NIHS Notification no. 2728

26th July 2000

Director-General Pharmaceuticals and Medical Safety Bureau,
Ministry of Health and Welfare

National Institute of Health Science

Evaluation Report

The Pharmaceutical and Medical Device Evaluation Centre has evaluated a drug approval application and the result is given in this report.

[Product Name] Zefix Tablet 100

[Generic Name] Lamivudine

[Applicant] Nippon Glaxo Ltd. (Currently Glaxo Wellcome Ltd.)

[Date of Submission] 19th December 1997

[Therapeutic Category] 625 Anti-viral agent

[Application Classification] 1-(1) (New Drug)

[Chemical Structure]

- Molecular formula: $C_8H_{11}N_3O_3S$
- Molecular weight: 229.26
- Structure: omitted

[Chemical Name] (-)-1-[(2R, 5S)-2-hydroxymethyl-1, 3-oxathiolan-5-yl] cytosine

[Remarks] None

[Evaluated by] Evaluation Division I

Evaluation Results

26th July 2000

[Product Name] Zefix tablet 100

[Generic Name] Lamivudine

[Applicant] Nippon Glaxo Ltd. (Currently Glaxo Wellcome Ltd.)

[Date of Submission] 19th December 1997 (Import Approval Application)

[Result of Evaluation]

As a result of evaluation by the Pharmaceuticals and Medical Device Evaluation Centre and discussion by the 1st Subcommittee on New Drugs, we have no objection in granting an approval for the drug.

[Indication]

Improvement of virus markers, liver function and liver histology in chronic hepatitis B patients with evidence of liver function abnormalities accompanying proliferation of hepatitis type B virus.

<Precaution for Use Relevant to Indication>

1. Prior to Zefix treatment, confirm replication of the virus with the HBV-DNA, DNA polymerise or HBeAg tests.
2. Note that asymptomatic carriers or patients on other therapies whose liver function test values are within the normal ranges should not be treated with Zefix.
3. Clinical experience in patients diagnosed with cirrhosis is limited and efficacy and safety is not established. Experience in patients with a reduced spare capacity of the liver, for example decompensated cirrhosis, is particularly limited.

Dosage and Administration Method

Usually for adults, orally administer 100mg of lamivudine once daily.

<Precautions for Use Concerning Dosage and Administration Method>

1. In general, treatment with Zefix needs to be long-term. Deterioration of liver function or worsening of hepatitis may be seen after discontinuation of the

treatment (see “Clinical Results”). Patients need to be fully informed of this and must be advised not to stop taking Zefix without consulting the doctor.

2. Discontinuation of Zefix therapy can be considered if the following occur during treatment:
   (1) When a HBeAg positive patient sustained seroconversion of HBeAg to HBeAb (HBe-SC);
   (2) When a HBeAg negative patient sustained negative HBsAg or negative HBV-DNA with ALT (GPT) normalisation for more than 6 months.

   However, liver function may deteriorate after discontinuation (see “Clinical Results”). In either case, clinical symptoms and lab test results (HBV-DNA, ALT (GPT), and if required, total bilirubin) should be monitored every 2 weeks, as a general rule, for at least 4 months after withdrawal. Monitoring of the patient should be continued beyond this period.
3. Limited data is available on the long-term durability of seroconversion after discontinuation of treatment following sustained HBe-SC.
4. For patients with HBV and HIV co-infection, administer a lamivudine preparation (Epivir Tablet, Combivir Tablet) with the dosage and administration for HIV infection. (Usually, as combination therapy with other anti-HIV agents, administer 150mg lamivudine twice daily).

19th July 1999

Evaluation Summary (Part 1)

Pharmaceuticals and Medical Device Evaluation Centre

1. Summary of the Drug

[Product Name]	Zefix Tablet 100
[Generic Name]	Lamivudine
[Date of Submission]	19th December 1997 (Importing Approval Application)
[Applicant]	Nippon Glaxo Ltd. (Currently Glaxo Wellcome Ltd.)
[Formulation and Contents]	Pale brownish orange film-coated tablets containing 100mg of lamivudine per tablet
[Indication]	Improvement of virus markers, liver function and liver histology in chronic hepatitis B patients
[Dosage and Administration]	Usually for adults, orally administer 100mg of lamivudine once daily
[Remarks]	An anti-AIDS agent Epivir Tablet (150mg/tablet), which contains the same active ingredient, was approved on 14th February 1997.

2. Summary of the Submitted Data and Evaluation by the Evaluation Centre

A. Data On Origin, Details of Discovery, Use in Overseas Countries, etc.

Lamivudine is a nucleotide derivative anti-viral agent developed by GlaxoWellcome in the UK. It is phosphorylated by endoenzymes to triphosphate metabolite with anti-viral activity, which exerts its anti-HBV action by 1) competitive antagonism of reverse transcripase of hepatitis type B virus (hereinafter referred as HBV) and 2) incorporation into negative strand DNA as a substrate during virus replication, causing termination of growing DNA chains. However, clinical study data confirmed that liver function deteriorated because of re-growth of HBV after cessation of lamivudine therapy.

Therefore, anti-viral effect of lamivudine is not considered to be eradication of virus but suppression of proliferation.

The Evaluation Centre requested the applicant to include results of long-term studies implemented abroad in the approval application document. Also, the Evaluation Centre instructed the applicant to provide the incidence of emergence of resistance virus and data on acute deterioration from overseas clinical studies with regard to the risk/benefit of lamivudine anticipated from the findings.

B. Data on Physical and Chemical Properties, Specification and Test Methods, etc.

Importing of an anti-HIV agent Epivir Tablet, which is a drug product of lamivudine (contains 100mg of lamivudine per tablet), was approved on 14th February 1997. During the evaluation, the Subcommittee on AIDS Drugs instructed that the applicant should "reorganise the specification and test methods of Epivir following the Japanese guidance on quality specifications. If indication for hepatitis B is approved, the Epivir specifications will need to be reviewed so that it is consistent with lamivudine for hepatitis B." Based on this instruction, specification and test methods of the drug substance (lamivudine) and the drug product (Zefix Tablet 100), including the standard lamivudine in this submission, were amended in accordance with the Japanese Pharmacopoeia.

Description, Identification (infrared spectrophotometry), Optical Rotation, Purity Tests (heavy metal, related substance ((+) enantiomer, (±) diastereomer, carobxylate, etc.), residual solvents), Water, Residue on Ignition, and Assay (liquid chromatography) of the drug substance and Description, Identification (infrared spectrophotometry), Content Uniformity Test, Dissolution Test and Assay (liquid chromatography) of the drug product were established in the specifications and test methods.

During development of Zefix, the method of synthesis of the drug substance has been altered twice (in a chronological order, referred as "Method A", "Method B" and "Method B' (the final manufacturing method)". Drug substances and formulations

produced using various synthesis methods were used in studies including non-clinical and clinical studies. The Evaluation Centre requested the applicant to clarify differences in physical and chemical characteristics of the drug substances produced by each synthesis method. The applicant submitted measured values of the drug substances produced by each method. The drug substance produced by Method A contained slightly different types of related substances from the drug substances produced by Method B or Method B', as a result of differences in the synthesis methods. However, the Evaluation Centre considered the differences in the synthesis methods did not affect quality of the drug substance for the drug production and did not cause problems, because the amount of the related substances that were only present in the drug substance made by Method A were trace quantity, there was no specific deference in the types and the amounts of the related substances in the drug substances produced by Method B and Method B'and other data on the solid state properties showed no specific difference due to the different synthesis methods.

With regard to the i) Content (Assay), ii) Purity Test (heavy metal), iii) Purity Test (related substance) and iv) Water Content for the drug product and v) Content Uniformity Test and vi) Dissolution Test for the drug substance, the Evaluation Centre instructed the applicant to provide measured values and comprehensive rationales for the specifications from a view point of efficacy and safety of the drug and to review the specifications if necessary. The applicant submitted product data on i), iii) and iv) which were obtained in a recent production run at the manufacturing scale and gave rationales for the specifications based on these data. Also, with regard to ii), v) and vi), the applicant stated they would reset the specifications based on the measured values. The Evaluation Centre considered all of the specifications for i) to vi) were generally appropriate, even though the rationales for the specifications for i) and vi) were slightly weak (the Evaluation Centre is currently instructing the applicant on this matter). In the Special Examination, the applicant was instructed to review the specifications for the Purity Test (residual solvent) of the drug substance. Appropriate amendments were made. The Evaluation Centre instructed the applicant to amend the application forms and data, and appropriate amendments were made.

