CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-564 / S-007
20-596 / S-007

Trade Name: Epivir

Generic Name: (Lamivudine)

Sponsor: GlaxoSmithKline

Approval Date: March 23, 1999

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APPLICATION NUMBER:

20-564 / S-007
20-596 / S-007

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APPLICATION NUMBER:

20-564 / S-007
20-596 / S-007

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-564/S-007
NDA 20-596/S-007

GlaxoWellcome, Inc.
Attention: David M. Cocchetto, Ph.D.
Five Moore Drive
Research Triangle Park, NC 27709

MAR 23 1999

Dear Dr. Cocchetto:

Please refer to your supplemental new drug applications dated March 27, 1998 submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Epivir® (lamivudine), 150mg tablets and 10mg/ml oral solution.

We acknowledge receipt of your submissions dated:

June 12, 1998	June 25, 1998	August 28, 1998
September 10, 1998	November 3, 1998	December 18, 1998
February 1, 1999	March 5, 1999	March 10, 1999

We note that these supplemental applications supercede your supplemental applications submitted on June 1, 1998 and June 10, 1998.

These supplemental applications provide for the inclusion of additional pediatric information into the labeling.

We have completed the review of these supplemental applications, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for the use as recommended in the enclosed marked-up draft labeling submitted on March 19, 1999. Accordingly, the supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the March 19, 1999, draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten copies on heavy weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-564/S-007 and NDA 20-596/S-007. Approval of this submission by FDA is not required before the labeling is used.

Please also refer to approved NDA's 21-003 and 21-004 for Epivir-HBV. We remind you of your phase 4 commitment letter dated December 8, 1998, in which you agreed to submit labeling supplements for Epivir products that would provide consistency of information in the package inserts for different products containing lamivudine and to ensure differentiation between Epivir and Epivir-HBV. We request that you submit proposed draft labeling within sixty days of receipt of this letter that addresses these issues.

Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

We remind you that you must comply with the requirement for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Terrie L. Crescenzi, R.Ph., Regulatory Project Manager, at (301) 827-2335.

Sincerely yours,

Heidi Jolson

Heidi Jolson, M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-564 / S-007
20-596 / S-007

LABELING

EPIVIR® Tablets

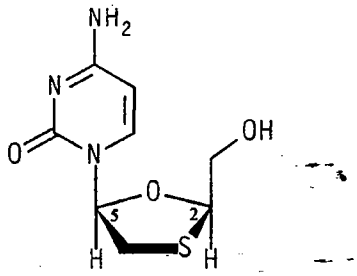
(lamivudine tablets)

EPIVIR® Oral Solution

(lamivudine oral solution)

WARNING: LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING LAMIVUDINE AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

DESCRIPTION: EPIVIR (formerly known as 3TC) is the brand name for lamivudine, a synthetic nucleoside analogue with activity against HIV. The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2′,3′-dideoxy, 3′-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3. It has the following structural formula:



Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.

EPIVIR Tablets are for oral administration. Each tablet contains 150 mg of lamivudine and the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. Opadry YS-1-7706-G White is the coloring agent in the tablet coating.

EPIVIR Oral Solution is for oral administration. One milliliter (1 mL) of EPIVIR Oral Solution contains 10 mg of lamivudine (10 mg/mL) in an aqueous solution and the inactive ingredients

artificial strawberry and banana flavors, citric acid (anhydrous), edetate disodium, ethanol (6% v/v), methylparaben, propylene glycol, propylparaben, and sucrose.

CLINICAL PHARMACOLOGY:

Mechanism of Action: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (L-TP). The principal mode of action of L-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleoside analogue. L-TP is a weak inhibitor of mammalian DNA polymerases α and β, and mitochondrial DNA polymerase.

Microbiology: ***Antiviral Activity In Vitro:*** The relationship between *in vitro* susceptibility of HIV to lamivudine and the inhibition of HIV replication in humans has not been established. *In vitro* activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. IC_{50} values (50% inhibitory concentrations) were in the range of 2 nM to 15 μM. Lamivudine had anti–HIV-1 activity in all acute virus-cell infections tested. In HIV-1–infected MT-4 cells, lamivudine in combination with zidovudine had synergistic antiretroviral activity. Synergistic activity of lamivudine/zidovudine was also shown in a variable-ratio study.

Drug Resistance: Lamivudine-resistant isolates of HIV-1 have been selected *in vitro*. The resistant isolates showed reduced susceptibility to lamivudine and genotypic analysis showed that the resistance was due to specific substitution mutations in the HIV-1 reverse transcriptase at codon 184 from methionine to either isoleucine or valine. HIV-1 strains resistant to both lamivudine and zidovudine have been isolated.

Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harboring zidovudine-resistant virus, phenotypic sensitivity to zidovudine by 12 weeks of treatment was restored. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Cross-Resistance: Cross-resistance among certain reverse transcriptase inhibitors has been observed. Cross-resistance between lamivudine and zidovudine has not been reported. In some patients treated with lamivudine alone or in combination with zidovudine, isolates have emerged with a mutation at codon 184 which confers resistance to lamivudine. In the presence of the 184 mutation, cross-resistance to didanosine and zalcitabine has been seen in some patients; the clinical significance is unknown. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Pharmacokinetics in Adults: The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV-infected adult patients after administration of single intravenous (IV) doses ranging from 0.25 to 8 mg/kg, as well as single and multiple (b.i.d. regimen) oral doses ranging from 0.25 to 10 mg/kg.

Absorption and Bioavailability: Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute bioavailability in 12 adult patients was 86% ± 16% (mean ± SD) for the tablet and 87% ± 13% for the oral solution. After oral administration of 2 mg/kg twice a day to nine adults with HIV, the peak serum lamivudine concentration (C_{max}) was 1.5 ± 0.5 µg/mL (mean ± SD). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to oral dose over the range from 0.25 to 10 mg/kg.

An investigational 25-mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-infected patients on two occasions, once in the fasted state and once with food (1099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate). Absorption of lamivudine was slower in the fed state (T_{max}: 3.2 ± 1.3 hours) compared with the fasted state (T_{max}: 0.9 ± 0.3 hours); C_{max} in the fed state was 40% ± 23% (mean ± SD) lower than in the fasted state. There was no significant difference in systemic exposure (AUC_∞) in the fed and fasted states; therefore, EPIVIR Tablets and Oral Solution may be administered with or without food.

The accumulation ratio of lamivudine in HIV-positive asymptomatic adults with normal renal function was 1.50 following 15 days of oral administration of 2 mg/kg b.i.d.

Distribution: The apparent volume of distribution after IV administration of lamivudine to 20 patients was 1.3 ± 0.4 L/kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight.

Binding of lamivudine to human plasma proteins is low (<36%). *In vitro* studies showed that, over the concentration range of 0.1 to 100 µg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

Metabolism: Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose of lamivudine in six HIV-infected adults, 5.2% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite have not been determined.

Elimination: The majority of lamivudine is eliminated unchanged in urine. In 20 patients given a single IV dose, renal clearance was 0.22 ± 0.06 L/hr*kg (mean ± SD), representing 71% ± 16% (mean ± SD) of total clearance of lamivudine.

In most single-dose studies in HIV-infected patients with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{½}$) ranged from 5 to 7 hours. Oral clearance was 0.37 ± 0.05 L/hr*kg (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range from 0.25 to 10 mg/kg.

