SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Zeffix. This scientific discussion has been updated until 1 March 2004. For information on changes after this date please refer to module 8B

1. Introduction

Hepatitis B virus (HBV) is the causative agent for acute and chronic hepatitis. Chronic hepatitis B is a common disease with an estimated prevalence of more than 300 million long-term carriers of the virus. In adult HBV carriers, 40 to 70 % have evidence of hepatitis B viral replication and are at highest risk of developing long-term complications, such as chronic hepatitis, cirrhosis and hepatocellular carcinoma (approximately 1 % per year). The majority of infected patients will however spontaneously recover. HBV is a hepadnavirus (DNA virus). The infectious virus is a small-enveloped particle with an outer protein coat (hepatitis B surface antigen or HBsAg) and an inner protein core (hepatitis B core antigen or HBcAg). Hepatitis B e antigen or HBeAg is synthetised from a messenger RNA (mRNA) starting from core (HBcAg) mRNA. Detection of HBeAg, HBsAg or HBV DNA in the serum for more than 6 months after initial infection indicates a chronic HBV infection.

Currently the only established treatment for hepatitis B is repeated subcutaneous injections of alpha-interferon, an immune modulator, which is not very well tolerated. In a meta-analysis the overall response rate was approximately 33 % after 4-6 months of treatment, as assessed by the disappearance of HBeAg in serum. However, subgroups of patients cannot benefit from interferon therapy (transplanted patients, severe decompensated cirrhotic patients) and others are not good responders (pre-core mutants, patients with high level of HBV replication).

Two oral formulations of Zeffix are available: film-coated tablet (each contains 100 mg lamivudine) and oral solution (each ml contains 5 mg lamivudine). Lamivudine is a nucleoside analogue with evidence of potent antiviral activity against Human Immunodeficiency Virus (HIV). Two formulations containing lamivudine (150 mg film-coated tablets and 10 mg/ml oral solution) have already been granted a Marketing Authorisation for the treatment of HIV infection in combination with other antiretrovirals.

The approved indication of Zeffix at the recommended dose of 100 mg lamivudine once daily is the following:

Lamivudine is indicated for the treatment of adult patients with chronic hepatitis B and evidence of viral replication

- with decompensated liver disease

or

- with histologically documented active liver inflammation and/or fibrosis.

This indication is based on the analysis of serological and histological end points that were mainly derived from studies of one-year duration in HBeAg positive patients with compensated liver disease.

2. Chemical, pharmaceutical and biological aspects

Composition

The pharmaceutical development of Zeffix is relatively straightforward since the two proposed pharmaceutical forms, film-coated tablet and oral solution are standard formulations and are similar to the formulations of lamivudine already approved for the treatment of HIV, although they differ in strength.

Film-coated tablet

The excipients entering in the composition are common for immediate release film-coated tablets. The film-coat applied to mask the unpleasant taste of the active substance meets an in house specification.

The proposed container is double foil blister unit made of aluminium foil laminated with polyvinyl chloride (product contact) with an external coating of polyamide and a push-through aluminium lidding. The blister contains 14 tablets per blister card (2 or 6 blister cards per carton).

Oral solution

The oral solution consists of a conventional aqueous solution. The proposed container is a 240 ml opaque white round high-density polyethylene bottle with child resistant closure. The 10 ml dosing device consists of a medium density polyethylene syringe-adapter and a clear polypropylene oral dosing syringe. Results of dose assurance and compatibility studies have been submitted, but these studies have been conducted with the formulation of lamivudine already approved for the treatment of HIV.

Active substance

Lamivudine is the same active substance as that used in the medicinal products containing lamivudine already approved for the treatment of HIV infection. The quality of the active substance is therefore well established. The (-) enantiomer of lamivudine, which is less cytotoxic than the (+) enantiomer or the racemate is selected for the manufacture of the finished medicinal product. Two polymorphic forms form I (partial hydrate) and form II have been identified. Manufacture of lamivudine involves four-step synthesis, which includes isolation of the desired stable crystalline form (II). Evidence of structure is appropriate and complete, and the identification test ensures that only form II is used for the manufacture of the finished product. Validation results show consistency of the process and the quality of the product.

Stability studies have been carried both under accelerated and long-term storage conditions. Lamivudine met specifications at all storage conditions up to 18 months, and no degradation was observed.

Other ingredients

All other ingredients entering into the preparation of the tablets or the oral solution as well as the packaging components meet pharmacopoeial requirements except the film-coating material and the flavours, which meet in-house specifications.

Product development and finished product

Film-coated tablets

The pharmaceutical development of the tablet consisted of the selection of components allowing a satisfactory flow and compression as well as a rapid disintegration/dissolution and good stability. The process development has been adequately addressed based on a detailed study of the critical steps of the direct compression. Several different formulations were used during the clinical trials, including hard gelatin capsules in early studies. In addition, the active substance used in the clinical trials was manufactured through two synthetic routes, which produced equivalent material. Results from bioavailability studies indicated that the differences in the formulations and the synthetic routes of the active substance did not have any effect on the bioavailability.

The manufacturing process of the tablets consists of the conventional stages of blending, direct compression, aqueous film coating and packaging. Appropriate in-process controls and limits are specified and tests methods are adequately described. Results from the validation programme including 6 batches of different size are sufficient to demonstrate the consistency of the process and quality of the product.

Stability tests have been carried out on three-production scale batches stored under long term and accelerated conditions. Based on the observed results at 24 months, the proposed shelf life of 36 months when stored below 30ºC is acceptable**.** Long-term stability data will be further evaluated.

Oral solution

During the development of the formulation, the pH of 6 has been shown to be the most appropriate to ensure preservation and stability of the oral solution. In-use testing studies, performed during the stability programme, did not show any significant changes in the product 30 days after opening.

The composition of the batches used during the clinical trials varied in terms of the amount of the active substance and in terms of the percentage of ethanol incorporated. The ethanol was later withdrawn to provide greater dosing accuracy. The bioavailability between solutions with and without ethanol has been demonstrated as well as the bioavailability between the tablet formulation and the oral solution at equivalent doses.

The manufacturing process is simple, including the preparation of the bulk solution, filtration, filling, capping and packaging. In-process controls are acceptable, limits are specified and tests methods are adequately described. The validation data have demonstrated that the manufacturing process is well controlled and reproducible.

Stability tests have been carried out on three-production scale batches stored under stronger stress conditions compared to the international requirements, which is therefore acceptable. The results obtained at 12 months support the proposed shelf life of 24 months when stored at or below 25ºC. Data also showed that the oral solution is stable 30 days after opening. Long-term stability will be further evaluated.

3. Toxico-pharmacological aspects

Pharmacodynamics

Mechanism of action

Lamivudine is an antiviral agent with a pyrimidine nucleoside analogue structure, which suppresses HBV viral replication by terminating HBV DNA chain elongation.