C. Data on Stability

A 36-month long-term storage study of the drug substance in double layers of polyethylene bags (sealed) in dark place at 30°C/60%RH is taking place. Data up to 12 months have been submitted. The data did not show time-changes for a minimum period of 12 months and the drug substance was stable.

A 36-month long-term storage study of the drug product in blister packs in a dark place at 25°C/60%RH is taking place. Data up to 12 months have been submitted. The data did not show time-changes apart from 0.8 to 1.0% increase in the water content compared with the content at the start of the study. The increase in the water content did not affect quality of the drug product. The drug product was considered to be stable for a minimum of one year.

Based on the above study results, the drug substance and drug products should be stored in sealed containers and tentative shelf life was set at one year.

D. Data on Acute Toxicity, Subacute Toxicity, Chronic Toxicity, Reproductive and Developmental Toxicity and Other Toxicity

Oral acute toxicity studies were carried out in mice receiving lamivudine twice daily for one day and in dogs receiving lamivudine twice daily for 14 days. There were no findings with any significance in mice. In dogs, soft stool, mild reductions in red blood cell counts, haemoglobin and white blood cell counts were observed. LD_{50} was not less than 2000mg/kg twice daily in mice and not less than 1500mg/kg twice daily in dogs. Subacute and chronic toxicity studies were carried out in rat receiving oral doses for one and six months and dogs receiving oral doses for three and 12 months. In a similar way to the acute toxicity study, findings that indicated changes in haematocyte and mild liver function impairment were observed in these studies. In addition, the six-month study in the rat showed diffuse mucosal hyperplasia and inflammation at caecum. The applicant believed that these were caused by a chronic and slight stimulation by lamivudine. The No Toxicity Doses were not more than 300mg/kg twice daily in the rat one-month study,

425mg/kg twice daily in the rat six-month study, 260mg/kg twice daily in the dog three-month study and 45mg/kg twice daily in the dog 12-month study. The haematological damage observed in the above studies was considered to be macrocytic erythrocytopenia. In the three-month dog study, three female animals in the high dose group died. This was considered to be because of malnutrition following a decrease in food consumption. Reproductive and developmental toxicity studies were carried out in rats and rabbits with oral doses. Suppression of body weight gain and a reduced locomotor activity were observed in offspring in a rat female fertility study and a general reproductive study, but there were no other abnormal findings. In a rat organogenesis study, a foetus with compound abnormalities was observed in the medium dose group, but it was considered to be a chance occurrence because no abnormality was observed in a supplemental study. In a rabbit organogenesis study, there was evidence of an increase in early embryolethality before and after implantation, but no teratogenicity was observed. In a rat peri-and post-natal study, and a study in offspring, reduced testis and spleen weight, and reduced red blood cell counts in offspring were observed in the high dose group. In a mutagenicity study, results of reverse mutation assays using bacteria were negative, but results of a gene mutation assay using cultured mouse lymphoma cells and a chromosomal aberration assay using cultured human lymphocyte were positive. However, results of a rat bone marrow chromosomal aberration assay, a rat bone marrow micronucleus assay, rat hepatocyte unscheduled DNA synthesis assay and cell transformation assays in mouse cultured cells (BALB/3T3) were all negative. Carcinogenicity studies were carried out in mice and rats. In the mouse carcinogenicity study, an increase in histocytic sarcoma was observed, but there was no dose dependency and it was within a range of background data. Therefore, it was considered to be a chance occurrence. In the rat carcinogenicity study, endometrial adenocarcinoma was increased at the high dose. It was higher than background data, but the degree was a minimal and an increase in hyperplastic lesions in the epithelium was not observed. Therefore, it was considered to be irrelevant to lamivudine.

The Evaluation Centre questioned the appropriateness of using lamivudine test materials that were synthesised by a different method from the clinical formulation production method. The applicant replied that their toxicological effects were considered to be

equivalent because there was no large difference in their physical and chemical characteristics and toxicological findings observed did not indicate differences due to the production methods. The Evaluation Centre accepted the reply. Concerning the bone marrow suppressive effects observed in the general toxicity study, the Evaluation Centre requested the applicant to illustrate safety in humans together with their mode of action. The applicant argued that these findings were also observed with AZT, which had similar pharmacological actions to lamivudine, and the suppressive effects of lamivudine were weaker than that of AZT. They did not accompany histological changes and were reversible. The applicant concluded that humans were unlikely to experience the toxicity considering the clinical dosage. The Evaluation Centre accepted the response. To summarise, subacute and chronic toxicity studies, the Evaluation Centre asked the applicant to discuss haematological actions and effects on the liver and kidney. As lamivudine was regarded as a chromosomal aberration inducer, discussion on safety in humans was also requested.

E. Data on Pharmacological Actions

An in vitro study with reverse-transcriptase in core particles of duck hepatitis B virus (DHBV) and DNA revealed that lamivudine exerted its anti-HBV action as follows: After uptake of lamivudine by cells, lamivudine is converted to its active lamivudine 5'-triphosphate form. It competes with cytosine for incorporation into polymerase molecules and thus inhibits reverse transcription activities. At the same time, it is incorporated into DNA strands during HBV replication and stops prolongation of DNA. In *in vitro* studies, lamivudine dose-dependently inhibited DNA synthesis of HBV in the primary human hepatoma HepG2 cell line and the established human hepatoblastoma cell line (HB611 cells) that were transfected with HBV. When chronic HBV infected chimpanzees orally received 10mg/kg of lamivudine twice daily for 28 days in an in vivo study, serum HBV DNA was undetectable by the dot-blot hybridisation method on Day 4 and decreases in serum HbeAg concentrations were also observed. In a separate study in chronic HBV infected chimpanzees, the dose amount of lamivudine was increased every 14 days from 0.1, 0.3, 1, 3 to 6 mg/kg (twice daily). The minimum effective dose

of reducing serum HBV DNA to the undetectable level was estimated at 0.3mg/kg twice daily.

Apart from HBV, lamivudine showed anti-viral effects on HIV, which also has reverse-transcriptase, but it did not show inhibitory effect on viruses without transcriptase.

In HBV transfected HepG2 and BH611 cells, IC_{50} for [6-^{3}H] dThd up-take inhibition by lamivudine, which was an index for differentiation and proliferation of cells, was 2900μM for both cell lines and it was about 100,000 times of IC_{50} for the HBV DNA inhibitory effect. IC_{50} of cytotoxicity in human bone marrow precursor cells (precursor cells of erythroblast, granulocyte-macrophage precursor cells, pluripotential precursor cells and interstitial cells) was over 100μM. Therefore, it is not likely to cause bone marrow toxicity. The applicant argues that lamivudine is not likely to affect DNA replication, DNA repair and replication of mitochondrial DNA in normal cells, because exonuclease activities of polymerase γ carry out excision-repair of DNA that has incorporated 5' triphosphate.

The Evaluation Centre asked the applicant to illustrate lamivudine exposures in pharmacological studies and the clinical dosage. The applicant responded that they expected to see an anti HBV effect with a daily dose of lamivudine at 100mg in humans because plasma concentration after 24 hours of a 100mg oral dose (approximately 10ng/mL) in human was higher than HBV DNA production IC_{50} [0.018mM (approximately 4.1ng/mL) and 0.032mM (approximately 7.3ng/mL)]. The Evaluation Centre accepted the response.

With regard to use of DHBV as an infection model, the Evaluation Centre requested the applicant to submit reference literature showing similarities of DHBA and HBV and justifications for the use of the model. The applicant believed that DHBV models were suitable infection models for finding out treatment effects and mode of action for the following reasons. (i) Both HBV and DHBV are DNA viruses with affinity for the liver and are classified as hepadnaviruses. (ii) Their genome size and structure are similar and their virus DNA is replicated by reverse transcriptase after transcribed as RNA. (iii) No

other suitable models that can be used in HBV infection studies are available, apart from expensive chimpanzee models and the tissues cannot be cultured. Therefore, other hepadnaviruses are recognised as HBV substitutions. (iv) Considering its safety, simplicity and economy, DHBV infection models are among the best-suited models. They are widely used for studies of liver pathologies, mechanisms of anti-HBV actions and other investigations and there are many publications. The Evaluation Centre accepted the response.

F. Data on Absorption, Distribution, Metabolism and Excretion

Absorption, distribution, metabolism and excretion of lamivudine were investigated in rats, dogs and humans.