Special Populations: ***Adults With Impaired Renal Function:*** The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-infected adults with impaired renal function, as summarized in Table 1.

Table 1: Pharmacokinetic Parameters (Mean ± SD) After a Single 300-mg Oral Dose of Lamivudine in Three Groups of Adults With Varying Degrees of Renal Function (CrCl>60 mL/min, CrCl = 10-30 mL/min, and CrCl<10 mL/min)

Number of subjects	6	4	6
Creatinine clearance criterion	>60 mL/min	10-30 mL/min	<10 mL/min
Creatinine clearance (mL/min)	111 ± 14	28 ± 8	6 ± 2
C_{max} (µg/mL)	2.6 ± 0.5	3.6 ± 0.8	5.8 ± 1.2
AUC∞ (µg•h/mL)	11.0 ± 1.7	48.0 ± 19	157 ± 74
Cl/F (mL/min)	464 ± 76	114 ± 34	36 ± 11

Exposure (AUC∞), C_{max}, and half-life increased with diminishing renal function (as expressed by creatinine clearance). Apparent total oral clearance (Cl/F) of lamivudine decreased as creatinine clearance decreased. T_{max} was not significantly affected by renal function. Based on these observations, it is recommended that the dosage of lamivudine be modified in patients with renal impairment (see DOSAGE AND ADMINISTRATION). The effects of renal impairment on lamivudine pharmacokinetics in pediatric patients are not known.

Pediatric Patients: For pharmacokinetic properties of lamivudine in pediatric patients, see PRECAUTIONS: Pediatric Use.

Geriatric Patients: Lamivudine pharmacokinetics have not been specifically studied in patients over 65 years of age.

Gender: There are no significant gender differences in lamivudine pharmacokinetics.

Race: There are no significant racial differences in lamivudine pharmacokinetics.

Drug Interactions: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 h).

Lamivudine and trimethoprim/sulfamethoxazole (TMP/SMX) were coadministered to 14 HIV-positive patients in a single-center, open-label, randomized, crossover study. Each patient received treatment with a single 300-mg dose of lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with lamivudine resulted in an increase of 44% ± 23% (mean ± SD) in lamivudine AUC∞, a decrease of 29% ± 13% in lamivudine oral clearance, and a decrease of 30% ± 36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine.

INDICATIONS AND USAGE: EPIVIR in combination with other antiretroviral agents is indicated for the treatment of HIV infection (see Description of Clinical Studies).

Description of Clinical Studies: ***Clinical Endpoint Study in Adults:*** B3007 (CAESAR) was a multicenter, double-blind, placebo-controlled study comparing continued current therapy [zidovudine alone (62% of patients) or zidovudine with didanosine or zalcitabine (38% of patients)] to the addition of EPIVIR or EPIVIR plus an investigational non-nucleoside reverse transcriptase inhibitor, randomized 1:2:1. A total of 1816 HIV-infected adults with 25 to 250 CD4 cells/mm^3 (median = 122 cells/mm^3) at baseline were enrolled: median age was 36 years, 87% were male, 84% were nucleoside-experienced, and 16% were therapy-naive. The median duration on study was 12 months. Results are summarized in Table 2.

Table 2: Number of Patients (%) With At Least One HIV Disease Progression Event or Death

Endpoint	Current Therapy (n = 460)	EPIVIR plus Current Therapy (n = 896)	EPIVIR plus a NNRTI* plus Current Therapy (n = 460)
HIV progression or death	90 (19.6%)	86 (9.6%)	41 (8.9%)
Death	27 (5.9%)	23 (2.6%)	14 (3.0%)

*An investigational non-nucleoside reverse transcriptase inhibitor not approved in the United States.

Clinical Endpoint Study in Pediatric Patients: ACTG300 was a multicenter, randomized, double-blind study that provided for comparison of EPIVIR plus RETROVIR to didanosine monotherapy. A total of 471 symptomatic, HIV-infected therapy-naive (≤56 days of antiretroviral therapy) pediatric patients were enrolled in these two treatment arms. The median age was 2.7 years (range 6 weeks to 14 years), 58% were female, and 86% were non-Caucasian. The mean baseline CD4 cell count was 868 cells/mm^3 (mean: 1060 cells/mm^3 and range: 0 to 4650 cells/mm^3 for patients ≤5 years of age; mean 419 cells/mm^3 and range: 0 to 1555 cells/mm^3 for patients >5 years of age) and the mean baseline plasma HIV RNA was 5.0 $\log_{10}$ copies/mL. The median duration on study was 10.1 months for the patients receiving EPIVIR plus RETROVIR and 9.2 months for patients receiving didanosine monotherapy. Results are summarized in Table 3.

Table 3: Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	EPIVIR plus RETROVIR (n = 236)	Didanosine (n = 235)
HIV disease progression or death (total)	15 (6.4%)	37 (15.7%)
Physical growth failure	7 (3.0%)	6 (2.6%)
Central nervous system deterioration	4 (1.7%)	12 (5.1%)
CDC Clinical Category C	2 (0.8%)	8 (3.4%)
Death	2 (0.8%)	11 (4.7%)

Surrogate Endpoint Studies: Therapy-Naive Adults: A3001 was a randomized, double-blind study comparing EPIVIR 150 mg b.i.d. plus RETROVIR 200 mg t.i.d.; EPIVIR 300 mg b.i.d. plus RETROVIR; EPIVIR 300 mg b.i.d.; and RETROVIR. Three hundred sixty-six adults enrolled: male (87%), Caucasian (61%), median age of 34 years, asymptomatic HIV infection (80%), baseline CD4 cell counts of 200 to 500 cells/mm^3 (median = 352 cells/mm^3), and mean baseline plasma HIV RNA of 4.47 (log_{10} copies/mL). B3001 was a randomized, double-blind study comparing EPIVIR 300 mg b.i.d. plus RETROVIR 200 mg t.i.d. versus RETROVIR. One hundred twenty-nine adults enrolled: male (74%), Caucasian (82%), median age of 33 years, asymptomatic HIV infection (64%), and baseline CD4 cell counts of 100 to 400 cells/mm^3 (median = 260 cells/mm^3). Mean changes in CD4 cell count and HIV RNA through 24 weeks of treatment for study A3001 are summarized in Figures 1 and 2, respectively. Mean change in CD4 cell count through 24 weeks of treatment for study B3001 is summarized in Figure 3.