Lamivudine has been shown to enter HBV transfected and non-transfected HepG2cells (a human hepatoma-derived cell-line) where it is phosphorylated to lamivudine 5'-monophosphate (active form of the parent compound) by cytoplasmic deoxycytidine kinase. Intracellular phosphorylation of the monophosphate results in the formation of the 5'di- and 5'tri-phosphates. Lamivudine triphosphate has *in vitro* a long half-life in HBV-transfected cells (17 to 19 hours), supporting the use of the once daily regimen in humans. Lamivudine triphosphate acts as a substrate of HBV viral polymerase. The formation of further viral DNA is blocked by incorporation of lamivudine triphosphate into the chain. Lamivudine 5'-triphosphate is selective and only a weak inhibitor of mammalian DNA polymerases α and β.

Antiviral activity

The specificity of lamivudine for HBV has been demonstrated by its lack of activity against a number of RNA and DNA viruses, apart from HIV and other microorganisms.

Concentrations leading to 50 % inhibition of viral replication (IC_{50}) are equivalent to 0.018 μM and 0.022 μM *in vitro* in two different hepatoma cell lines. Lamivudine also decreases *in vitro* the intracellular duck hepatitis B virus DNA in duck hepatocytes with an $IC_{50\ value}$ of 0.44 μM. *In vivo*, lamivudine decreases serum HBV DNA levels in chronically infected chimpanzees at dosages of

0.1 mg/kg b.i.d and above, and reduces HBV DNA polymerase activity to below 10 % of pre-treatment levels at dosages of 1-6 mg/kg b.i.d. Serum levels of HBeAg decrease by two-fold in chronically infected chimpanzees treated with lamivudine at 10 mg/kg bid for 28 days.

A rebound in HBV replication has however been observed *in vitro* and *in vivo* after cessation of treatment. Chronic infection of the hepatocytes may, however, be maintained by the presence in the nucleus of viral covalently closed circular (CCC) DNA, which is a template for viral transcription.

The *in vitro* efficacy of lamivudine in combination with other compounds active against HBV is under investigation.

Cytotoxicity

In human hepatoma cell lines stably transfected with HBV-DNA, lamivudine shows relatively low cytotoxicity, which leads to a favourable therapeutic index.

Genotypic changes associated with reduced sensitivity of HBV to lamivudine

In patients with clinical evidence of HBV infection and reduced sensitivity to lamivudine, amino acid changes in the YMDD region of HBV polymerase gene have been identified. Three consistent mutations have resulted in the following changes in the YMDD motif:

- Methionine to valine at amino acid 552 (M552V) plus leucine to methionine at amino acid 528 (L528M) – Group B, C domains and I.
- Methionine to isoleucine at amino acid 552 (M552I) – Group II, B domain.

In vitro, lamivudine has a markedly reduced inhibitory effect on the replication of Groups II mutants and I compared to the wild type. Both mutant groups have IC_{50s} in excess of 500 000 nM, which is more than 10 000 fold higher than that of the wild type (IC_{50} = 49 nM). Their effects have also been analysed separately. The issue of mutations is further described in part IV of this document.

Studies intended to investigate potential secondary pharmacological effects of lamivudine have been previously evaluated and did not reveal any clinically significant effect on the central or autonomic nervous systems, nor on the cardiovascular or respiratory systems. Only a few new studies have therefore been carried out. A single dose safety pharmacology study in rats revealed that at

300-mg/kg lamivudine slightly increased K^+ excretion and osmolality by 36 % and 23 %, respectively compared to controls. A safety margin of 50 times greater than the approximate clinical dose of

2 mg/kg has however been defined which justifies the clinical use. A second study on dogs revealed slight, transient heart rate increase and slight ECG wave changes at a dose of 150 mg/kg. The no-effect dose of 50 mg/kg intravenously, determined in this study, is expected to provide a safety factor of more than 50 times the human exposure.

Pharmacokinetics

The pharmacokinetics of lamivudine has been previously well established in the main animal species used in the toxicity studies. Nevertheless, further data characterising the profile have been submitted.

Lamivudine is rapidly and extensively absorbed following oral administration with an oral bioavailability of around 60 % in the rat and 80 % in the dog. Further investigations of *in situ* loops in the digestive tract in male rats showed that lamivudine is poorly absorbed from the stomach

(3.6 %) but well absorbed from the duodenum (41.4 %), jejunum (54.8 %) and ileum (47.9 %) during a period up to 1 hour after installation *in situ* (2 mg/kg) and 4.8 %, 66.4 %, 85.7 % and 47.9 % respectively during a period up to 2 hours. The pharmacokinetics of lamivudine is linear.

Lamivudine shows *in vitro* very low plasma protein binding in rat (3.1 - 5.1 %), dog (3.8 - 4.6 %) and man (4.7 - 7.0 %) in a concentration range of 0.01 - 10 μg/ml lamivudine. The ratios of distribution to the erythrocytes reported do not indicate any specific binding to erythrocytes. Lamivudine distributes rapidly and widely to tissues and no signs of tissue accumulation have been found. Lamivudine crosses the placenta of pregnant rats and rabbits and is distributed into milk. Appropriate information has therefore been included into section 4.6 of the Summary of Product Characteristics.

Following oral or intravenous administration of lamivudine (2 mg/kg) to rats, the majority of the dose (63 – 87 %) is excreted unchanged in the urine within the first 10 hours through active tubular renal excretion. One of the metabolites identified is the trans-sulphoxide derivative of lamivudine. The metabolic profile of lamivudine in humans is closer to the one observed in rats than in dogs. The (+) enantiomer was not detected in plasma or serum samples from either dog or man. This confirmed the absence of *in vivo* chiral inversion of lamivudine.

Toxicokinetics data, previously submitted showed that the systemic exposure in animals exceeded the one in humans given therapeutic doses.

No new interaction studies have been performed but previous data suggested a lack of interactions between lamivudine and a number of concomitantly administered drugs. Interactions have been reported between lamivudine and ganciclovir (weakening of the anti-HIV activity) and trimethoprim (impeding elimination).

Toxicology

Considering that the administration route of Zeffix is identical to the one of the formulations of lamivudine already approved for HIV treatment, and that lower clinical dose is used for hepatitis B infection compared to HIV infection (100 mg/day and 300 mg/day respectively) the toxicological programme previously carried out provides relevant data. No new studies have therefore been performed. The main findings are listed below;

Single dose toxicity showed that the acute toxicity of lamivudine is low, where doses up to 2000 mg/kg intravenously (mice and rats) or 2 x 2000 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 main target organ of toxicity in both species was the haematopoietic system (anaemia, decreased platelet count, leucopenia 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. The No Observed Effect Level (NOEL) was 300-425 mg/kg/day b.i.d. in rats and < 45-mg/kg/day b.i.d. in dogs. In monkeys, white blood cell counts were also decreased and bone marrow examinations revealed progressive delay in the maturation of all cell lines.