When rats received a single oral dose of 2, 5 or 10mg/kg of lamivudine, the maximum plasma concentration (C_{max}) of plasma unchanged lamivudine was increased with increases in the dosed amount and the area under plasma concentration-time curve (AUC) was linear within the range of 2 to 10mg/kg. When rats received repeated oral doses of ^{3}H-lamivudine once daily for 14 days, plasma radioactivity reached the steady state after three days. The absorption rate in rats was 74% and the bioavailability was around 80%. In rats, ^{3}H-lamivudine was hardly absorbed by the stomach and it was extensively absorbed by the whole of the small intestine. When a single oral dose of ^{3}H-lamivudine was administered with food, C_{max} and AUC of plasma radioactivity were decreased.

After a single oral dose in rats, ^{3}H-lamivudine was mainly distributed in the digestive tract (jejunum, ileum, colon) and the kidney and the maximum levels were observed at one hour after administration. When pregnant rats received a single oral dose of ^{3}H-lamivudine, transmigration to the foetus was observed, but the rate of transmigration was only 0.02% of the dosed amount. The plasma protein-binding rate of lamivudine was low, less than 7%, in rats, dogs and humans. Specific distribution to the blood cells was not observed.

Comparatively, metabolism of lamivudine in rats was poor. Within 24 hours of a single oral dose of ^{3}H-lamivudine, around 68% of the dosed amount was found unchanged in the urine. In contrast, within 24 hours after a single oral dose of ^{3}H-lamivudine in dogs, around 31% of the dosed amount was found unchanged in the urine, around 33% a trans-sulfoxide metabolite and around 18% a cytosine metabolite. There were differences in metabolism of species, but sex difference was not observed.

When rats received a single oral dose of ^{3}H-lamivudine, around 70% of radioactivity was excreted in the urine and around 20 to 30% in the faeces. The majority of radioactivity was excreted within 24 hours after administration. When dogs received a single oral dose of ^{3}H-lamivudine, around 90% of radioactivity was excreted in the urine and the majority of radioactivity was excreted within 24 hours after administration. In conclusion, in rats and dogs, excretion of lamivudine was fast, the main excretion route was via urine and no sex difference was observed.

When fasting healthy adult male volunteers received 50, 100 or 300mg of lamivudine, C_{max} and AUC increased proportionally to the dosed amount. Within a range of 50 to 300mg, AUC showed linearity. When 100mg of lamivudine was administered under fasting condition, plasma lamivudine concentrations reached C_{max} at T_{max} of one hour and eliminated at $T_{1/2}(\alpha)$ of about one hour and $T_{1/2}(\beta)$ of about eight hours. When healthy adult male volunteers received oral repeated doses of 200mg lamivudine once daily for seven days, no significant changes in T_{max}, $T_{1/2}$ and AUC on Day 1, Day 4 and Day 7 were observed. The plasma lamivudine concentration (Cmin) at 24 hours after administration suggested that steady state was achieved on Day 4 and a repeated dose did not cause accumulation and pharmacokinetic changes. When lamivudine was dosed after a meal, C_{max} was reduced by 25%, but T_{max}, $T_{1/2}$ and AUC were not different from those without a meal. It was concluded that there was no need to consider the food effect because there was no change in the AUC, even though food had a slight effect on the absorption process. There was no significant difference in pharmacokinetic parameters in the Japanese and overseas populations and it was concluded that there was no difference in pharmacokinetics for the Japanese and overseas population.

When fasting healthy adult male volunteers received a single oral dose of 100mg lamivudine, around 59% of the dosed amount was excreted to the urine within 24 hours after administration. The rate of excretion via urine of administration after a meal was around 52%. Around 5% of the dosed amount was excreted as a trans-sulphoxide metabolite, which was the primary metabolite in the urine.

When a single oral dose of lamivudine was administered to elderly volunteers, T_{max} was delayed, AUC was increased by 1.4 times and systemic clearance and renal clearance were reduced by 0.71 and 0.67 times respectively. However, changes in blood concentrations by repeated doses in elderly subjects were simulated and accumulation in elderly subjects was considered to be absent. Therefore, a dose reduction in elderly patients without renal function impairment was considered unnecessary in clinical practice. When otherwise healthy adult volunteers with compromised renal function received a single dose of 100 or 300mg of lamivudine under fasting condition, T_{max} was significantly delayed and C_{max} and AUC were significantly increased compared with healthy adults. The lower the renal function, the higher AUC became. Adults with severe renal impairment showed a significant prolongation of $T_{1/2}$. It was believed that dose reductions were required in adults with compromised renal function.

The Evaluation Centre asked the applicant to provide an explanation of effects of lamivudine on kidney excretion of other concurrent medications. The applicant investigated effects of lamivudine on uptake of a typical organic cation tetraethylammonium (TEA) by brush boarder microvesicle (BBMV) of the rat renal cortex. This is because lamivudine is a cationic agent therefore it could inhibit tubular secretion of concurrent cationic agents. The results showed no inhibition of TEA uptake by BBMV when lamivudine was present. The applicant concluded that therefore lamivudine was not likely to affect tubular secretion of other cationic agents. The Evaluation Centre accepted the response.

The Evaluation Centre instructed the applicant that narratives on patients receiving dialysis had to be included in the *Gaiyo* because they were mentioned in the draft prescribing information. The applicant responded by adding a section, (3) Investigations

in Renally Compromised Adults. The Evaluation Centre considered the amendment appropriate and accepted the response.

G. Data on Clinical Study Results

Two phase I studies were carried out. One was a single dose study in 12 healthy adult male volunteers. In this study, six subjects each received 50mg (in the fasting state), 100mg (in the fasting state and fed state) and 300mg (in the fasting state). Another study was a repeated dose study with a 200mg group (six subjects) and a placebo group (two subjects), and the subjects received administration once daily after a meal for seven days. In the single dose study, no adverse drug reaction was seen at the dose level of 50mg, but one subject who received 100mg in the fasting state, one subject who received 100mg lamivudine in the fed state and four subjects who received 300mg lamivudine showed adverse drug reactions. In the repeated study, no adverse drug reactions were observed in the active drug group. The observed adverse drug reactions included sleepiness, headache and general malaise.

A Japanese phase II study targeted 124 HBeAg positive chronic hepatitis B patients receiving four dose levels at 2.5mg, 25mg, 100mg and 200mg for four weeks in a double-blind fashion. The primary endpoint, the serum HBV-DNA reduction rate shown as –log (post-treatment value/pre-treatment value) after four-week treatment was 0.88±0.96 in the 2.5mg group, 2.52±0.67 in the 25mg group, 2.82±0.66 in the 100mg group and 2.98±0.73 in the 200mg group. There were significant differences between the 2.5mg group and other groups and the reduction rates had relatively large differences. Looking at the 25mg, 100mg and 200mg groups, the 25mg group and the 200mg group showed a significant difference, but there was no clear difference between 25mg and 100mg or between 100mg and 200mg. The ratio of patients whose blood HBV-DNA levels were decreased below the detection limit (2.5pg/mL) was 18% in the 2.5mg group, 60% in the 25mg group, 70% in the 100mg group and 70% in the 200mg group. With regard to overall safety, a rate of patients who scored “practically safe” or “safe” was over 90% in all groups. No clear indication of dose correlation on safety was observed. Common adverse drug reactions were sleepiness and headache.

A Japanese phase III study targeted 137 HBV-DNA positive chronic hepatitis B patients. It was a placebo controlled double blind parallel comparison study which compared 100mg lamivudine with placebo and the primary endpoints were HBV-DNA improvement and GPT improvement. Duration of trial treatment was 32 weeks, which was divided into two phases. During the first phase, two groups received placebo or 100mg lamivudine once daily, and during the second phase both groups received 100mg lamivudine once daily. At the end of the first phase, blood HBV-DNA levels (logarithmic values, long (pg/mL)) were changed from 1.5±1.4 predose to 2.4±1.3 in the placebo group and from 2.6±1.4 predose to 0.2±0.4 in the 100mg group. In the 100mg group, the ratio of patients whose blood HBV-DNA levels were decreased below the detection limit (2.5pg/mL) at the end of the first phase was 8% in the placebo group and 74% in the 100mg group (ITT analysis). Blood HBV-DNA levels at the end of the second phase (logarithmic values, log(pg/mL)) were 0.2±0.4 and 0.2±0.5 respectively. Eight weeks after the completion of the study treatment, blood HBV-DNA levels were increased almost to the predose levels and they were 2.1±1.6 in the 100mg group and 2.2±1.6 in the placebo group. GPT also showed similar movement to the blood HBV-DNA level, but the change was slow compared with the virus levels. At the end of the first phase, the GPT level was changed from 125±88 predose to 151±129 in the placebo group and from 137±100 predose to 39±22 in the 100mg group. In the 100mg group, the ratio of patients whose GPT levels were normalised at the end of the first phase was 3% in the placebo group and 37% in the 100mg group (ITT analysis). GPT levels at the end of the second phase were 37±20 and 27±15 respectively. Eight weeks after the completion of the study treatment, GPT levels were 165±250 in the placebo group and 126±167 in the lamivudine group. At the end of the first phase, HBe Ag levels (logarithmic values, log(U/mL)) were changed from 2.5±1.4 predose to 2.7±1.3 in the placebo group and from 2.7±1.2 predose to 1.9±1.2 in the 100mg group. In the 100mg groups, the ratio of patients whose HBe Ag levels were decreased below the detection limit at the end of the first phase was 6% in the placebo group and 20% in the 100mg group (ITT analysis). HBe Ag levels (logarithmic value, log(U/mL)) at the end of the second phase were 1.9±1.2 and 1.7±1.1 respectively. No difference in the incidence of

adverse events during the first phase was observed, 45% in both the 100mg group and the placebo group. Lab tests abnormality was raised eosinophil count in 14% of patients.