182 **Figure 1: Mean Absolute CD4 Cell Count Change (cells/mm^3)**

183 **From Baseline in Study A3001**

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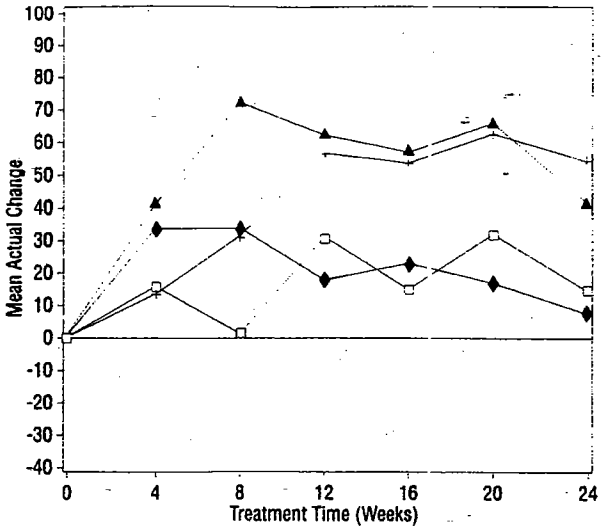

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187 **Figure 2: Mean Change From Baseline**

188 **in Plasma HIV RNA (log_{10} copies/mL) in Study A3001**

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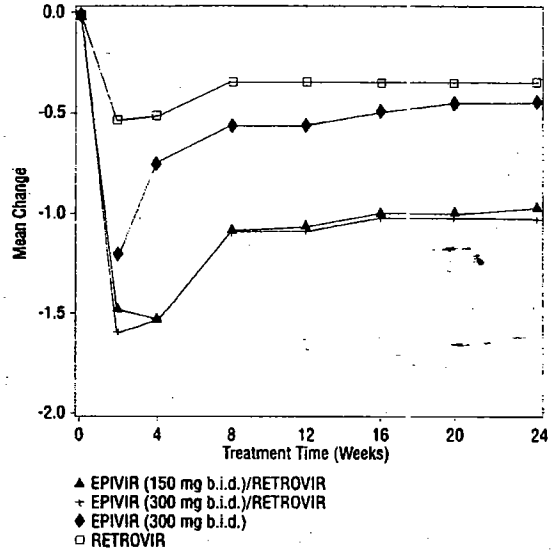

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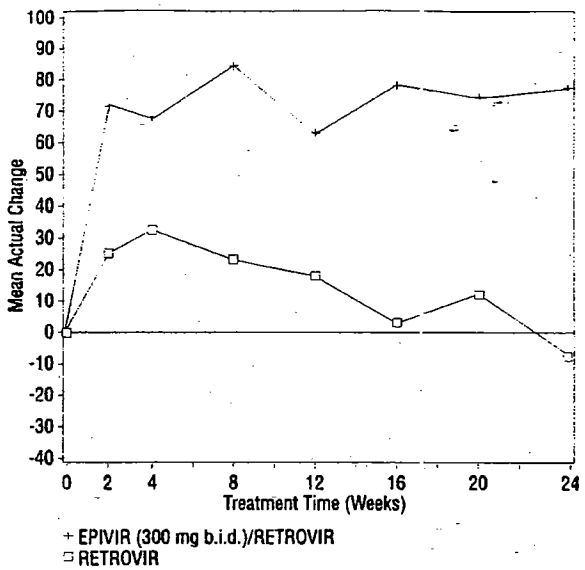
Figure 3: Mean Absolute CD4 Cell Count Change (cells/mm^3) From Baseline in Study B3001



Therapy-Experienced Adults (≥24 Weeks of Prior Zidovudine Therapy): A3002 was a randomized, double-blind study comparing EPIVIR 150 mg b.i.d. plus RETROVIR 200 mg t.i.d.; EPIVIR 300 mg b.i.d. plus RETROVIR; and RETROVIR plus zalcitabine 0.75 mg t.i.d. Two hundred fifty-four adults enrolled: male (83%), Caucasian (63%), median age of 37 years, asymptomatic HIV infection (58%), median duration of prior zidovudine use of 24 months, baseline CD4 cell counts of 100 to 300 cells/mm^3 (median = 211 cells/mm^3), and mean baseline plasma HIV RNA of 4.60 ($\log_{10}$ copies/mL). B3002 was a randomized, double-blind study comparing EPIVIR 150 mg b.i.d. plus RETROVIR, EPIVIR 300 mg b.i.d. plus RETROVIR, and RETROVIR. Two hundred twenty-three adults enrolled: male (83%), Caucasian (96%), median age of 36 years, asymptomatic HIV infection (53%), median duration of prior zidovudine use of 23 months, and baseline CD4 cell counts of 100 to 400 cells/mm^3 (median = 241 cells/mm^3). Mean changes in CD4 cell count and HIV RNA through 24 weeks of treatment in study A3002 are summarized in Figures 4 and 5, respectively. Mean change in CD4 cell count through 24 weeks of treatment for study B3002 is summarized in Figure 6.

Figure 4: Mean Absolute CD4 Cell Count Change (cells/mm^3) From Baseline in Study A3002

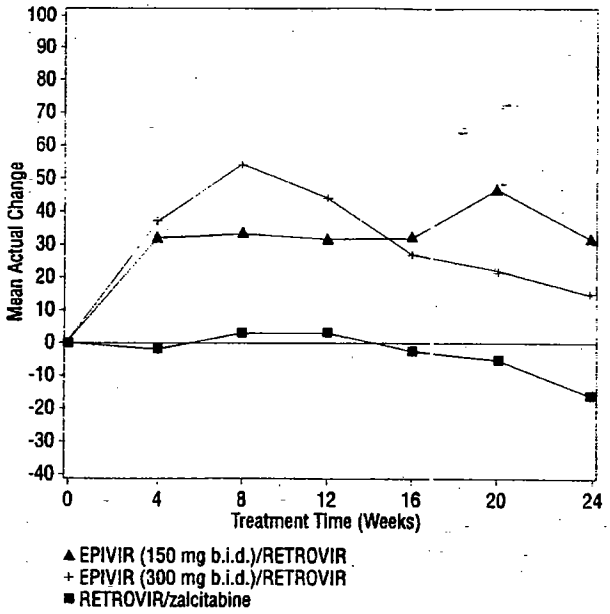


Figure 5: Mean Change From Baseline in Plasma HIV RNA (log_{10} copies/mL) in Study A3002

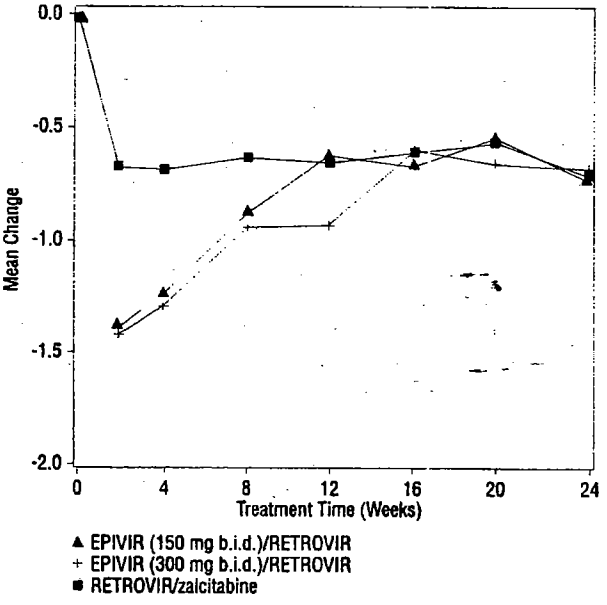
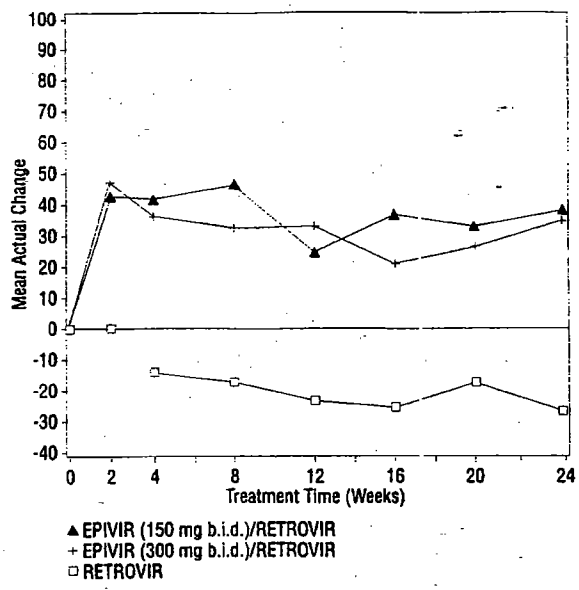


Figure 6: Mean Absolute CD4 Cell Count Change (cells/mm^3) From Baseline in Study B3002



CONTRAINDICATIONS: EPIVIR Tablets and Oral Solution are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the products.