Reproductive function: Lamivudine did not impair the overall reproductive performance in rats. Embryonic deaths occurred in rabbits when lamivudine was given to pregnant females, at exposure levels comparable to those in human. In rats, there was however no evidence of embryonic loss at exposure levels of approximately 60 times the clinical exposure. Lamivudine showed no teratogenic potential in either species. Peri-post natal studies in rats did not raise any concerns. On the basis of these results, lamivudine should only be used in pregnant women if the benefit outweighs the risk as indicated into section 4.6 of the Summary of Product Characteristics.

Genotoxicity: Lamivudine induced gene mutations in the mouse lymphoma assay (at doses ≥ 1000 μg/ml). 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 for the treatment of HIV. However, no chromosomal damage was seen in *in vivo* tests in rats. Other *in vitro* and *in vivo* tests performed were also negative. Since these genotoxic effects have been observed only at concentrations considerably higher than those administered in clinical use, the genotoxic potential of lamivudine is considered acceptable.

The carcinogenic potential of lamivudine was studied in conventional 24-month studies in rats and mice. No signs of carcinogenic effects have been reported.

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

4. Clinical aspects

The clinical programme consisted of 13 pharmacokinetics studies, 8 phase II studies and 5 main phase III studies, including three placebo-controlled and two comparative trials with interferon to evaluate the efficacy and safety of lamivudine. In addition 5 open label studies have been carried out. A total of 1692 patients were included in the phase III clinical studies. Of the 1692 patients, 1174 received different dosages of lamivudine in monotherapy, 159 a combination of lamivudine and interferon, 70-interferon monotherapy and 289 placebos. An overview of the main clinical studies performed with lamivudine is presented in the clinical efficacy section of this document.

Clinical pharmacology

Pharmacodynamics

Lamivudine is a nucleoside analogue with an activity against HBV and HIV demonstrated *in vitr*o, as well as in animal models as further discussed in part III of this report. Lamivudine is well tolerated in symptomatic and asymptomatic patients infected with HBV or HIV, healthy volunteers and in combination with commonly co-prescribed medications. There were no clinically significant adverse effects on haemodynamic measurements or laboratory safety tests and no serious adverse events related to lamivudine. However no special pharmacodynamics studies have been conducted in the intended indication. The HBV genotypes (genotypes A-F) have been shown to be geographically distinct and their importance has been demonstrated but in the absence of genotyping in the different studies performed, it is not possible to predict whether some strains may be more susceptible to lamivudine than others.

Genotypic changes within the YMDD locus of the HBV polymerase, which are very rarely spontaneously observed, have been reported with lamivudine therapy. Worldwide, the incidence of YMDD mutants is 23 % after 1-year treatment. In the Asian study (NUCB3018) this incidence was 16 % after 1-year treatment, 42 % after 2-year or 53 % after 3-year lamivudine treatment. The incidence of this mutation may be influenced by the immune status of the patient (range 20 to 27 % in pre- and post-transplantation recipients, and 64 % in post-transplant patients only). These mutants were not detected before 24-week of treatment. As a result, no YMDD mutants could be detected in any patients treated with the combination lamivudine/alpha-interferon since the duration of treatment was only 24 weeks (lamivudine for 8 weeks followed by the combination of lamivudine and interferon for 16 weeks). The recommended daily dose was questioned as to whether it was the optimal one in terms of YMDD incidence but not enough data were available to suggest a lower mutation rate based on higher lamivudine dose. The occurrence and selection of YMDD mutations could be associated with the following factors: race, high baseline Knodell Histological Activity Index (HAI) score, weight and body mass index. Other baseline variables significantly correlated with YMDD mutations are HBV DNA, gender, height and ALT ($p < 0.1$). YMDD mutants can arise in patients with mild or severe hepatitis but baseline viral load below 100 pg/ml seems to be associated with a lower risk of YMDD mutations. The effect of lamivudine on YMDD mutants is further addressed the clinical efficacy section.

In addition, a total of 18 mutations (excluding those in the YMDD locus at amino acid 552 and at amino acid 528) have been described, but these mutations have only been found in the presence of the YMDD variants. The effect of these additional mutations on the sensitivity of the polymerase to lamivudine is currently unknown.

Pharmacokinetics

Data from earlier clinical studies carried out in asymptomatic HIV infected patients were submitted together with new studies conducted in healthy subjects and HBV positive patients.

The pharmacokinetic profile of lamivudine has been established in 13 Phase I studies where 224 subjects have been exposed to lamivudine. Although a limited number of patients with hepatitis B was included at steady state, the pharmacokinetics of lamivudine at 100 mg dose per day has been well characterised.

Absorption and distribution

Lamivudine is rapidly absorbed from the gastro-intestinal tract. The average maximal serum concentration is reached in approximately one hour. At the therapeutic dose of 100 mg once daily, C_{max} is approximately equivalent to 1.1 – 1.5 μg/ml and trough levels are 0.015 – 0.020 μg/ml. The oral bioavailability of lamivudine is approximately 85 %. Food intake results in slowing down the absorption (longer T_{max} by 0.75 hours and decrease Cmax by 15 %), but does not significantly affect the extent of the absorption. Results from new studies confirm that lamivudine can be given with food or without food.

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range of 50-300 mg. The volume of distribution is about 1.3 l/kg suggesting a wide tissue distribution. Binding to plasma proteins is low, and accounts for less than 10 %. Limited data show that lamivudine penetrates the

central nervous system and reaches cerebrospinal fluid. The mean lamivudine CSF/serum concentration ratio 2-4 hours after oral administration was approximately 0.2.

Metabolism and elimination

The hepatic metabolism of lamivudine is low (5-10 %). Lamivudine is primary excreted through renal route via glomerular filtration and active tubular secretion (most likely the organic cationic transport system) mainly as unchanged drug (> 70 %) with a mean systemic clearance of approximately 0.32 l/h/kg. The amount of urinary trans-sulfoxide metabolite recovered in urine is minor. The observed half-life of elimination is 5 to 7 hours.

Special population

Results from study NUCB 1003, which involved 9 subjects with normal renal function (Clcr > 60 ml/mn) and 20 patients with renal impairment showed that there is a linear relationship between lamivudine clearance and renal function (assessed as creatinine clearance). In case of creatinine clearance reduction between 20 and 50 ml/min, the AUC average increase is 3 fold. In another study (NUCB 1004) carried out in HIV infected patients with end-stage renal impairment, the AUC average increase was 4 fold. Based on these data, dose adjustment of lamivudine in HBV infected patients is also recommended according to the value of the creatinine clearance. This recommendation, which has been included in section 4.2, is in line with the one already included in the Summary of Product Characteristics of the lamivudine formulations approved for HIV treatment.