A long-term study targeted 134 HBV-DNA positive or DNA-polymerase positive chronic hepatitis B patients who received 100mg lamivudine once daily for 24 to 52 weeks continuously. It was an open study. The HBV-DNA level (logarithmic values log (pg/mL)) was 2.7±1.2 before starting the treatment. Once treatment was started, the level decreased. However, a proportion of subjects showed increases after 24 weeks and it was 1.9±1.6 on the eighth week from withdrawal. The GPT value was 162±105 predose which decreased once the treatment started. It remained low until Week 52 but returned to the predose level after eight weeks from withdrawal. Liver biopsy was performed on 11 patients immediately before starting the treatment and at the end of the treatment. The HAI score was 8.9±3.0 predose and 4.1±2.5 postdose, achieving a reduction of 4.8±3.1 points (p=0.003). In the long-term study, 65 patients showed GPT increases during the follow-up period after withdrawal. Specifically, ten patients showed deterioration of liver function and required hospitalisation, and of these, one patient (a 39 year old male) had hepatic failure on 60 days after withdrawal and died on 97 days after withdrawal. Nine patients who were hospitalised had severe jaundice with total bilirubin levels above 10mg/dL or GPT above 500 (above 2,000 in three of them), clearly demonstrating induction of fulminant hepatitis.

As a part of a five year long-term study, a histology investigative study was carried out in 20 HBV-DNA positive or DNA-polymerase positive chronic hepatitis B patients. In this study, liver biopsy at the start of treatment and at Week 52 was performed. HBV-DNA levels were reduced once treatment was started. However the HBV-DNA levels increased after Week 24 in some patients and average GPT values were increased after Week 52. It was shown that emergence of YMDD mutant HBV (lamivudine resistant HBV) was involved in deteriorations (as described later). Histologcally, the HAI scores were 10.9±3.0 predose and 5.2±2.9 at Week 52, achieving a significant reduction of 5.8±3.5 points.

In the phase III comparative study, 14 patients in total, i.e., two out of 63 patients who received 32-weeks treatment and 12 out of 119 who received over 24-weeks treatment, required hospitalisation due to liver function deterioration after withdrawal of treatment. To check the safety of subjects, a follow-up investigation was carried out. The results identified the following. (1) Their HBV-DNA levels were decreased during lamivudine treatment, but they increased after withdrawal and deteriorated to near predose levels. (2) After eight to 12 weeks from withdrawal, GPT was higher than the predose level and it returned to the predose level after 16 to 20 weeks. (3) Investigators assessed that 51% (123/242) of patients showed acute deterioration after withdrawal. Patient's background factors showed that deterioration after withdrawal was more likely in patients whose 1) HBV-DNA levels were high, 2) GPT levels were high and 3) HBeAg levels were high before lamivudine treatment. Also, a similar tendency was observed in patients whose 4) HBeAg remained positive and 5) seroconversion was not induced during lamivudine treatment and 6) duration of lamivudine therapy was long. Only two patients in the placebo group of the comparative study (4%, none had GPT normalisation), five patients in lamivudine group in the comparative study (9%, two had GPT normalisation) and 10 patients in the long-term study (10%, seven had GPT normalisation) sustained HBeAg-/Ab+ seroconversion.

Emergence of lamivudine resistant HBV was confirmed in patients in the long-term study. Post-hoc gene analysis was carried out. The rate of developing resistance was 37% (44/120) in patients who received 36 to 52 weeks treatment in the long-term study and 35% (7/20) in patients in the second year of the five-year study (patients who were included in the histological investigation). In the core studies implemented abroad, the average rate of lamivudine resistant HBV emergence in the first year was 23% (54/236) and that in the second year was 42% (31/74).

Five overseas clinical studies were submitted as approval application data. A 52-week placebo controlled double-blinded study with 100mg lamivudine in 143 treatment naïve HBeAg positive chronic hepatitis B patients in the US used histological improvement as a primary endpoint. The ratio of over two-point reduction in Knodell HAI total scores at the end of treatment was 52% (34/66) in the lamivudine group and 23% (16/71) in the

placebo group. The rate of HBeAg serovnversion at the end of treatment (Week 52) was 17% (11/66) in the lamivudine group and 6% (4/71) in the placebo group, showing a significant difference. However, there was no significant difference at Week 68, with 17% (11/66) in the lamivudine group and 9% (6/71) in the placebo group.

A placebo-controlled 52-week double blind comparative study with 25mg and 100mg lamivudine in Asian countries including Hong Kong and Singapore targeted 358 HBeAg positive chronic hepatitis B patients. One of the primary endpoints was histological improvement. Patients with severe hepatitis and moderate hepatitis were analysed separately. Overall results showed that the rate of over one-point reduction in Knodell Necroinflammatory Score was 33% (24/72) in the placebo group, 58% (82/142) in the 25mg group and 64% (92/143) in the 100mg group. Improvement in HBcAg or HBV-DNA levels in the hepatic tissues (cytoplasm and nucleus) were also the primary endpoint. The improvement rate was 56% (40/72) in the placebo group, 52% (74/142) in the 25mg group and 57% (81/143) in the 100mg group, indicating that lamivudine did not have the ability to decrease virus markers within the hepatic issues. At the end of the study (Week 52), a long-term study arm was continued. The study was designed to administer placebo or the same doses as the previous arm to the 25mg and 100mg groups, and 100mg to the placebo group. When HBV-DNA levels of 5pg/mL or above were recorded twice during treatment, the patient received 100mg lamivudine in open fashion. The rate of patients with sustained negative HBV-DNA was 25% (24/96) in the group that received 25 mg for 104 weeks, whereas it was 7% (2/29) in the group that switched from 25mg to placebo at Week 52. The rate of patients with sustained negative HBV-DNA was 52% (47/90) in the group that received 100 mg for 104 weeks, whereas it was 5% (2/41) in the group that switched from 100mg to placebo at Week 52.

In a study targeting 230 chronic hepatitis B patients who have not received interferon, the patients were assigned to one of three groups with lamivudine immunotherapy, interferon immunotherapy, and lamivudine and interferon combination therapy. The study took place mainly in Europe. The primary endpoint HBeAg serovoncersion rate (at Week 64) was 19% (15/80) in the lamivudine monotherapy group (100mg of lamivudine for 52 weeks), 17% (11/64) in the interferon monotherapy group (5MU

Intron A three times per week for 1 week and 10 MU Intron A three times per week for 15 weeks) and 24% (16/68) in the combination therapy group (100mg lamivudine for 8 weeks followed by 5 MU Intron A three times per week for 1 week and 10 MU Intron A three times per week for 15 weeks in addition to 100mg lamivudine). There was no difference among the groups. As far as changes in HBV-DNA are concerned, many patients experienced reappearance of HBV-DNA following withdrawal of lamivudine and the study failed to show additive benefit of concomitant use of interferon.

In Europe, a placebo control partially double blind study (52 weeks with 100mg lamivudine then followed for observation up till Week 76) was carried out in 125 HBeAg positive patients. Of patients who were included in ITT analysis, 57 patients were withdrawn prematurely. No study results, other than data up to the end of 52-week treatment, were submitted and follow-up data were not provided. The rate of negative HBV-DNA accompanied by GPT normalisation, which was the primary endpoint, was 9% (5/54) in the placebo group and 65% (35/54) in the lamivudine group.

An evaluation meeting questioned the emergence of lamivudine resistant HBV and acute deterioration of liver function including occurrences of fulminant hepatitis that were seen one to six months after cessation of lamivudine treatment.

