone. As Combivir contains lamivudine and zidovudine, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no evidence of added toxicity following concurrent administration of the two compounds.

The main finding for lamivudine in combination with zidovudine was neutropenia and anaemia, both occasionally severe. The most commonly reported adverse events with lamivudine include headache, insomnia, cough, nasal symptoms, nausea, vomiting, abdominal pain or cramps, diarrhoea, rash, alopecia, arthralgia, muscle disorders, fatigue, malaise and feverThe most commonly reported adverse events with zidovudine include anaemia, neutropenia, leucopenia, headache, dizziness, nausea, vomiting, abdominal pain and diarrhoea, myalgia and malaise.

Alopecia and arthralgia were reported as common adverse events and rhabdomyolysis was reported as a rare adverse event related to lamivudine.

Following the evaluation of additional data submitted the CPMP requested to harmonise the labelling on pancreatitis and peripheral neuropathy of all medicinal products containing lamivudine.

Cardiomyopathy was reported as a rare adverse event related to zidovudine.

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.

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. In response to the request for supplementary information, the applicant introduced pharmacokinetic parameters in healthy volunteers for lamivudine and zidovudine.

A pilot study demonstrated that zidovudine is incorporated into leukocyte nuclear DNA of adults, including pregnant women, taking zidovudine as treatment for HIV-1 infection, or for the prevention of mother to child viral transmission. Zidovudine was also incorporated into DNA from cord blood leukocytes of infants from zidovudine-treated mothers. A transplacental genotoxicity study conducted in monkeys demonstrates that foetuses exposed *in utero* to the combination of zidovudine plus lamivudine, at human-equivalent exposures, sustain a higher level of nucleoside analogue-DNA incorporation into multiple foetal organs. There was also evidence of more telomere shortening than in monkey foetuses exposed to zidovudine alone. The clinical significance of these findings is unknown.

To further support the safe use of Combivir 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.

Risk/Benefit Assessment

The combination of lamivudine plus zidovudine has been proven to be effective and well tolerated and is widely used in antiretroviral combination therapy. Pharmacodynamic and pharmacokinetic interactions between zidovudine and lamivudine have shown no differences in zidovudine or lamivudine exposure when co-administered. Additionally, *in vitro* experiments have found no intracelullar interaction with respect to zidovudine triphosphate or lamivudine triphosphate as expected, since different enzyme systems are required for their phosphorylation. Lastly, synergy between these compounds has been observed both *in vitro* and clinically. Hence, taking into account the bioequivalence between the fixed dose combination tablet and the two individual marketed formulations, and the results of the study NUCB 3027, Combivir is expected to provide similar efficacy and safety profile to that observed with the two separate formulations.

The combined lamivudine/zidovudine fixed dose tablet may improve patient's compliance and offer an interest in minimising the risk of emergence of resistance. In populations requiring dosage adjustment the use of this fixed dose combination tablet will not be appropriate.

5. Overall conclusions and benefit/risk assessment

The chemical and pharmaceutical data submitted are acceptable to ensure the quality and the consistency of the fixed dose combination tablets.

Since zidovudine and lamivudine have been extensively and safely used in humans in similar daily doses (similar AUC) for a long period, studies in animals with the combination were limited to one haematoxicity study.

The CPMP has considered during the review process that, on the basis of the current efficacy and safety data of both separated substances, the bioequivalence and efficacy studies which compared the fixed dose combination tablet to the individual marketed formulations, the overall risk/benefit ratio for Combivir is favourable. Consequently, the CPMP gave a favourable opinion for granting a marketing authorisation for Combivir, fixed dose combination tablets of 150 mg lamivudine 300 mg zidovudine for the following indication: Combivir is indicated in antiretroviral combination therapy for the treatment of HIV infected adults and adolescents over 12 years of age.