Data obtained in non-HBV infected patients with moderate to severe hepatic impairment (NUCB 1002) showed that lamivudine pharmacokinetics is not significantly affected by hepatic dysfunction. These results support the use of lamivudine in patients with hepatic impairment without any dose adjustment unless accompanied by renal impairment. These results are reflected section 4.2 of the Summary of Product Characteristics.

The pharmacokinetics of lamivudine has been evaluated in the elderly (6 subjects over 65 years old) compared to younger subjects (6 of approximately 20 years old). Results indicated that no dose modification is warranted based on the age only.

No data on the pharmacokinetics of lamivudine in HBV infected paediatric patients are currently available and therefore lamivudine should not be used in this population.

Interactions

Lamivudine does not interact with the cytochrome P450 and therefore potential metabolic interactions are limited. Potential interactions with substances excreted by the active renal secretion cannot be excluded considering that lamivudine is predominantly eliminated by this route. Trimethoprim/sulphamethoxazole (160 mg/800 mg) increases lamivudine exposure by 40 % by reducing renal elimination whereas lamivudine has no effects on the pharmacokinetics of trimethoprim or sulphamethoxazole. No dosage change is therefore recommended. Previous studies performed in HIV infected patients showed no interaction between lamivudine and zidovudine.

Two studies have been carried out to investigate the potential interaction of lamivudine (100 mg) with alpha-interferon (10 MUI). One study involved 8 patients with hepatitis B (NUCB 2007) and one study involved 24 healthy volunteers (NUCB 1007). Results from both studies revealed no clinically significant changes of the pharmacokinetics of either substance when co-administered.

Clinical efficacy

All the studies were conducted according to GCP standards and agreed international ethical principles. The five completed main studies as well as the five open label studies aim to evaluate the efficacy of lamivudine in different type of population (e.g. naive, pre-core mutant patients, Asian). An overview of the main clinical studies is presented in the table below.

Study	Population	Study design	Treatment	Duration of treatment/ follow-up period	Primary endpoint
NUCA 3010	Interferon naive male and female patients, mostly Caucasian (141 AT) (137 ITTm)	Randomised, Double blind, Multicentre	LAM 100 mg/day Placebo	52 weeks/ 4 months	Histological response (Knodell HAI score) at week 52
NUCB 3014	Pre-core mutants male and female patients, mostly Caucasian (125 AT) (124 ITTm)	Randomised, Partially blinded, Multicentre	LAM 100 mg/day Placebo	52 weeks/ 6 months	Loss HBV DNA combined with ALT normalisation at 52 weeks
NUCB 3009	Asiatic male and female patients (358 AT) (357 ITTm)	Randomised, Double blind, Multicentre	LAM 25 mg/day LAM 100 mg/day Placebo	52 weeks/ patients continue into NUCB3018	Histological response (Knodell HAI score) at week 52
NUCB 3010	Interferon naive male and female patients, mostly Caucasian (230 AT) (226 ITTm)	Randomised, Partially blinded, Multicentre	LAM 100 mg/day Alpha-interferon 10 MU tid LAM/alpha-interferon	52 w. /4 months (lamivudine alone) 8 w. placebo/then 16 w. interferon /9 months. 8 w. LAM then 16 w. combination/ 9 months	HBeAg seroconversion at 52 weeks (primary) Histological response (Knodell HAI score) at week 52 (secondary)
NUCAB3011	Non responders to interferon male and female patients, mostly Caucasian (238 ITTm and AT)	Randomised, Partially blinded, Multicentre	LAM 100 mg/day Placebo LAM 100 mg for 8 weeks followed LAM/alpha-interferon (10 MU tid) for 16 weeks	52 weeks/4 months or 68 weeks 68 weeks 8 w LAM, then16 weeks for the combination/10 months	Histological response (Knodell HAI score) at week 52

ITTm = modified intent-to-treat population, all patients with confirmed chronic hepatitis B, randomised to take treatment regardless of whether or not study drug was taken
AT = As treated, all patients for whom no clear evidence is available of failure to take study medication
LAM: lamivudine

Dose response studies and main clinical studies

Dose response studies

Six phase II studies were conducted to define the recommended dose of lamivudine. The primary endpoint was the suppression of HBV DNA as assessed by Genostics assay (sensitivity limit equivalent to 1.3 pg/ml). Secondary endpoints were ALT reductions and/or HBeAg seroconversion. Lamivudine was administered once daily for 1 to 6 months at doses ranging from 5 mg to 600 mg (placebo, 5, 20, 25, 100, 300 and 600 mg). In these studies a strong dose response relationship was observed. The maximal HBV DNA suppression occurred at the dose of ≥ 100 mg once daily. At this dose, the HBV DNA levels were reduced by median 95-99 % from baseline in all studies after 1-2 weeks of treatment. However HBV DNA levels returned to baseline values shortly after treatment was

stopped. Slight ALT reductions were observed in each treatment group but these changes were too small to show any difference between treatment groups. On the basis of these results, the dose of 100 mg lamivudine once daily was considered to be optimal in wild-type active chronic hepatitis B.

Main clinical studies

Population in the main studies

Patients involved in the 5 main studies were in majority adult males Caucasian and Asian. No patients under 16 years old were enrolled. The inclusion criteria were the similar across the studies and patients had compensated chronic hepatitis B and evidence of HBV replication. The studies excluded patients co-infected with hepatitis C or delta virus, autoimmune hepatitis or HIV infection, decompensated liver disease and previous treatment with antiviral, immunomodulatory, and systemic cytotoxic or corticosteroid therapy during the 6 months prior to screen.

The overall percentage of withdrawal across the studies ranged between 3 and 21 % in the lamivudine groups compared to 4 to 78 % in the placebo group.

Clinical endpoints

Clinical endpoints for assessing the efficacy of a substance in chronic hepatitis B are prevention of cirrhosis, decompensated liver disease, oesophageal varices, ascites, hepatocellular carcinoma and survival. Different surrogate and histological evaluation criteria have been used to assess the efficacy of lamivudine:

- Markers of the viral replication:
  - HBV DNA suppression which represents a direct parameter to evaluate the activity of an antiviral agent
  - HBeAg seroconversion (defined as HBeAg and HBV DNA loss and appearance of HBeAb that occur at least during 2 consecutive measurements and until the end of study) indicates a reduction of viral replication and a non-active disease, which is associated with a better prognosis in terms of progression of chronic liver disease.
- Markers of the liver damage:
  - Histological response (as measured by Knodell HAI score which comprises three components: necrosis, inflammation and fibrosis). An improvement was defined as a reduction in HAI score of at least 2 points
  - Normalisation of elevated ALT levels as indicator of hepatocyte damage.