Clinical studies clearly demonstrated that lamivudine suppressed blood HBV-DNA to below the detection limit during treatment but it did not eradicate the virus. They also demonstrated a high rate of emergence of lamivudine resistant HBV with treatment beyond 36 weeks and accompanied deterioration of hepatic function. However, they indicated that lamivudine might have encouraged seroconversion in HBeAg positive patients and suppressed deterioration of hepatic function during treatment, even after emergence of resistant virus. Liver biopsy at the end of treatment showed histological improvements, reductions of cytopathy in the liver may only mean improvements of GPT. It does not necessarily suggest long-term improvement of outcome. It was also clear that withdrawal of lamivudine led to fast proliferation of wild type virus followed by acute deterioration of hepatic function in over a half of patients after eight to 12 weeks from the withdrawal, which could cause fulminant hepatitis. There was no report

of fulminant hepatitis in overseas clinical studies, however in HIV patients; over 10 cases of serious adverse drug reactions associated with deterioration of hepatitis including fulminant hepatitis were reported.

In the meeting, appropriateness of the chosen optimum dose was questioned based on the following reasons. 1) There was no large difference in effectiveness of 25mg, 100mg and 200mg (once daily) when HBV-DNA was used as a surrogate maker. 2) Daily doses up to 300mg were used for HIV infection. There was no reduction in HBeAg with daily doses at 100mg when HBeAg was used as a surrogate maker. Also, rebound was observed after withdrawal. These suggested that 100mg might not be sufficient. However, the incidences of adverse events remained the same up to 200mg and reference data from studies including an overseas dose response study revealed a trend of better effectiveness with 100mg compared with 25mg. Therefore, 100mg could be seen as an optimum dose.

Even though lamivudine is associated with a risk of 1) emergence of resistant virus and 2) acute deterioration and fulminant hepatitis after withdrawal, it is expected to be effective in suppressing HBV proliferation during acute deterioration of chronic hepatitis B and seroconversion is significantly likely with lamivudine compared with placebo. The Evaluation Centre believed that lamivudine was approvable provided that a warning in the prescribing information was amended as below, and it was contraindicated to patients with hepatitis that was likely to deteriorate and become severe hepatitis (patients with jaundice and patients with or suspected with cirrhosis). The applicant insisted the indication should be “improvement of virus market, hepatic function and liver histology in chronic hepatitis B”. However, it was not clear whether lamivudine improved the long-term outcome of chronic hepatitis B and that improvement of hepatic function impairment was considered to be associated with suppression of HBV proliferation. Therefore, the Evaluation Centre is considering the indications of “improvement of viremia in HBeAg positive chronic hepatitis B.” The Evaluation Centre believes those issues should be discussed in the subcommittee meeting.

Warnings

The frequency of emergence of lamivudine resistant virus was high in long-term Zefix treatment (37% with 36 to 52 weeks treatment). In addition, acute deterioration of hepatic function after 8 to 12 weeks of withdrawal was observed in more than a half of patients in Japanese clinical studies (7.7% of patients required hospitalisation and some patients had fulminant hepatitis and died). Even after resistant virus emerges, cessation of Zefix treatment may be difficult. Zefix treatment should start after full information is given to the patient and consent is obtained.

(Suggestion of the applicant)

After withdrawal of Zefix, re-growth of virus accompanied by relapse of hepatitis or deterioration may occur. When withdrawing Zefix, clinical symptoms and lab test values (HBV-DNA and GPT and if necessary total bilirubin) of the patient should be monitored every two weeks, as a rule, for at least four months after withdrawal, and then further observation should be continued.

This is particularly important in patients with strong immune response (e.g. patients with a history of jaundice and severe acute deterioration of hepatitis) or in decompensated hepatitis patients (including patients with advanced histology and have inadequate spare hepatic capacity), as hepatitis may become severe after withdrawal and these patients require even more careful follow-up observation after cessation of treatment. Making a decision to withdraw Zefix may be difficult in such patients, and long-term treatment may be required.

Contraindication

Patients with jaundice.

Patients with or suspected with cirrhosis.

Other issues, Japanese safety evaluation and overseas safety evaluation of acute deterioration

Draft indication, dosage and administration method, precaution for use (draft) and the rationales

The Evaluation Centre instructed the applicant to describe guidance on cessation of treatment in “precaution for use concerning dosage and administration method”.

The Evaluation Centre instructed the applicant to describe information on countermeasures to be taken when a patient has a relapse after withdrawal and treatment when resistant virus emerges in “important basic cautions”.

The Evaluation Centre instructed the applicant to make appropriate amendments on indication, dosage and administration method, precautions for use (draft) and the rationale based on the instructions given.

[Overall Assessment]

3. RESULT FROM A COMPATIBILITY CHECK BY KIKO AND INTERPRETATION BY THE EVALUATION CENTRE

1) Interpretation of the compatibility check

The *Kiko* has carried out an audit on documents as stipulated in the last paragraph of Section 4, Article 14 of the Pharmaceutical Affairs Law. There was incompatibility in some parts (e.g. protocol violations in some clinical study results). However, the Evaluation Centre considered that there was no problem in carrying out the evaluation based on the approval evaluation data submitted after reviewing handling of data from these patients in efficacy and safety evaluations.

2) Interpretation of the GCP inspection

The GCP meeting found protocol violations in some studies and eight subjects (4 xx, 2 xx and 2 xx) were found to be GCP incompliant. The applicant then voluntarily checked

for the presence of similar violations. A further five subjects (4 xx and 1 xx) were found to be GCP incompliant and excluded from data. The Evaluation Centre considered that there was no problem in carrying out the evaluation based on the approval evaluation data submitted after exclusion of those patients.

4. OVERALL ASSESSMENT OF THE EVALUATION CENTRE

Lamivudine presents risks of the emergence of resistant virus and acute deterioration and fulminant hepatitis after withdrawal. However, lamivudine is expected to show efficacy though suppressing HBV proliferation in chronic hepatitis B patients, including those in acute deterioration period. Patients under lamivudine treatment are significantly more likely to experience seroconversion than patients under placebo. Therefore, the Evaluation Centre concluded that lamivudine was approvable on condition that strict warnings were provided and with a restriction on patient groups that may be treated.

However, the Evaluation Centre believes that the subcommittee needs to review remaining issues such as wording in the indications, the indicated patient population and risk/benefit of the drug.

Evaluation Report (Part 2)

14th February 2000

[Product Name]	Zefix Tablet 100
[Generic Name]	Lamivudine
[Date of Submission]	19th December 1998
[Applicant]	Nippon Glaxo Ltd. (Currently Glaxo Wellcome Ltd.)

Evaluated Issues

The filed articles were discussed in the first subcommittee meeting of the old system. Date of the Subcommittee Meeting: 26th July 1999.

Five instructions listed below were raised during discussion in the first subcommittee meeting.

1) Re-analyse data including overseas data (especially the studies implemented in Asia) and review the therapeutic indications of Zefix and the target population. The re-analysis and the review should be focused on identifying groups of patients who are less likely to experience rebound and emergence of resistant virus after cessation of Zefix treatment, which are unique to Zefix.

2) Identify background factors that are associated with rebound (e.g. GPT levels, acute exacerbation, a stronger trend in the younger population and the relationship to immunocompetence and the subtypes of virus and compliance). Review the progress of the disease as far as possible, for example an induction of seroconversion in the follow-up investigation of patients who experienced rebound. Furthermore, submit clinical outcome after re-initiation of Zefix therapy.

3) Provide results of analysis of the resistant virus emergence stratified by the background factors and review the factors that may be involved.

4) Clarify the rationale for the criteria of discontinuation of Zefix therapy described in "Precautions for Use Concerning Dosage and Administration Method" (Approval Application Data p439).

5) Once started, Zefix therapy needs to be long maybe for a lifetime and the action of Zefix is not in irradiation of virus but suppression of replication. Therefore, the recommended clinical dose has to be set carefully. Resubmit the view of the applicant on the chosen recommended clinical dose of 100mg and expand the discussion to the dose levels below 100mg.

Evaluation by the Evaluation Centre after the Subcommittee Meeting

In the hearings, which were taken place after November 1999, the Evaluation Centre examined the responses of the applicant to the subcommittee instructions and other issues.

During the course of reviews of the responses, the Evaluation Centre advised to replace wordings of "rebound" and "resistant viruses" in the submitted documents with more scientific wordings. The applicant replied that they were going to replace them with "deterioration of liver functions after discontinuation of therapy" and "YMDD mutant virus", which were accepted by the Evaluation Centre. These wordings in the responses as well as the submitted data and the prescribing information (draft) were amended.