WARNINGS: In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, EPIVIR should be used with caution.Treatment with EPIVIR should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see ADVERSE REACTIONS).

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering EPIVIR to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with EPIVIR should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

PRECAUTIONS:

Patients With Impaired Renal Function: Reduction of the dosage of EPIVIR is recommended for patients with impaired renal function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Patients With HIV and Hepatitis B Virus Coinfection: In clinical trials and postmarketing experience, some patients with HIV infection who have chronic liver disease due to hepatitis B virus infection experienced clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine. Consequences may be more severe in patients with decompensated liver disease.

Information for Patients: EPIVIR is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using EPIVIR. Patients should be advised that the use of EPIVIR has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Patients should be advised that the long-term effects of EPIVIR are unknown at this time.

EPIVIR Tablets and Oral Solution are for oral ingestion only.

Patients should be advised of the importance of taking EPIVIR exactly as it is prescribed.

Parents or guardians should be advised to monitor pediatric patients for signs and symptoms of pancreatitis.

Drug Interaction: TMP 160 mg/SMX 800 mg once daily has been shown to increase lamivudine exposure (AUC). The effect of higher doses of TMP/SMX on lamivudine pharmacokinetics has not been investigated (see CLINICAL PHARMACOLOGY).

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Lamivudine long-term carcinogenicity studies in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose. Lamivudine was not active in a microbial mutagenicity screen or an *in vitro* cell transformation assay, but showed weak *in vitro* mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2000 mg/kg (approximately 65 times the recommended human dose based on body surface area comparisons). In a study of reproductive performance, lamivudine, administered to rats at doses up to 130 times the usual adult dose based on body surface area comparisons, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

Pregnancy: Pregnancy Category C. Reproduction studies have been performed in rats and rabbits at orally administered doses up to approximately 130 and 60 times, respectively, the usual adult dose and have revealed no evidence of harm to the fetus due to lamivudine. Some evidence

of early embryolethality was seen in the rabbit at doses similar to those produced by the usual adult dose and higher, but there was no indication of this effect in the rat at orally administered doses up to 130 times the usual adult dose. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta. There are no adequate and well-controlled studies in pregnant women. Because animal reproductive toxicity studies are not always predictive of human response, lamivudine should be used during pregnancy only if the potential benefits outweigh the risks.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to EPIVIR, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection.

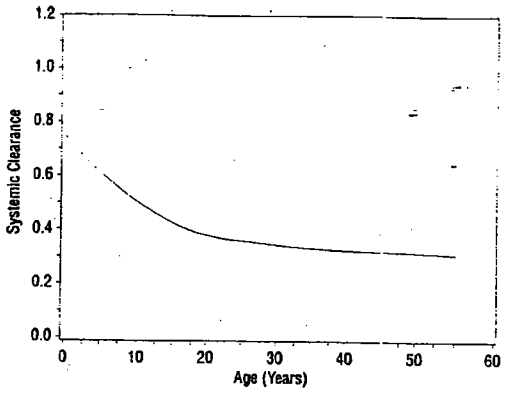
A study in which lactating rats were administered 45 mg/kg of lamivudine showed that lamivudine concentrations in milk were slightly greater than those in plasma. Although it is not known if lamivudine is excreted in human milk, there is the potential for adverse effects from lamivudine in nursing infants. **Mothers should be instructed not to breastfeed if they are receiving EPIVIR.**

Pediatric Use: The safety and effectiveness of EPIVIR in combination with other antiretroviral agents have been established in pediatric patients 3 months of age and older.

In Study A2002, pharmacokinetic properties of lamivudine were assessed in a subset of 57 HIV-infected pediatric patients (age range: 4.8 months to 16 years, weight range: 5 to 66 kg) after oral and IV administration of 1, 2, 4, 8, 12, and 20 mg/kg per day. In the nine infants and children (range: 5 months to 12 years of age) receiving oral solution 4 mg/kg twice daily (the usual recommended pediatric dose), absolute bioavailability was 66% ± 26% (mean ± SD), which was less than the 86% ± 16% (mean ± SD) observed in adults. The mechanism for the diminished absolute bioavailability of lamivudine in infants and children is unknown.

Systemic clearance decreased with increasing age in pediatric patients, as shown in Figure 7.

Figure 7: Systemic Clearance (L/hr*kg) of Lamivudine in Relation to Age



After oral administration of lamivudine 4 mg/kg twice daily to 11 pediatric patients ranging from 4 months to 14 years of age, C_{max} was 1.1 ± 0.6 µg/mL and half-life was 2.0 ± 0.6 hours. (In adults with similar blood sampling, the half-life was 3.7 ± 1 hours.) Total exposure to lamivudine, as reflected by mean AUC values, was comparable between pediatric patients receiving an 8-mg/kg-per-day dose and adults receiving a 4-mg/kg-per-day dose.

Distribution of lamivudine into cerebrospinal fluid (CSF) was assessed in 38 pediatric patients after multiple oral dosing with lamivudine. CSF samples were collected between 2 and 4 hours postdose. At the dose of 8 mg/kg per day, CSF lamivudine concentrations in eight patients ranged from 5.6% to 30.9% (mean ± SD of 14.2% ± 7.9%) of the concentration in a simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to 0.3 µg/mL.

The safety and pharmacokinetic properties of EPIVIR in combination with other antiretroviral agents have not been established in pediatric patients less than 3 months of age.

See INDICATIONS AND USAGE: Description of Clinical Studies, CLINICAL PHARMACOLOGY, WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.

ADVERSE REACTIONS:

Adults: Selected clinical adverse events with a ≥5% frequency during therapy with EPIVIR 150 mg b.i.d. plus RETROVIR 200 mg t.i.d. compared with zidovudine are listed in Table 4.

Table 4: Selected Clinical Adverse Events (≥5% Frequency) in Four Controlled Clinical Trials (A3001, A3002, B3001, B3002)

Adverse Event	EPIVIR 150 mg b.i.d. plus RETROVIR (n = 251)	RETROVIR (n = 230)
Body as a whole		
Headache	35%	27%
Malaise & fatigue	27%	23%
Fever or chills	10%	12%
Digestive		
Nausea	33%	29%
Diarrhea	18%	22%
Nausea & vomiting	13%	12%
Anorexia and/or decreased appetite	10%	7%
Abdominal pain	9%	11%
Abdominal cramps	6%	3%
Dyspepsia	5%	5%
Nervous system		
Neuropathy	12%	10%
Insomnia & other sleep disorders	11%	7%
Dizziness	10%	4%
Depressive disorders	9%	4%
Respiratory		
Nasal signs & symptoms	20%	11%
Cough	18%	13%
Skin		
Skin rashes	9%	6%
Musculoskeletal		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

Pancreatitis was observed in three of the 656 adult patients (<0.5%) who received EPIVIR in controlled clinical trials.