The use of several endpoints has been judged appropriate although it is difficult to make comparison among the studies since the primary endpoint differs from one study to another one.

Lamivudine in compensated hepatitis B patients

Study NUCA 3010

The primary objective of this study was to compare lamivudine 100 mg to placebo with regard to safety and effects upon liver histology after 52 weeks treatment. HBeAg seroconversion and ALT normalisation were secondary endpoints. Patients enrolled in this study were characterised by the following criteria:

Age	HBV DNA	HBeAg	HBeAb	HBsAg	ALT	Liver biopsies	Median HAI score
≥18	+ve (≥ 1.6 pg/ml at screening)	+ve ≥ 1 month	-ve ≥ 3 months	+ve ≥ 6 months	≥1.3 to 10 x upper limit normal (ULN)	≤ 12months before screening	placebo 11 100 mg LAM 10

Results

		Placebo (n = 71)	Lamivudine (n = 66)	P-value
% of patients with improvement in the Knodell HAI score (≥ 2 points)		23 %	52 %	≤ 0.001
Fibrosis response rate at 1 year	Improved	15 %	39 %	
	Unchanged	58 %	55 %	
	Progression	27 %	6 %	0.004
% of patients with 2 consecutive ALT values < ULN and maintained to end of time-period at 1 year		7 %	41 %	0.001
Percentage of sustained HBV DNA suppression at year 1		16 %	44 %	0.001
Percentage of HBeAg seroconversion at year 1		6 %	17 %	0.036

Analysis of histological response from baseline to week 52 revealed a statistically significant difference in Knodell HAI score in favour of the lamivudine treatment group.
Lamivudine slowed down the progression of fibrosis compared to placebo. Fibrosis data have been further reported according to the Ishak system, which is a modification of the Knodell HAI grading system using a 6 point score for fibrosis. The magnitude of reduction in Ishak staging score was greater with lamivudine compared to placebo but the clinical relevance of this reduction is unknown.

With respect to the ALT normalisation, the response was statistically significant in favour of lamivudine. Lamivudine has demonstrated a rapid effective suppression of HBV DNA replication. The proportion of patients with HBV DNA suppression at one year was statistically significant in favour to lamivudine as compared to placebo. However in terms of HBeAg seroconversion, the difference was not statistically significant after one year.

Study NUCB 3009

Originally this Asian study was planned to have a 24 weeks follow up after 52 weeks on active treatment. This protocol has been amended and patients were transferred after 52 weeks to study NUCB3018 without interruption for further treatment with lamivudine. The latter study is ongoing and preliminary results are discussed later. Patients were allocated according to their liver histology to two strata: stratum 1 comprised patients with a median Knodell HAI score of 10.0 (moderate to severe hepatitis) and 16 patients had evidence of liver cirrhosis. Patients of stratum 2 had a median score of 4.0 (mild hepatitis). The patients in each group were well matched. The primary efficacy parameter for stratum 1 was any decrease in Knodell HAI score at 12 months and for stratum 2 any decrease in **liver** HBcAg or **liver** HBV DNA at 12 months compared with screening/baseline. The inclusion criteria were the following:

Age	HBV DNA	HBeAg	HBeAb	HBsAg	ALT	Liver biopsies	Median HAI score
16-70	> 5 pg/ml ≥ 3 months before and at screening	+ve ≥ 6 months	NA	+ve ≥ 6 months	< 10 x ULN ≥ 3months	≤ 6 months before screening	placebo 7 25 mg LAM7.5 100 mg LAM 7

Results

		Placebo (n = 72)	Lamivudine 25 mg (n= 142)	Lamivudine 100 mg (n = 143)	P-value (LAM versus Placebo)
% of patients with improvement in the total Knodell HAI score (≥ 2 points)		25 %	48 %	52 %	< 0.001
Fibrosis response rate at 1 year	Improved	0	4 %	2 %	
	Unchanged	85 %	90 %	95 %	
	Progression	15 %	6 %	3 %	< 0.01
% of patients with 2 consecutive ALT values < ULN and maintained to end of time-period at 1 year		24 %	65 %	72 %	≤0.001
Percentage of sustained HBV DNA suppression at year 1		3 %	25 %	57 %	0.001
Percentage of HBeAg seroconversion at year 1		4 %	13 %	16 %	0.014

Lamivudine has demonstrated a rapid effective suppression of HBV DNA replication. This suppression while on lamivudine was associated with significant improvement in the Knodell HAI score (≥ 2 points reduction) and prevention of the hepatic fibrosis progression compared to placebo. The percentage of HBeAg seroconversion was statistically significant in favour of lamivudine.

In patients treated with lamivudine 100 mg, results from the stratification according to the severity of the hepatitis showed that the response to Knodell HAI score was greater in patients with more severe liver damage at baseline. The percentage of HBeAg seroconversion at week 52 was 22 % in the stratum 1 compared to 2 % in stratum 2 respectively.

Patients who completed study NUCB 3009 who were on treatment and who attended the 52 weeks assessment were enrolled in study NUCB 3018. Patients received either lamivudine (25 or 100 mg once daily) for 2 years, or for 1 year followed by placebo or 1-year placebo followed by lamivudine therapy. The proportion of patients with sustained HBV DNA responses is 57 % at the end of the first year of treatment and 52% at the end of the second year of treatment with lamivudine and with ALT responses the proportion decreases from 72 to 50 %. The proportion of patients with HBeAg seroconversion with HBV DNA loss is 16 % after one year and 23 % at the end of the second year of treatment. In a subgroup of patients (n = 58) who are followed for three years, preliminary data showed that HBeAg seroconversion occurred at the rate of 22 % at year-1, 29 % at year-2 and 40 % at year-3.

Lamivudine in pre-core mutants

Pre-core mutation accounts for 7-30 % of patients with chronic hepatitis B and is particularly common in Mediterranean and Middle East populations (40-80 %). This mutation at nucleotide 1896 in the pre-core region of the HBV DNA genome results in the generation of a stop codon that blocks the HBeAg synthesis but still permits HBV replication and HBcAg production. This mutation does not affect the binding pocket of the viral polymerase, which is the site of action of lamivudine. This is further addressed in the clinical efficacy section of this report.