Instruction 1) to 3)

1. Indications and the target population

The applicant stated that in a Japanese histological study in 20 HBV-DNA or DNA-polymerise positive chronic hepatitis B patients, data was stratified into a group with GPT below 100IU/L and a group with GPT 100IU/L or higher and the analysis demonstrated an improvement in the HAI score in both groups. They mentioned the

South East Asian placebo controlled comparative study (duration of treatment: 52 weeks) in 330 HBeAg positive chronic hepatitis B patients with HBV-DNA over 5pg/ml which demonstrated improvements in the liver histology compared with placebo in both stratified groups of severe hepatitis patients and mild hepatitis patients according to their liver histology. They also stated the fact that GPT level of a patient with chronic hepatitis B fluctuated largely. From those reasons, the applicant believed that they did not need to restrict patient groups treated with Zefix according to their GPT levels or histology of the liver prior to treatment. Furthermore, as mentioned below, results of investigations into the background factors of the deterioration of liver functions and the emergence of YMDD mutant after withdrawal suggested a clinical benefit of Zefix therapy in patients who were likely to experience the deterioration of liver function and the emergence of YMDD mutant virus. They concluded, therefore, that continuation of Zefix therapy was meaningful and there was no need to restrict treatment of patients with those factors. Considering the above and reviews of patients who received Zefix therapy in the existing clinical studies, the applicant suggested changing the indications from the original "improvement on virological markers, liver function and histology of cancer of chronic hepatitis B patients" to "improvement on virological markers, liver function and histology of chronic hepatitis B patients with an evidence of liver dysfunction accompanying replication of hepatitis virus B".

The Evaluation Centre acknowledged that pre-treatment virus tests and liver function tests were essential and they must clearly state that patients without an evidence of replication of virus or abnormalities in hepatic function tests should not be treated with Zefix. In response, the applicant suggested adding the following descriptions to "Precaution for Use Concerning Indication". The Evaluation Centre accepted the suggestion.

<Precautions for Use Concerning Indication (Draft)>

1. Prier to Zefix treatment, replication of virus have to be evident from the HBV-DNA, DNA polymerise or HBeAg tests.

2. Note that asymptomatic carriers or patients on other therapies whose liver function test values are within the normal ranges should not be treated with Zefix.
3. Efficacy and safety of Zefix in cirrhosis is not established (clinical experience is limited)

2. Deterioration of liver function after discontinuation

In a follow-up investigation of the Japanese placebo controlled double blind comparative study xxx in 137 HBV-DNA positive chronic hepatitis B patients and the long term study xxx in 134 HBV-DNA or DNA-polymerase positive chronic hepatitis B patients, stratified analysis of the background factors of patients whose GPT levels were above 500IU/L and below 500IU/L at the end of the studies was performed. The following six characteristics were identified in the patients who showed deterioration of hepatic function. Before starting Zefix therapy, 1) HBV-DNA levels were high, 2) GPT was high and 3) HBeAg levels were high. After withdrawal of Zefix, 4) HBeAg remained positive, 5) seroconversion was not induced and 6) duration of Zefix therapy was long. The applicant suggested these were indicative of active replication of virus and hepatic cell destruction due to the immunological response. They claimed that long term Zefix treatment would provide such patients with a large clinical benefit through inhibiting virus replication and slowing advance of histology.

With regard to “a stronger trend in the younger population”, the applicant argued that no relationship between age and deterioration of liver function was observed (extended Mantel test, p=0.187).

With regard to subtypes of serum HBsAg, data on subtypes were not collected in the Japanese and overseas clinical studies. Data from the clinical studies carried out Japan and the West, where the subtypes were known to be different, demonstrated a similar anti-virus effect of Zefix. They concluded, therefore, that subtypes did not affect the effect of Zefix. Deterioration of liver function after discontinuation of treatment was not examined because data on subtypes was not available.

The compliance was over 90% in majority of patients including patients who had deterioration of liver functions. The applicant believed that compliance and deterioration of liver function after cessation of therapy were unlikely to be related.

With regard to early detection of deterioration of liver function after discontinuation of Zefix and the countermeasures, the applicant stated that as liver function tests were carried out every two weeks after withdrawal of Zefix in clinical studies, therefore, liver function tests should be carried out every two weeks, in principle, for four month after discontinuation of Zefix in the clinical practice. Other effective treatment for deterioration of liver function was not established. Therefore, re-initiation of Zefix treatment was the best countermeasure for the deterioration in the applicant's opinion and if it was not possible, common treatment for acute exacerbation should be taken (e.g., Stronger Neo-Minophagen C, interferon preparations).

The Evaluation Centre advised the applicant to add (i) the incidence of deterioration of liver function after treatment cessation in the "Clinical Trial Results", (ii) the background factors of patients who experienced deterioration of liver function after discontinuation in "Important Basic Precautions" and (iii) methods of an early detection of liver function deterioration after discontinuation and the countermeasures in "Warning" and "Precaution for Use Concerning Dosage and Administration Method". In response, the applicant suggested the following additions and the Evaluation Centre accepted the response.

(i) The incidence of deterioration of liver function after discontinuation

The Clinical Trial Results:

2. Deterioration of liver function after discontinuation

The incidence of deterioration of liver function (GPT 500 IU/L or over) during the 24-week follow-up period after completion of 16-week Zefix therapy was 15.0% (9/60), after 32-week therapy was 15.9% (10/63) and after 52-week was 26.9% (32/119) (see Warnings and Precautions for Use Concerning Dosage and Administration Method).

(ii) The background factors of patients who experienced deterioration of liver function after cessation of Zefix therapy

2. Important Basic Precautions

(2) It has been reported that deterioration of liver function after cessation of Zefix therapy is more likely to happen in patients with (i) high HBV-DNA levels, (ii) high GPT levels (iii) high HBe levels before initiating treatment. Therefore, such patients require even more careful follow-up observation after discontinuation of Zefix treatment.

(iii) Early detection of deterioration of liver function after discontinuation and the countermeasure

Warnings, Precautions for Use Concerning Dosage and Administration Method:

After cessation of Zefix therapy, deterioration of liver function or worsening of hepatitis accompanying replication of virus may be observed (see "Clinical Trial Results"). When discontinuing Zefix treatment, clinical symptoms of the patient and lab test values (HBV-DNA, GPT and if required total bilirubin) need to be monitored every two weeks, as a general rule, for four months after the cessation. Monitoring of the patient should be continued further.

3. Appearance of YMDD mutant virus

YMDD mutant virus has lower sensitivity to Zefix because mutation occurs at the active centre of HBV-DNA polymerase where the site of action of Zefix is located. The replication competence of the mutants is known to be lower than wild type virus because the locus of the mutation is in the active centre of the essential enzyme for replication. The incidence of emergence of YMDD mutants in Japanese clinical studies was 37% (44/120) according to the one-year long-term study and 20% (4/20) according to the one-year histology investigation. These were similar to results from three overseas studies with one-year treatment (xxx 32% (14/44), xxx 16% (21/131), xxx 31% (19/61)). The incidence was 53% (27/51) in the overseas three-year study, but, six out

of the 27 patients with YMDD mutants showed HBe seroconversion during Zefix therapy and their liver histology also showed some improvement.

In the Japanese 52-week study and the overseas three-year study, patients were stratified into PCR negative patients, patients with wild virus and patients with mutant virus. Their HBV-DNA levels and GPT values were analysed. It demonstrated patients with YMDD mutants had raised GPT levels following increases in HBV-DNA levels, but the GPT levels were lower than the pre-treatment levels. Two out of all patients who had YMDD mutant virus (7/20) in the Japanese histological investigation showed a sudden elevation of GPT when YMDD mutant virus proliferated. However, concurrent use of interferon when GPT was elevated lead to an improvement and stabilisation of the liver function without discontinuing Zefix. Analysis of predictors of YMDD mutation in Japan and abroad showed patients with active hepatitis or histologically advanced hepatitis had a higher incidence of YMDD mutation. The applicant believed these patients groups should also be treated with Zefix because the patients who were more likely to develop YMMD mutant virus would benefit from Zefix therapy, emergence of YMDD mutation did not necessarily associate with deterioration of liver function, and some patients with liver function deterioration were recovered with combination therapy of Zefix and an existing therapy, such as interferon.

The Evaluation Centre requested additional follow-up data on the changes in the HBV-DNA levels and GPT values, and data on two patients who received interferon combination treatment in the Japanese 52-week study and the overseas 3-year study. Overseas data was not available, but follow-up data on the Japanese study and data on patients who received concurrent interferon treatment were submitted. The applicant also suggested adding the following statements concerning YMDD mutant virus to "2. Important Basic Precautions" under the Precautions for Use. The Evaluation Centre accepted this suggestion.