Selected laboratory abnormalities observed during therapy are summarized in Table 5.

Table 5: Frequencies of Selected Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Studies (A3001, A3002, B3001, B3002) and a Clinical Endpoint Study (B3007)

Test (Abnormal Level)	24-Week Surrogate Endpoint Studies		Clinical Endpoint Study*	
	EPIVIR plus RETROVIR	RETROVIR	EPIVIR plus Current Therapy	Placebo plus Current Therapy†
Neutropenia (ANC<750/mm^3)	7.2%	5.4%	15%	13%
Anemia (Hgb<8.0 g/dL)	2.9%	1.8%	2.2%	3.4%
Thrombocytopenia (platelets<50,000/mm^3)	0.4%	1.3%	2.8%	3.8%
ALT (>5.0 x ULN)	3.7%	3.6%	3.8%	1.9%
AST (>5.0 x ULN)	1.7%	1.8%	4.0%	2.1%
Bilirubin (>2.5 x ULN)	0.8%	0.4%	ND	ND
Amylase (>2.0 x ULN)	4.2%	1.5%	2.2%	1.1%

* The median duration on study was 12 months.

† Current therapy was either zidovudine, zidovudine plus didanosine, or zidovudine plus zalcitabine.

ULN = Upper limit of normal.

ANC = Absolute neutrophil count.

ND = Not done.

Pediatric Patients: Selected clinical adverse events and physical findings with a ≥5% frequency during therapy with EPIVIR 4 mg/kg twice daily plus RETROVIR 160 mg/m^2 three times daily compared with didanosine in therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 6.

Table 6: Selected Clinical Adverse Events and Physical Findings (≥5% Frequency) in Pediatric Patients in Study ACTG300

Adverse Event	EPIVIR plus RETROVIR (n = 236)	Didanosine (n = 235)
Body as a whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
Respiratory		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
Ear, Nose and Throat		
Signs or symptoms of ears*	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

*Includes pain, discharge, erythema, or swelling of an ear.

Selected laboratory abnormalities experienced by therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 7.

Table 7: Frequencies of Selected Laboratory Abnormalities in Pediatric Patients in Study ACTG300

Test (Abnormal Level)	EPIVIR plus RETROVIR	Didanosine
Neutropenia (ANC<400/mm^3)	8%	3%
Anemia (Hgb<7.0 g/dL)	4%	2%
Thrombocytopenia (platelets<50,000/mm^3)	1%	3%
ALT (>10 x ULN)	1%	3%
AST (>10 x ULN)	2%	4%
Lipase (>2.5 x ULN)	3%	3%
Total Amylase (>2.5 x ULN)	3%	3%

ULN = Upper limit of normal.

ANC = Absolute neutrophil count.

Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric patients receiving EPIVIR alone or in combination with other antiretroviral agents. In an open-label dose-escalation study (A2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with EPIVIR. Three of these patients died of complications of pancreatitis. In a second open-label study (A2005), 12 patients (18%) developed pancreatitis. In Study ACTG300, pancreatitis was not observed in 236 patients randomized to

EPIVIR plus RETROVIR. Pancreatitis was observed in one patient in this study who received open-label EPIVIR in combination with RETROVIR and ritonavir following discontinuation of didanosine monotherapy.

Paresthesias and peripheral neuropathies were reported in 15 patients (15%) in Study A2002, six patients (9%) in Study A2005, and two patients (<1%) in Study ACTG300.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of EPIVIR. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to EPIVIR.

Endocrine and Metabolic: Hyperglycemia.

General: Anaphylaxis, weakness.

Hepatobiliary Tract and Pancreas: Lactic acidosis and hepatic steatosis (see WARNINGS).

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Peripheral neuropathy.

Skin: Alopecia, rash, pruritus, urticaria.

OVERDOSAGE: There is no known antidote for EPIVIR. One case of an adult ingesting 6 g of EPIVIR was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Two cases of pediatric overdose were reported in ACTG300. One case was a single dose of 7 mg/kg of EPIVIR; the second case involved use of 5 mg/kg of EPIVIR twice daily for 30 days. There were no clinical signs or symptoms noted in either case. It is not known whether lamivudine can be removed by peritoneal dialysis or hemodialysis.

DOSAGE AND ADMINISTRATION:

Adults and Adolescents (12 to 16 Years): The recommended oral dose of EPIVIR for adults and adolescents is 150 mg twice daily administered in combination with other antiretroviral agents.

Pediatric Patients (3 months to 12 years): The recommended oral dose of EPIVIR for pediatric patients is 4 mg/kg twice daily (up to a maximum of 150 mg twice a day) administered in combination with other antiretroviral agents.

Dose Adjustment: It is recommended that doses of EPIVIR be adjusted in accordance with renal function (see Table 8). (See CLINICAL PHARMACOLOGY section.)

Table 8: Adjustment of Dosage of EPIVIR in Adults and Adolescents in Accordance With Creatinine Clearance

Creatinine Clearance (mL/min)	Recommended Dosage of EPIVIR
≥50	150 mg twice daily
30-49	150 mg once daily
15-29	150 mg first dose, then 100 mg once daily
5-14	150 mg first dose, then 50 mg once daily
<5	50 mg first dose, then 25 mg once daily

Insufficient data are available to recommend a dosage of EPIVIR in patients undergoing dialysis. Although there are insufficient data to recommend a specific dose adjustment of EPIVIR in pediatric patients (3 months to 12 years) with renal impairment, a reduction in the dose and/or an increase in the dosing interval should be considered.

HOW SUPPLIED: EPIVIR Tablets, 150 mg, are white, modified diamond-shaped, film-coated tablets imprinted with "150" on one side and "GX CJ7" on the reverse side. They are available in bottles of 60 tablets (NDC 0173-0470-01) with child-resistant closures. **Store between 2° and 30°C (36° and 86°F) in tightly closed bottles.**

EPIVIR Oral Solution, a clear, colorless to pale yellow, strawberry-banana flavored liquid, contains 10 mg of lamivudine in each 1 mL in plastic bottles of 240 mL (NDC 0173-0471-00) with child-resistant closures. This product does not require reconstitution. **Store between 2° and 25°C (36° and 77°F) in tightly closed bottles.**

GlaxoWellcome
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

Manufactured under agreement from
BioChem Pharma Inc.
275 Armand Frappier Blvd.
Laval, Quebec, Canada H7V 4A7

EPIVIR® Oral Solution Manufactured in England

US Patent No. 5,047,407

445

447

448 Date of Issue RL-

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-564 / S-007
20-596 / S-007

MEDICAL REVIEW

MEDICAL OFFICER'S REVIEW OF SUPPLEMENTAL APPLICATION
NDA 20-564 AND NDA 20-596

Date received:	03/30/1998
Date assigned:	07/15/1998
Date completed:	02/10/1999
Drug:	Lamivudine (3TC)
Trade name:	Epivir®
Chemical name:	(2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidine-2-one
Dosage:	4 mg/Kg BID
Applicant:	Glaxo Wellcome

TABLE OF CONTENTS

1. RESUME

The applicant submitted safety and efficacy data from a randomized, double-blind, clinical-endpoint pediatric study (ACTG 300) to support approval for the use of 3TC in combination with ZDV in HIV-infected children. In addition, the applicant submitted final study reports of two open-label pediatric studies (NUCA2002 and NUCA 2005) for additional safety information.