Study NUCB 3014

The primary objective of this study was loss of serum HBV DNA combined with normalisation of ALT at week 52 (complete response). Secondary endpoints were comparison of pre- and post-treatment liver histology and HBsAg seroconversion between treatment groups. Patients were characterised by the following inclusion criteria:

Age	HBV DNA	HBeAg	HBeAb	HBsAg	ALT	Liver biopsies	Median HAI score
16-70	+ ve ≥ 3 months before, and at screening	-ve ≥ 6 months	+ve ≥ 6 months	+ve ≥ 6 months	1.510 x ULN ≥ 3 months	≤ 12 months before screening	placebo 8 100 mg LAM 6

Results at one year are displayed in the following table:

	Placebo (n = 60)	Lamivudine (n = 65)	P-value
% of patients with improvement in the Knodell HAI score (≥ 2 points)	2 %	38 %	Not performed
% of patients with 2 consecutive ALT values< ULN and maintained to end of time-period at 1 year	5 %	67 %	≤ 0.001
Percentage of sustained HBV DNA suppression at year 1	15 %	71 %	≤ 0.001

The efficacy analysis in study NUCB3014 was not considered acceptable. After 26 weeks, the code was broken and only the responders were treated for another 16 weeks. Thus at week 52, patients included in the placebo group, because they had no available data at that time, were considered as failure.

To support the use of lamivudine in this population, the applicant provided new data from the ongoing long-term treatment study NUCB3017 that includes 77 HBeAg negative/HBV DNA positive patients (who were previously enrolled in NUCB 3014). These preliminary data show that lamivudine decreases HBV DNA and ALT levels. This is supported by data from the compassionate use programme (n = 255).

Lamivudine versus interferon

Study NUCB 3010

In this study, the efficacy of lamivudine monotherapy is compared to the efficacy of alpha-interferon monotherapy and the combination of lamivudine and alpha interferon. The primary endpoint was HBeAg seroconversion (HBeAg loss with HBeAb gain) with concomitant clearance of serum HBV DNA. Serum ALT normalisation, HBV DNA suppression and liver histology were evaluated as secondary endpoints. The inclusion criteria are the following:

Age	HBV DNA	HBeAg	HBeAb	HBsAg	ALT	Liver biopsies	Median HAI score
16-70	+ve at screening	+ve ≥ 3 months	NA	+ve ≥ 6 months	≥ 1.3·10 x ULN	≤ 12 months before screening	interferon 4 interferon/LAM 4 100 mg LAM 4

Results

		Lamivudine 100 mg (n= 82)	Interferon (n = 69)	Lamivudine + interferon (n = 75)	P-value
% of patients with improvement in the Knodell HAI score (≥ 2 points)		38 %	36 %	28 %	NS
Fibrosis response rate at 1 year	Improved	47 %	22 %	19 %	
	Unchanged	36%	48 %	49 %	
	Progression	17%	30 %	32 %	< 0.01
% of patients with 2 consecutive ALT values < ULN and maintained to end of time-period at 1 year		40 %	17 %	25 %	NS
Percentage of sustained HBV DNA suppression at year 1		34 %	19 %	25 %	NS
Percentage of HBeAg seroconversion at year 1		15 %	17 %	24 %	NS

HBeAg seroconversion was evaluated at week 52. This time point corresponded to the end of treatment for lamivudine whereas it corresponded to 28 weeks of post-treatment for patients who received a standard course of interferon. No difference has been observed between the treatment groups.

Another study (NUCAB 3011) has been conducted to further assess the efficacy and safety of lamivudine monotherapy versus placebo versus lamivudine/interferon in combination in patients who had previously failed to respond to alpha-interferon therapy. In this controlled, multicentre, randomised, partially-blinded study, patients received one of the three treatment regimens: lamivudine 100 mg once daily for 52 weeks, with either 16 week placebo follow-up or 16 weeks continued lamivudine treatment (randomised at week 52), placebo for 68 weeks or lamivudine 100 mg/day for 8 weeks followed by alpha-interferon 10 MU t.i.d in combination with lamivudine for 16 weeks. Patients of this group did not receive any follow-up treatment at the end of the 16 weeks combination therapy. One-year lamivudine treatment has therefore been compared to 2 months lamivudine followed by 4 months combination. A total of 238 have been included in ITTm, which consist of all patients randomised (119 in the lamivudine group, 56 placebo and 63 lamivudine/interferon respectively). Most of the patients included were Caucasian/White (194/238 [82%]) or Asian (19/ [8%]).

Although lamivudine and interferon have been shown *in vitro* to act synergistically on the virus, the rational for a sequential treatment strategy was to produce a reduction in viral load by pre-treating with lamivudine before initiating combination treatment.

The efficacy results of the study at 52 weeks are displayed in the following table:

		Placebo (n = 56)	Lamivudine 100 mg (n=119)	Lamivudine + interferon (n = 63)	P-value
% of patients with improvement in the Knodell HAI score (≥ 2 points)		25 %	52 %	32 %	0.002
Fibrosis response rate at 1 year	Improved	19 %	34 %	20 %	
	Unchanged	74 %	62 %	61 %	
	Progression	7 %	4 %	18 %	NS
% of patients with 2 consecutive ALT values < ULN and maintained to end of time-period at 1 year		15 %	44 %	18 %	< 0.001
Percentage of sustained HBV DNA suppression at year 1		17 %	55 %	23 %	< 0.001
Percentage of HBeAg seroconversion at year 1		13 %	18 %	12 %	NS

On the basis of the results from this study and from study NUCB 3010 previously described, it was concluded that for the time being, it was not possible to make a clear clinical comparison between lamivudine, alpha-interferon and their combination.

No data are currently available concerning the susceptibility to interferon therapy in those patients who are failures or relapses to lamivudine therapy.

Lamivudine in patients with YMDD mutations

Worldwide, the incidence of YMDD mutants is 23 % after 1-year treatment. In the Asian studies (NUCB3009/3018) this incidence was 16 % after 1-year treatment, 42 % after 2-year or 53 % after 3-year lamivudine treatment. Although this mutant is less replication competent and seems to be less pathogenic than the wild type the clinical evolution of the patients infected remains unknown.

The integrated summary of efficacy results associated with YMDD mutant HBV 52-week lamivudine therapy in naive and Asiatic patients (NUCB3009, NUCA3010, NUCB3010) are presented below:

Results with lamivudine 25 mg and 100 mg have been pooled.

Effect of lamivudine in YMDD non-mutants / YMDD mutants

	LAM 25 and 100 mg YMDD non-mutants	**LAM 25 and 100 mg YMDD mutants**	**PLACEBO**
Year 1*			
- sust. HBV DNA suppression	60 % (170/282)	19 % (14/72)	16 % (22/140)
- HBeAg seroconversion at 1 year	17 % (49/282)	4 % (3/72)	6 % (9/139)
- improv. in Knodell HAI score	59 % (157/266)	52 % (33/64)	30 % (34/113)
- sust. ALT response	71 % (148/209)	34 % (24/70)	14 % (17/119)
Year 2*			
- sust. HBV DNA suppression	41 % (72/175)	26 % (22/85)	
- HBeAg seroconversion at year 2	17 % (29/175)	21 % (18/85)	
- improv. in Knodell HAI score	58 % (15/26)	40 % (4/10)	
- sust. ALT response	54 % (57/106)	32 % (22/68)	

*duration of lamivudine treatment. The delay between mutation and these cut off dates is unknown.