2. Important Basic Precautions

   YMDD mutant virus has mutations in amino acid sequence at the active centre of DNA polymerise, YMDD to YIDD or YVDD, and their sensitivity to Zefix is

reduced, therefore, the anti-virus effect of Zefix is not anticipated. If the mutants emerge during Zefix therapy, it is, in general, beneficial to continue Zefix treatment in order to suppress wild type virus, because withdrawal of Zefix may lead to reappearance of wild type virus which was under control. Treatment should be continued under sufficient monitoring and with care because liver function may deteriorate due to overgrowth of YMDD mutant virus during therapy. If the benefit of the treatment is lost despite continued Zefix administration, for example hepatitis symptoms deteriorate beyond the pre-treatment level because of YMDD mutants, withdrawal of Zefix should be considered. Experiments have demonstrated that replication competence of YMDD mutant virus was low. Even though data are limited, it has been reported that hepatic function deterioration caused by YDMM mutant virus in some patients was ameliorated when currently available therapy (e.g. interferon) was used concurrently.

4. Follow-up investigation of patients with liver function deterioration after discontinuation

Results of the follow-up investigation for six months after treatment in the double blind comparison study xxx and the long-term study xxx were presented. In the investigation, post-treatment deterioration of liver function was defined as an increase in the peak GPT level for more than 100 from the post-treatment level. The investigation was carried out in 211 patients and 144 patients (68%) showed deterioration of liver function within six months of the discontinuation. Of these, 12 patients experienced seroconversion (HBe-SC) after their liver function was deteriorated. However, the review of pre- and post-treatment background factors in 12 patients with HBe-SC and 132 patients without HBe-SC suggested that “induction of HBe-SC and an increase in HBe antibody levels after Zefix therapy” was the only characteristic of patients who were likely to experience HBe-SC. The Japanese and overseas clinical studies suggested that the rate of HBe-SC increased with longer treatment (in Japan, 1 year xxx 14% (1/7), two years xxx 43% (3/7); overseas, one year xxx 22% (13/58), two years xxx 29% (17/58), three years 40% (23/58)). Therefore, the applicant argued, it was better to induce HBe-SC in long-term

Zefix therapy rather than to treat patients with Zefix for a short period expecting rebound to induce HBe-SC after discontinuation.

The Evaluation Centre understood the claim of the applicant based on the follow-up investigation which showed the rate of HBc-SC tent increasing with longer treatment. However, the Evaluation Centre concluded that detailed clinical monitoring will be required because of the fact that about 70% of patients showed deterioration within six months of treatment cessation (the peak GPT level was more than 100 higher than the post-treatment level). An addition of statements to call for attention, for example the Warnings in the PI, was imposed.

5. Clinical outcome of patients who resumed treatment

In the phase III comparative study xxx and the long-term study xxx, ten patients resumed Zefix treatment for deterioration of liver function after the completion of the studies. These patients were divided by presence/absence of YMDD mutant virus and the effect of resumed therapy was investigated. The outcome of the ten patients was as follows; (i) outcome of re-initiated treatment in five patients who did not have YMDD mutant virus was better than all other patients who re-initiated the treatment, (ii) of three patients who had YMDD mutant virus during the study, two patients who had longer period of discontinuation showed improvement soon after re-initiating the therapy, but the remaining one patient who had shorter period of discontinuation and re-initiated the treatment before breakthrough infection of wild type virus did not show a reduction in DNA polymerase immediately after re-initiation, (iii) two patients who had YMDD mutation before resuming treatment had kept good liver function for more than one year of re-initiation of the treatment, but as soon as YMDD mutations occurred, the liver function was deteriorated.

In conclusion, the applicant argued that it was important to continue Zefix treatment and suppress replication of wild type virus, even when YMDD mutants emerged.

The Evaluation Centre prompted the applicant to describe the above under the "2. Important Basic Cautions" in Precautions for Use.

Instruction 4)

The Evaluation Centre believed that unless seroconversion was confirmed, Zefix treatment was likely to be very long once started and it was difficult to make a decision on discontinuation of Zefix. They instructed to make a clear statement on the above. The Evaluation Centre also insisted a clear guideline for discontinuation of treatment should be provided and that the statement "continue observation after treatment" had to be replaced with a more precise statement. The applicant presented findings from 24 patients in the Japanese clinical studies and 42 patients in the overseas clinical studies who showed seroconversion at the withdrawal as a rationale for the criteria for discontinuing therapy of HBeAg positive patients. The rate of patients who had a good outcome in GPT levels (changes within 50) for six months after discontinuation of the treatment was significantly higher in patients who seroconverted at the cessation. Observation of the highest GPT values of each patient up to six months after discontinuation indicated patients who seroconverted at the withdrawal showed a significantly lower degree of liver function deterioration.

The applicant presented the following rationale for the criteria for discontinuing treatment of HBeAg negative patients. Disappearance of HBeAg was used as guidance for cessation of the therapy because seroconversion was not suitable. Fifty-nine HBeAg negative patients in the Japanese clinical study were reviewed. Fifty eight percent (7/21) of patients who sustained negative HBV-DNA accompanying GOT normalisation for 6 month or longer and 30% (14/47) of remaining patients showed good outcome. The applicant suggested including this rationale in the "Precautions for Use (Draft) and the Rationale". They also suggested amending the prescribing information so that difficulty in discontinuing Zefix and instructions to patients were described at the begging of "Precautions for Use Concerning Dosage and Administration Method" to alert people. They also suggested defining guidelines for discontinuing treatment of "HBeAg positive patients" and "HBeAg negative patients" separately and repeating the statement in the

"Warning" relating to post-treatment observation in the "Precautions for Use Concerning Dosage and Administration Method". The Evaluation Centre accepted the response.

Suggested amendments on "Precautions for Use Concerning Dosage and Administration Method":

1. In general, treatment with Zefix needs to be a long term. Deterioration of liver function or worsening of hepatitis may be seen after discontinuation of the treatment (see "Clinical Results"). Patients need to be fully informed with this and must be advised not to stop taking Zefix without consulting the doctor.
2. Discontinuation of Zefix therapy can be considered if the followings occur during treatment.
   (1) When a HBeAg positive patient sustained seroconversion of HBeAg to HBe antibody (HBe-SC)
   (2) When a HBeAg negative patient sustained negative HBsAg or negative HBV-DNA with GPT normalisation for more than 6 months

   However, liver function may deteriorate after discontinuation (see "Clinical Results"). Clinical symptoms and lab test results (HBV-DNA and GPT, and bilirubin if required) should be monitored every 2 weeks, as a general rule, for at least 4 months after withdrawal. Monitoring of the patient should be continued further.
3. Limited data on the long-term durability of seroconversion after discontinuation of treatment following sustained HBe-SC is available.

Instruction 5)

The applicant presented results of a clinical trial performed in South East Asia xxx, because GPT improvements and histological improvements were not used as endpoints of the Japanese dose selection studies. Comparison of the placebo group, the 25mg group and the 100 group demonstrated followings. (i) Histology improvements seen in Knodell HAI scores at week-52 of treatment were significantly better in the 25mg group

(2-point reduction) and the 100mg group (3-point reduction) than the placebo group (1-point increase). Although there was no significant difference between the 25mg group and the 100mg group, it was suggested that the effect seen in the 100mg group was higher than the effect seen in the 25mg group. (ii) The rate of durable negative HBV-DNA (remained negative for 52 weeks) with 52-week treatment was 16% (11/70) in the placebo group, 39% (52/135) in the 25mg group and 68% (95/140) in the 100mg group. Compared with placebo, 25mg and 100mg showed significant differences and 100mg showed a significantly higher rate than 25mg ($p<0.001$, χ^2-test). (iii) The rate of sustained normalisation of GPT (when GPT was normal in at least two successive tests and not abnormal in at least two following tests) was 24% (12/50) in the placebo group, 65% (64/98) in the 25mg group and 72% (68/95) in the 100mg group, showing a higher rate of sustained normalisation in the 100mg group, though not statistically significant. (iv) The cumulative seroconversion rate for treatment up to 52-week was 4% (3/70) in the placebo group, 13% (17/131) in the 25mg group and 16% (22/131) in the 100mg group. The rate for up to 104-week treatment was 20% (19/96) in the 25mg group and 23% (21/90) in the 100mg group (reference data). The data for the placebo group was not available. Taking the data up to 52 weeks and the time-changes into account, there was a difference between the placebo group and the 100mg group ($p=0.014$, log rank test), though there was no difference between the placebo group and the 25mg group ($p=0.062$, log rank test). In consequence of the above, the applicant concluded that it was appropriate to select 100mg as the clinical recommended dose and these results were in agreement with the Japanese clinical study results.