Results from Study ACTG 300 support the applicant's claim that 3TC + ZDV therapy is superior to ddI monotherapy in children with respect to clinical disease progression events, and surrogate markers (HIV RNA, CD4 cell count). 3TC treatment (as monotherapy or in combination with an NRTI) appears to be safe and well-tolerated in the majority of children. However, treatment-emergent pancreatitis among the children in the open-label studies is clinically significant to warrant the retention of the WARNINGS section in the label. Additionally, the submitted data provide further support for the DOSAGE AND ADMINISTRATION recommendations for 3TC in children 3 months and older.

2. MATERIAL REVIEWED

This NDA supplement consists of 26 volumes.

3. CHEMISTRY, MANUFACTURING AND CONTROLS

There is no new information on chemistry, manufacturing and controls contained in this submission.

4. ANIMAL PHARMACOLOGY AND TOXICOLOGY

There are no new animal pharmacological and toxicological studies contained in this submission.

5. MICROBIOLOGY

There are no new microbiological studies contained in this submission.

6. CLINICAL BACKGROUND

6.1. Related INDs and NDAs

Lamivudine (tablets, NDA 20-564; oral solution, NDA 20-596) received accelerated approval on November 17, 1995 for use in combination with zidovudine for the treatment of HIV infection. The approval was based on results from four surrogate endpoint clinical trials NUCA3001, NUCA 3002, NUCB3001 and NUCB3002. Subsequently,

lamivudine was granted traditional approval on April 11, 1997 when the results of a clinical endpoint study NUCB3007 (CAESAR trial) confirmed its clinical benefit.

This supplemental application includes results from a comparative clinical endpoint pediatric study (ACTG 300) conducted in HIV-infected pediatric patients six weeks of age or older. Safety updates on two open-label pediatric studies, NUCA 2002 and NUCA 2005 (conducted under IND 37,158) are also submitted to provide additional safety information on the use of lamivudine in pediatric population.

6.2. Human Pharmacology, Pharmacokinetics, Pharmacodynamics

Please see Dr. P. Rajagopalan's Biopharmaceutics review of this supplement.

6.3. Foreign Experiences

Lamivudine tablets and oral solution have been approved in a number of countries. No drug product containing lamivudine has been withdrawn from marketing in these countries.

7. BRIEF DESCRIPTION OF CLINICAL TRIALS

ACTG 300 was a double blind clinical endpoint study to compare the effects of lamivudine/zidovudine combination therapy versus didanosine monotherapy on progression of HIV disease and survival in HIV-infected pediatric patients. The study commenced on 7/12/1995 and was stopped prematurely on 6/19/1997 when a significant difference in efficacy between treatment arms was detected.

NUCA 2002 was an open-label, dose-escalation study to evaluate safety, pharmacokinetics, and preliminary antiretroviral activity of lamivudine monotherapy in pediatric patients. The study was launched on 04/07/1992 and terminated on 04/30/1996.

NUCA 2005 was an open-label study to assess safety, pharmacokinetics, and preliminary activity of lamivudine in combination with zidovudine and/or didanosine in pediatric patients. The study was conducted between 01/17/1994 and 01/12/1997.

8. CLINICAL TRIALS

8.1. Study ACTG 300

"A Randomized Comparative Study of Combined Zidovudine (ZDV)-Lamivudine (3TC) vs. the Better of ddI monotherapy vs. Zidovudine plus ddI in Symptomatic HIV-1 Infected Children"

8.1.1. Objective

The primary objective was to compare the efficacy of treatment with 3TC/ZDV versus the better of ddI or ddI/ZDV combination therapy based on time to progression of HIV disease, death, failure of weight/growth velocity, or neurological/neuropsychological decline.

The secondary objectives addressed in this submission were to evaluate (1) safety and tolerance of 3TC/ZDV, (2) the effects of 3TC/ZDV vs. ddI vs. ddI/ZDV on HIV RNA levels and CD4 cell counts.

8.1.2. Study Design

This study was a phase 3, randomized, comparative, double blind, three-arm, multicenter study. The treatment arms were (1) 3TC/ZDV, (2) ddI monotherapy, and (3) ddI/ZDV. The study was to be converted into a two-arm trial, i.e., 3TC/ZDV versus the better of either the ddI arm or ddI/ZDV arm, contingent on results of ACTG 152. Treatment-naïve patients (≤ 56 days of antiretroviral therapy) were stratified into two groups by age (less than 3 years and over three years) and randomized into treatment arms in 1:1:1 ratio. The protocol planned a total of 740 patients aged 90 days to 15 years. The duration of the study was 24 months. Once patients reached a primary endpoint, study medication was discontinued and patients were switched to the best available alternative therapy.

Clinical assessments of HIV-associated symptoms were performed every four weeks. Height, weight and head circumference were assessed monthly. Neurological examinations were conducted every 12 weeks. Laboratory tests to include hematological and biochemical parameters were obtained monthly. Immunological studies (lymphocyte subsets) were sampled at weeks 4, 8, 12 and every 12 weeks thereafter. HIV RNA levels were collected every 12 weeks for real-time PCR quantification.

8.1.3. Study Treatments

Patients were randomized to receive one of the following treatment regimens:

Arm A: 3TC (4mg/Kg BID) + ZDV (160 mg/m^2 TID)
Arm B: ddI (120 mg/m^2 BID)
Arm C: ddI (120 mg/m^2 BID) + ZDV (160 mg/m^2 TID)

Reviewer's Comment

1. Randomization to the ddI/ZDV arm was eventually dropped from the study (5/16/96) when the results of ACTG 152, a randomized, double-blind clinical endpoint trial that compared the efficacy of ZDV, ddI and ZDV/ddI in HIV-infected, treatment-naïve children, revealed that ddI/ZDV had no additional benefit with respect to disease progression (24% of patients in the ddI group and 25% in the ddI/ZDV group) than ddI

on-study medication for the 3TC/ZDV, ddI and ddI/ZDV was 9.5, 9.1 and 12.6 months, respectively.