These results showed that there are fewer patients with HBV DNA suppression, HBeAg seroconversion and sustained ALT normalisation in YMDD mutant population after one year treatment as compared to non-mutant population. Limited data on the histological outcome of patients with YMDD variants for up to 3 years does not show significant worsening of histology.To assess HBeAg seroconversion in patients with YMDD variants additional data from a subgroup of Asian patients receiving both 25 and 100 mg were provided. These data showed that sustained HBeAg seroconversion occurring during treatment seemed to be similar in the group of patients with YMDD variants (10 /40 = 25 % at 3 years) and in the non-mutant group (11/50 = 22 %) taking into account that in the whole Asian population the percentage of HBeAg seronversion was 23 % (21/90) at year 2. The durability of the response after termination of therapy has not yet been assessed.

There are limited data on the re-treatment of patients following cessation lamivudine therapy due to the emergence of variants. The majority of the patients who developed variants continued to receive lamivudine therapy. In case of treatment cessation, 53 % revert to the wild type within 4 months after treatment stop (no data available beyond 4 months). Data were provided on 6 patients retreated with lamivudine, 5 of whom developed YMDD variants again after 2 to 9 months, and 1 had yet to demonstrate return of YMDD variant 1 year after restarting treatment.

Treatment stop

There are limited data regarding the maintenance of seroconversion after treatment stop with Zeffix.

Additional results from the ongoing study NUCAB3016, which has a follow-up period of 5 years, have been submitted. This study enrols patients from studies A2008-B2015-A3010-B3010-AB3011 who have HBeAg seroconverted and are followed off treatment. Out of the 29 patients who have been followed at for at least one year post HBeAg seroconversion, 26 maintained HBeAg seroconversion for this period of time.

Baseline characteristics of patients with durable HBeAg seroconversion

	Durable HBeAg seroconversion (n = 26)	***Integrated data (B3009-B3010-A3010-AB3011) (n = 958)***
Median baseline HBV DNA (pg/ml)	100.8 (4.7 - 3 000)	86.8 (0.8 - 2 264)
Median baseline ALT (x ULN)	3.4 (1.3 - 9.3)	2.2 (0.3 - 26.1)
Median baseline HAI score	12 (4 - 17)	8 (0 - 21)

Clinical studies in special populations

Asian

The impact of ethnicity has been appropriately assessed throughout the integrated data from studies NUCB 3010, NUCA 3010 and NUCAB 3011 where Asians and Caucasians are separated.

	Integrated data		Study NUCB 3009
	Caucasians (n = 185)	Asians (n = 44)	Asians (n = 143)
Sustained HBV DNA negative	49 %	48 %	57 %
HBeAg seroconversion	18 %	15 %	16 %
Sustained ALT normal	41 %	56 %	72 %
Histologic response	47 %	50 %	52 %
YMDD variant	29 %	24 %	16 %

These data indicate a similar response between Asian and Caucasian patients. When comparing the Asian patients from the integrated studies to those from NUCB3009, higher sustained ALT response and lower incidence of YMDD variants were noted which the different ALT and HBV DNA levels at baseline explained.

Liver transplant patients

In two open-label 1-year studies (NUCB 2008 and NUCA 3005), the efficacy of lamivudine has been evaluated in liver transplant patients. Lamivudine showed a substantial inhibitory effect on serum HBV DNA level. The percentage of patients with undetectable HBV DNA level at 6 months post transplant (n = 68) is 62-100 % and 51-75 % of these patients are still HBV DNA after 1 year treatment. A study is ongoing to assess the improvement of life with lamivudine in patients having end-stage liver disease secondary to hepatitis B who are waiting or undergone orthotopic liver transplant (OLT).

Children

The clinical efficacy of lamivudine for the treatment of hepatitis B has not yet been evaluated in children.

Supportive studies

Results from other studies, some of them above-mentioned were submitted to support the clinical efficacy of lamivudine.

Clinical safety

Patient exposure

The different phase II, III studies and I where 5088 were enrolled, contributed to the overall safety assessment, but the primary data for analysis was provided from the integrated phase III studies (NUCB 3009, NUCB 3010 and NUCA 3010). Of the 583 patients included in the analysis, 144 received placebo, 142 lamivudine 25 mg once daily and 297 lamivudine 100 mg once daily respectively for a median extent of exposure of one year. Of all patients, 91 % completed the studies with only 2 % withdrawal due to adverse events.

Adverse events and serious adverse events/deaths

In general, lamivudine appeared to be well tolerated and no severe adverse events were reported which could definitely be assigned to the lamivudine treatment. The incidence of adverse events and serious adverse events was similar in patients receiving placebo or lamivudine, except for a slightly higher frequency of abnormal liver function tests in those receiving lamivudine.

The most commonly adverse events reported were malaise and fatigue (22 %), headache (20 %), respiratory infections (20 %), abdominal discomfort/abdominal pain (16 %) and diarrhoea (14 %).

Laboratory findings

An analysis of laboratory data from the integrated Phase III studies demonstrated that during treatment ALT elevations occurred in 12 % of both lamivudine and placebo groups. In 32 % cases this elevation occurred in the first 8 weeks of treatment but no explanation for this increase was provided. The incidence of post-treatment ALT elevation (more than 3 times baseline) was higher in patients treated with lamivudine (20 %) in comparison to those receiving placebo (8 %). Out of the 1125 compensated hepatitis B patients included in the lamivudine programme, 10 reported transient and self-limiting elevation of ALT and bilirubin (7 post-treatment and 3 during the treatment): among them, 2 were asymptomatic, 1 was potentially associated with seroconversion and 2 were associated with YMDD mutant HBV. Moreover, 2 patients died because of their clinical deterioration post-treatment following the re-emergence of the hepatitis.

Data on post-treatment ALT elevations in patients with YMDD variant HBV and compensated liver disease (Integrated studies A3010-B3010-AB3011) showed that out of this cohort, only 2 % of each placebo, wild-type and variant patients experienced a post-treatment elevation of ALT and bilirubin.

Graded ALT elevation	***YMDD variant***	***Wild-type HBV***	***Placebo-treated***
ALT ≥ 3x baseline	6/45 (13 %)	29/118 (25 %)	3/52 (6 %)
ALT > 3x baseline and bilirubin > 2x baseline and > 2 x ULN (peak ALT values)	1/45 (2 %) (2066)	2/118 (2 %) (1590, 3141)	1/52 (2 %) (1926)

Haematological and other clinical chemistry profiles were similar between placebo and lamivudine. The difference in patients who experienced elevation of CPK was not considered statistically significant between the treatment (8 %) and the placebo groups (5 %).