The Evaluation Centre concluded that overall consideration of the responses including overseas clinical data supported the clinical recommended dose at 100mg, despite the lack of a significant difference in the primary endpoint of the rates of HBV-DNA reductions between 25mg and 100mg in the Japanese dose selection study.

Overall Decision

The Evaluation Centre judges the submitted responses answered the issues including indications, target population, long duration of treatment and possible deterioration of liver function after withdrawal and emergence of YMDD mutant virus and the countermeasure. The amendments provided have been reflected in the prescribing information (draft). The Evaluation Centre concludes the dose level at 100mg is appropriate as the clinical recommended dose based on the overall evaluation of the submitted data which includes overseas data.

In conclusion, The Evaluation Centre believes Zefix is approvable with the above-mentioned amendments.

Evaluation Report (3)

25th July 2000

1. Evaluated Issues

Based on the discussion of the expert committee, the Evaluation Centre made the following queries and they were discussed with the applicant.

Predictors of Deterioration of Liver Function after Discontinuation:

The Table G-1-66 (the incidence of patients who experienced deterioration of ALT (GPT) over 500 after discontinuation of Zefix) was used for searching a patient group which was likely to experience deterioration of liver function after discontinuation of Zefix therapy. The table pointed out that the incidence was higher in patients who i) had high pre-treatment levels of HBV-DNA, ii) had elevated pre-treatment ALT (GPT) and iii) had high pre-treatment levels of HBeAg. A similar trend was also seen in patients who iv) did not have negative HBeAg at the end of therapy and v) did not experience seroconversion by the end of therapy and vi) received long therapy. "Important Basic Precautions" in the prescribing information (draft) only mentioned pre-treatment predictors and did not mention predictors at the end of therapy. The results at the end of treatment were mentioned only in "Clinical Results". The Evaluation Centre considered health care workers had to be fully informed with deterioration of liver function after discontinuation of Zefix. They decided predictors at the end of therapy should be added to "Important Basic Precautions".

Treatments when YMDD Mutant Virus Emerges:

The presented prescribing information (draft) stated, "…it has been reported that … was ameliorated when currently available therapy (e.g. interferon) was used concurrently" as a countermeasure of YMDD mutant virus emergence. The number of the reported cases was limited and this treatment lacked foundation. The European and the USA's data-

sheets state that the long-term clinical significance of YMDD mutations had yet to be established and the clinical and experimental monitoring may be useful for choosing treatment when emergence of mutant virus was suspected. Therefore, the Evaluation Centre judged the prescribing information should only mention that the replication fitness of YMDD mutant virus was weak.

The applicant stated that they were preparing "Guideline for Lamivudine Therapy" edited by investigators participated clinical trials, which described information on YMDD mutant virus and currently available findings on countermeasures including case reports in order to provide physicians with additional information. The Evaluation Centre judged the reply was appropriate.

Treatment of Cirrhosis Patients:

A limited number of overseas data indicated that Zefix was effective in compensated cirrhosis patients and certain decompensated cirrhosis patients. The current Japanese prescribing information (draft) states; "Efficacy and safety in cirrhosis patients is established (clinical experience is limited)". However, effective treatment for "cirrhosis caused by hepatitis B virus" is not available. Therefore, when Zefix is launched, it will be used for cirrhosis as well as for chronic hepatitis. The applicant replied

The Evaluation Centre viewed these responses acceptable.

Actions After Launch:

The applicant is planning to implement post-marketing surveillance in 3000 cases and "a special investigation on long-term use" in 500 cases after the launch. They are going to

obtain information on guideline for discontinuing Zefix treatment, and emergence of YMDD mutant virus and the countermeasures. In order to provide information for appropriate use and safety data, an information leaflet for patients and homepage designed for interactive information exchange with clinicians will be set up after launch in addition to the above mentioned document. Furthermore, distribution materials for clinicians will be renewed as necessary, so that they will be provided with up-to date information. The applicant is also planning to set up a safety committee mainly consists of investigators participated in clinical trials so that they can reply to medical questions and urgent queries and to carry out periodical safety up-date after the launch.

Effect of Concurrent Medications:

Combination therapy with interferon α was investigated in a mouse 1-month repeated dose combination therapy toxicity study, the overseas clinical pharmacology study of combination therapy and the overseas clinical study of combination therapy. The applicant reported that undesirable effects from the combination therapy were not observed in those studies.

Drug interaction of concomitant Stronger Neo-Minophargen C was reviewed. The applicant concluded that glycyrrhizin was unlikely to affect ADME and pharmacokinetics of Zefix and Zefix to affect ADME and pharmacokinetics of glycyrrhizin from reasons such as differences between the main excretion route of the main component of Stronger Neo-Minophargen C, glycyrrhizin, and that of Zefix.

The list of concurrent drugs used in clinical studies was submitted. The applicant looked into agents that were likely to be used concurrently after launch (13 cases with Proheparum tablet, 10 cases with ursodesoxycholic acid, 7 cases with *Sho-sai-ko-to*, etc.). Even though the number of cases was insufficient for safety assessment, the applicant considered the majority of adverse events were associated with the primary disease or chance occurrences. They stated that in overseas countries, ST combination preparations were the only agents with concerns on concurrent use so far and it was

already mentioned under “Interactions” of the prescribing information (draft). The Evaluation Centre judged the responses acceptable.

Prescribing Information (Draft):

The Evaluation Centre requested the applicant to provide information on HIV co-infection refereeing to overseas data-sheets, for potential use of the drug. With regard to use in decompensated cirrhosis, data from only a limited number of Japanese patients who received Zefix treatment outside of protocol were available and efficacy and safety were not established. Therefore, the applicant suggested the following statement. “Clinical experience in patients diagnosed with cirrhosis is limited and efficacy and safety is not established. Especially, experience in patients with a reduced spare capacity of the liver, for example decompensated cirrhosis is minimal”. The Evaluation Centre accepted the response.

The Evaluation Centre instructed the applicant to repeat the statement on serious adverse drug reactions in the prescribing information of the already approved anti-HIV drug in the prescribing information of Zefix in order to provide information.

Stability:

An on-going stability study was completed and data up to 36 months for the drug substance and the drug product was submitted. Three-year stability of the drug substance and the drug product were confirmed. Therefore, a shelf life is not required.

Bone Marrow Toxicity of Lamivudine:

On 21st July 2000, the applicant reported that they found IC_{50} of pluripotent precursor cell CFU-gemm on the topic of the pharmacological study on human bone marrow precursor cells impairment by lamivudine in the original submission document was incorrect (correct: 10μM, incorrect: >100μM). According to the correct figure, IC_{50} of lamivudine against pluripotent precursor cells CFU-gemm was less than one tenth of ddI.

Compared with other anti-viral agents, cell toxicity of lamivudine was lower and the cell toxicity to other bone marrow precursor cells (CFU-gm14d, CFU-gm7d, BFU-e, Stromal Progenitors) was not observed even at 100μM. The Evaluation Centre accepted the applicant's view that the lamivudine's potential to suppress bone marrow was low.

2. Overall Assessment

In conclusion, the Evaluation Centre believes Zefix is clinically useful as long as sufficient information is available and used by physicians and patients who understand characteristics of Zefix. The Evaluation Centre has no objection in approving Zefix and recommends the application to be discussed in the 1st Special Committee Meeting.

Zefix is a drug with a new indication and a new dosage. This approval application is for an additional indication of the already approved drug (Epivir: for combination therapy with other anti-HIV agents for HIV infection), which is in the re-examination period. Epivir is approved as an orphan drug (re-examination period is 10 years). Therefore duration of the re-examination period of Zefix should be 5 years and 10 months.

4th August 2000

Evaluation and Licensing Division

Pharmaceutical and Medical Safety Bureau

Evaluation Report (2)

[Product Name]	Zefix Tablet 100
[Generic Name]	Lamivudine
[Applicant]	Nippon Glaxo Ltd. (Currently Glaxo Wellcome Ltd.)
[Date of Submission]	19th December 1998 (Application for Importing Approval)

Zefix is a drug product with different contents, dosage and administration method and indication from an existing approved orphan drug (Epivir tablet: for combination therapy with other anti-HIV gents for HIV infection). Therefore, duration of the re-examination period should be six years.