Table 8.1.6.1.1. Summary of Patient Accountability

Disposition Status	Number of Patients			
	3TC/ZDV	ddI	ddI/ZDV	All
Randomized	244	244	127	615
No treatment dispensation form	6	7	0	13
Excluded from analysis[1]	2	2	2	6
Total used in ITT[2] analysis	236	235	125	596
Status at Study Withdrawal:				
- No clinical progression	214	193	107	514
Ongoing	198	180	87	465
Off-treatment[3]	16	13	20	31
- Clinical progression	15	37	13	65
Ongoing	2	7	1	10
Off-treatment[4]	13	32	12	57
- Lost to follow-up	7	4	5	16

[1] Reasons of exclusion: one patient with patient/parental decisions against treatment, one had lymphoma at baseline.
[2] "Intent-to-treat" population.
[3] Includes protocol violation, request by investigator, drug toxicity, and patient/parental refusal of treatment.
[4] Includes withdrawal due to clinical endpoints, death, drug toxicity, and treatment refusal.
(Response to FDA Request for Information, Attachment 3, page 74)

8.1.6.1.2. Demographics and Baseline Characteristics

The distributions of demographic data by treatment group are summarized in Table 8.1.6.1.2.A. Approximately 43% of patients were male, and the median age was 2.7 years. The baseline disease characteristics are summarized in Table 8.1.6.1.2.B. Approximately 47% of patients were CDC clinical category A, with median baseline $\log_{10}$ HIV RNA level, CD4 cell count and CD4% of 5.1, 685 cells/mm^3 and 23%, respectively.
In the <3-year-old cohort, the median baseline CD4 cell counts were 1063 and 1080 for the 3TC/ZDV and ddI treatment groups, respectively. In the ≥3-year-old cohort, the median CD4 cell counts were 418 and 473 for the 3TC/ZDV and ddI groups, respectively. The younger cohort had median baseline $\log_{10}$ HIV RNA levels of 5.4 and 5.5 for the 3TC/ZDV and ddI groups, respectively. In the older cohort, the median baseline $\log_{10}$ HIV RNA level was 4.6 for both treatment groups.

monotherapy (Englund, J. NEJM, 336(24):1704-1712). Patients who initially entered on the ddI/ZDV arm continued their blinded therapy until study closure.

8.1.4. Endpoints

The principal evaluation in this study, as defined in the protocol, was the comparison between 3TC/ZDV and the "best" treatment regimen (ddI versus ddI/ZDV) as determined from ACTG 152 study.

The primary endpoints were evidence of HIV disease progression based on time to (1) development of the first new CDC Category C diagnoses, (2) death, (3) failure to achieve adequate weight growth velocity, or (4) decline in neurological or neuropsychological assessments

The secondary endpoints were (1) change from baseline of $\log_{10}$ HIV RNA and (2) CD4 cell count improvements from baseline.

Safety was assessed by the incidence of grade 3/4 (DAIDS Toxicity Table for Grading severity of Pediatric Adverse Experiences) clinical adverse events and laboratory abnormalities.

8.1.5. Statistical Considerations

Please see Dr. Hammerstrom's Statistical review of this supplement.

8.1.6. Results

This study was closed after review of an interim analysis by the DSMB 6/19/97.

8.1.6.1. Patient Disposition and Comparability

8.1.6.1.1. Patient Accountability

As of 4/4/1997 (the date at which the data set was frozen), 615 patients were randomized in this study. Eighteen patients were administratively excluded (incomplete dispensation form or refusal to participate). A total of 597 patients started study treatment; 236 patients on the 3TC/ZDV arm, 235 on the ddI arm, and 125 on the ddI/ZDV arm. As previously mentioned, the ddI/ZDV arm was dropped from the study on 5/16/1998, although patients on this arm continued on blinded study drug and were followed until the end of the study.

The disposition of all patients as of 4/4/98 is summarized in Table 8.1.6.1.1. Six patients (four in the 3TC/ZDV, and two in the ddI arm) were randomized just before study closure and thus did not provide any on-study information for the final analyses. The mean time-

Table 8.1.6.1.2.A. Demographic Data

Demography	Number (%) of Patients		
	3TC/ZDV (n = 236)	ddI (n = 235)	ddI/ZDV (n = 125)
Gender			
- Male	100 (42)	100 (42)	56 (45)
- Female	136 (58)	136 (58)	69 (55)
Ethnicity			
- White	33 (14)	33 (14)	19 (15)
- Black	141 (60)	162 (69)	75 (60)
- Hispanic	61 (26)	40 (17)	31 (25)
- Asian/Pacific Islander	0	1 (<1)	0
- American Indian/Alaskan	1 (<1)	0	0
Age (year)			
- Mean	3.9	3.9	3.7
- Median	2.7	2.8	1.9
- Range (year)	0.1 - 14.9	0.2 - 13.9	0.2 - 15.0
0 mo - < 3 mos	1 (<1)	2 (<1)	1 (<1)
3 mos - < 6 mos	24 (10)	22 (9)	16 (13)
6 mos - < 1 yr	37 (16)	39 (17)	23 (18)
1 yr - < 3 yrs	65 (27)	62 (26)	34 (27)
≥ 3 yrs	109 (46)	111 (47)	51 (41)

(FDA Analysis of Supplemental New Drug Application, NDA 20-564/NDA 20-596, Vol. 4, Table 11, page 77)

Reviewer's Comment

[ ]

received 3TC/ZDV. The absence of a broader safety (and efficacy) database does not support this label change.

Table 8.1.6.1.2.B. Baseline Disease Characteristics

Baseline Characteristics	Number (%) of Patients		
	3TC/ZDV (n = 236)	ddI (n = 235)	ddI/ZDV (n =125)
CDC clinical category			
- N (No signs/symptoms)	35 (15)	34 (14)	9 (7)
- A (Mild signs/symptoms)	116 (49)	105 (44)	71 (57)
- B (Moderate signs/symptoms)	50 (21)	65 (28)	33 (26)
- C (Severe signs/symptoms)	35 (15)	32 (14)	12 (10)
Immunologic category			
- No evidence of suppression	64 (27)	74 (31)	37 (30)
- Moderate suppression	99 (42)	93 (39)	50 (40)
- Severe suppression	73 (31)	69 (29)	38 (30)
CD4 (cells/mm^3)			
- n	235	232	125
- Mean	854	884	1116
- Median	703	659	759
- Range	0 - 4650	0 - 3452	12 - 6080
HIV RNA (log_{10})			
- n	225	224	121
- Mean	5.0	5.0	5.0
- Median	5.1	5.1	5.0
- Range	2.6 - 7.4	2.6 - 7.7	2.6 - 6.9

(Supplemental New Drug Application; NDA 20-564/NDA 20-596, Vol.1, Table 1, page 201; Vol. 4, Tables 11 and 13, pages 77 - 79)

8.1.6.2. Efficacy Outcomes

Please see Dr. Hammerstrom's statistical review for additional details.

8.1.6.2.1. Primary Efficacy Outcomes

As noted in Section 8.1.4, the primary efficacy endpoint of this study was the time to first clinical HIV disease progression (CDC Category C diagnosis, growth failure, CNS deterioration, or death). A summary of primary endpoint events is presented in Table 8.1.6.2.1.A. Primary endpoints were reached by 16% of patients in the ddI group, 11% in the ddI/ZDV group, and 6% in the 3TC/ZDV group at the time of study termination.