Data from the active-controlled studies showed that the addition of lamivudine to alpha-interferon did not appear to alter the safety profile of alpha-interferon. The addition of alpha-interferon to lamivudine seemed to result in a safety profile in which the nature and frequency of adverse events in the combination were similar to that of alpha-interferon alone.

The most common adverse events occurring in the integrated HBV and HIV studies (treated with lamivudine 150 mg) have been presented. As already indicated the nature and incidence of events with lamivudine was similar to placebo. So far, lamivudine is therefore well tolerated in HBV patients and severe adverse events of lamivudine and other nucleoside analogues reported in HIV patients (pancreatitis, myopathy, haemothologic effects or neuropathy) are not raised with the current safety data. All these effects need to be, however, closely monitored.

Interim analysis of study NUCA 2006 involving 77 HBV infected patients eligible for OLT, provided data to support the safety of treatment of OLT patients and those with impaired liver function. The safety profile of lamivudine is consistent with the severity of the underlying disease.

5. Overall conclusions and benefit/risk assessment

Quality

The quality of Zeffix 100 mg film-coated tablets and 5 mg/ml oral solution is considered acceptable when used in accordance with the conditions defined in the Summary of Product Characteristics. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Preclinical pharmacology and toxicology

- Overall the primary pharmacodynamics studies provide adequate evidence that lamivudine is active against HBV virus. The general pharmacology studies have not revealed any clinically significant effects of lamivudine.
- From the pharmacokinetic point of view, it was noted that renal clearance is the main excretion route for lamivudine.
- Overall the toxicology programme identifies the haematopoietic, hepatic and renal systems as the most commonly affected target organs, but no histological signs in the liver have been observed. Lamivudine shows a potential to induce embryotoxicity after administration to pregnant animals, is genotoxic in certain tests, but is not carcinogenic. This information has been adequately included into the Summary of Product Characteristics.

Clinical efficacy

- Zeffix may be a convenient once daily oral therapy for the treatment of chronic hepatitis B.
- The rational for the dosing recommendation in adults has been sufficiently substantiated.
  In HBeAg positive patients, lamivudine reduces HBV DNA consistently, improves liver histology and is well tolerated. Lamivudine also induces HBeAg seroconversion in 11 % of patients after 1-year treatment. HBeAg seroconversion continues to occur if lamivudine treatment is continued for 3 years. For the time being it is not possible to make a clear clinical comparison between lamivudine, alpha-interferon and their combination.
- The long term benefit of lamivudine therapy in terms of reduction in cirrhosis or development of hepatocellular carcinoma is however unknown so long term data are necessary to answer the question on long-term.
- In HBeAg negative patients, who are mainly encountered in Mediterranean Europe, with a clinical profile characterised by oscillation of ALT levels with rapid progression cirrhosis, limited data (n = 65) indicated that the efficacy of lamivudine may be similar to that seen in those infected wild type HBV based on HBV DNA and ALT levels.
- Worldwide, the incidence of YMDD mutants is 23 % after 1-year treatment. In Asian study (NUCB 3018) this incidence was 16% after 1-year treatment, 42 % after 2-year and 53 % after 3-year lamivudine treatment. The incidence of this mutation increases in liver transplant patients, being 64% after one year of treatment. For patients treated with lamivudine for more than 24 weeks, the presence of a single ALT value > 1.3 times the upper limit of the reference range and simultaneously single serum HBV DNA value over 20 pg/ml (solution hybridisation assay) was associated with a 99 % risk of harbouring YMDD variant HBV. Limited data showed that HBeAg seroconversion occurs at a similar rate in mutant and non-mutants. Long-term clinical and histological outcomes in these patients are presently unknown.
- In patients with decompensated liver disease, although limited data were provided, a beneficial effect of lamivudine was observed.

- There are not sufficient data to recommend the combination treatment of lamivudine and alpha-interferon. The efficacy of lamivudine appears to be equivalent between alpha-interferon naive and non-responder patients.
- With respect to the treatment duration the CPMP drew the following conclusions:
- In HBeAg positive patients treatment should be administered until HBeAg seroconversion (HBeAg and HBV DNA loss with HBeAb detection) on two consecutive serum samples or HBsAg seroconversion. Treatment discontinuation may be considered in HBeAg positive patients, in case of loss of efficacy, indicated by a persistent return of serum ALT and HBV DNA to pretreatment values, deterioration in liver histology or other signs of hepatitis.
- In HBeAg negative (precore mutant) patients, the optimal duration of treatment is unknown. Treatment discontinuation may be considered following HBsAg seroconversion, or in case of loss of efficacy as described above.
- In patients who develop YMDD variant HBV treatment discontinuation should be considered following HBeAg seroconversion or if there is evidence of loss of efficacy as described above.
- In patients with decompensated liver disease, treatment cessation is not recommended.

These conclusions have been reflected in the Summary of Product Characteristics.

Clinical safety

- Safety data indicated that lamivudine is well tolerated. Adverse events seem to be minor and no severe adverse events have been reported which could be assigned to the lamivudine treatment.

Benefit/risk assessment

In chronic HBV infection, lamivudine reduces viral replication, improves liver histology, increased sustained HBeAg seroconversion and is well tolerated. The major points for discussion pertained to define the population for which lamivudine should be indicated, the duration of treatment with lamivudine with respect to the different group of patients and the emergence of YMDD resistance. The CPMP agreed to convene the Ad-Hoc group of Experts on hepatitis B to discuss these points in the context of the whole evaluation of the application. The applicant addressed these issues during an oral presentation in front of the expert group of Experts and later in front of the CPMP.

Considering the scarcity of the data on the YMDD mutation, pre-core mutant population and on the duration of treatment in this population, the CPMP considered that the data on efficacy and safety were not comprehensive. Therefore the CPMP recommended the granting of a marketing authorisation under exceptional circumstances and complementary data on these issues would therefore have to be submitted as part of specific obligations to be fulfilled post opinion.

The CPMP recommended initially that Zeffix should be restricted to prescribers specialised in the hepatitis field as indicated in section 4.2 of the Summary of Product Characteristics.

Based on the CPMP review of data on quality, safety and efficacy the CPMP considered by consensus that the benefit/risk profile of Zeffix 100 mg film-coated tablets and 5 mg/ml oral suspension was favourable in the treatment of adult patients with chronic hepatitis B and evidence of viral replication with decompensated liver disease or with histologically documented active liver inflammation and/or fibrosis.

This indication is based on the analysis of serological and histological end points that were mainly derived from studies of one-year duration in HBeAg positive patients with compensated liver disease.