Table 8.1.6.2.1.A. Summary of Primary Endpoint Events

Primary Endpoints[1]	Number (%) of Patients		
	3TC/ZDV (n = 236)	ddI (n = 235)	ddI/ZDV (n = 125)
Clinical progression:			
- CDC clinical category C	2 (1)	8 (3)	1 (< 1)
- Growth failure	7 (3)	6 (3)	5 (4)
- CNS deterioration	4 (2)	12 (5)	4 (3)
- Death	2 (1)	11 (7)	3 (2)
Total	15 (6)	37 (16)	13 (11)

[1] In cases of multiple endpoints, only the first primary endpoint is counted.
(FDA analysis of applicant's Supplemental New Drug Application, NDA 20-564/NDA 20-596, Vol. 4, Listings 2 and 3, pages 210 - 214)

Reviewer's Comments

1. *With respect to primary outcome, analysis by Dr. Hammerstrom showed that patients on the 3TC/ZDV arm had longer time-to-first clinical progression of disease than those on the ddI arm ($p = 0.032$). Additionally, patients on the ddI arm had approximately twice the risk of disease progression than those on the 3TC/ZDV arm.*

2. *ACTG statistical and data analysis center (SDAC) performed statistical analyses to compare all three treatment arms using data on the cohort of 372 patients randomized prior to the date the ddI/ZDV arm was dropped (5/16/96). There were 123 patients on 3TC/ZDV arm, 124 on ddI arm, and 125 on ddI/ZDV arm. The results (reported in Supplemental Report to the Data and Safety Monitoring Review Board) showed that while both 3TC/ZDV and ddI/ZDV treatments are superior to ddI monotherapy, no significant difference was observed in time-to-first clinical progression event between these dual combination therapy arms. It is interesting to note these results differed from those of ACTG 152 which concluded that ddI monotherapy had similar clinical efficacy as that of ddI/ZDV combination regimen.*

8.1.6.2.2. Secondary Efficacy Outcomes

8.1.6.2.2.1. Quantitative HIV RNA Measurements

Plasma HIV RNA levels were measured by the
The mean change from baseline for $\log_{10}$ HIV RNA copies/mL through week 84 is summarized by treatment group and scheduled visits in Table 8.1.6.2.2.1.

Table 8.1.6.2.2.1. Summary of Mean Change from Baseline for Log_{10} HIV RNA copies/mL

Scheduled visit	Mean Change from Baseline in Log_{10} HIV RNA (copies/mL)		
	3TC/ZDV (n = 236)	ddI (n = 235)	ddI/ZDV (n = 125)
Week 12	-0.8 (n = 198)	-0.3 (n = 211)	-0.6 (n = 106)
Week 24	-0.7 (n = 189)	-0.3 (n = 181)	-0.6 (n = 102)
Week 36	-0.7 (n = 154)	-0.4 (n = 145)	-0.5 (n = 108)
Week 48	-0.7 (n = 123)	-0.6 (n = 105)	-0.6 (n = 102)
Week 60	-0.7 (n = 89)	-0.5 (n = 71)	-0.7 (n = 82)
Week 72	-0.8 (n = 49)	-0.6 (n = 44)	-0.7 (n = 46)
Week 84	-0.9 (n = 20)	-0.8 (n = 16)	-0.8 (n = 20)

(FDA Analysis of Supplemental New Drug Application, NDA 20-564/NDA 20-596, Vol. 1, Table 10, pages 215 - 216)

Reviewer's Comment

An exploratory (on-treatment) analysis on the proportion of patients with HIV RNA levels below the limit of quantification (< 400 copies/mL) for the three treatment arms are summarized below. The disappointing results appear to support the need for more aggressive therapy with three or more antiretroviral agents to improve clinical outcomes.

Scheduled visit	*Proportion (%) of Patients with HIV RNA levels < 400 copies/mL*[1]		
	3TC/ZDV (n = 236)	*ddI (n = 235)*	*ddI/ZDV (n = 125)*
Week 12	*3 (n = 99)*	*3 (n = 93)*	*4 (n = 50)*
Week 24	*13 (n = 204)*	*6 (n= 219)*	*9 (n = 110)*
Week 36	*7 (n = 198)*	*8 (n = 187)*	*9 (n = 108)*
Week 48	*5 (n = 162)*	*10 (n = 155)*	*8 (n = 111)*

[1] *On-treatment analysis only*

8.1.6.2.2.2. CD4 Cell Counts

A summary of mean change from baseline for CD4 cell counts is presented in Table 8.1.6.2.2.2.

Table 8.1.6.2.2.2. Summary of Mean Change from Baseline for CD4 Cell Count

Scheduled visit	Mean Change from Baseline for CD4 Cell Count (cells/mm^3)		
	3TC/ZDV (n = 236)	ddI (n = 235)	ddI/ZDV (n = 125)
Week 4	152.3 (n = 218)	1.9 (n = 216)	-54.3 (n = 112)
Week 8	130.8 (n = 199)	33.6 (n = 196)	-3.5 (n = 107)
Week 12	118.1 (n = 207)	-6.0 (n = 206)	16.9 (n = 113)
Week 24	171.1 (n = 174)	-27.3 (n = 170)	-76.8 (n = 110)
Week 36	125.1 (n = 137)	-26.0 (n = 127)	-98.0 (n = 108)
Week 48	94.7 (n = 102)	-23.7 (n = 89)	-127.0 (n = 95)
Week 60	-11.8 (n = 59)	-45.1 (n = 57)	- 83.7 (n = 63)
Week 72	-124.0 (n = 33)	-183.0 (n = 29)	- 308.0 (n = 32)
Week 84	-256.0 (n = 4)	-173.0 (n = 4)	- 250.0 (n = 3)

(FDA analysis of Supplemental New Drug Application, NDA 20-564/NDA 20-596, Vol. 1, Table 19, pages 235 – 237)

8.1.6.3. Safety Outcomes

8.1.6.3.1. Clinical Adverse Events

Approximately 60% of patients in the 3TC/ZDV group, 68% in the ddI group, and 69% in the ddI/ZDV group reported at least one adverse event. According to the applicant, the frequency of some adverse events among patients less than 3 years of age, (i.e., fever, breathing disorders, tympanic disorders, feeding and weight problems) were higher in the ddI group compared to those in the 3TC/ZDV group or ddI/ZDV. However, no apparent differences were detected across all treatment groups for the older patient cohort. The adverse event profile of 3TC/ZDV is comparable to that of ddI/ZDV. The incidence of stomatitis (12%) was higher among the patients receiving ddI monotherapy than in those receiving either combination regimens. The most common adverse events are summarized in Table 8.1.6.3.1.

Table 8.1.6.3.1. Summary of Selected Common Adverse Events in >5% of Patients

Adverse events	Percentage of Patients		
	3TC/ZDV (n = 236)	ddI (n = 235)	ddI/ZDV (n = 125)
Body as a whole			
Fever	25	32	34
Headache	< 1	2	2
Gastrointestinal			
Nausea/vomiting	8	7	4
Diarrhea	8	6	6
Stomatitis	6	12	3
Hepatic			
Hepatomegaly	11	11	15
Lymphatic			
Splenomegaly	5	8	5
Respiratory			
Cough	15	18	18
Abnormal breath sounds	7	9	12
Breathing disorders	3	8	2
Ears, nose, throat			
Nasal discharge/congestion	8	11	14
Ear disorders[1]	7	6	7
Other			
Skin rash	12	14	16
Lymphadenopathy	9	11	12

[1] Includes pain, discharge, erythema, or swelling of an ear.

(Supplemental New Drug Application; NDA 20-564/NDA 20-596, Vol. 1, Table 37, pages 262 – 267; Response to FDA Request for Information, Table 37.1, pages 1 - 7)

The majority of adverse events were mild to moderate in intensity. Severe (grade 3) adverse events were reported in 18%, 26 %, and 21% of patients in the 3TC/ZDV, ddI and ddI/ZDV treatment group, respectively. Life-threatening (grade 4) adverse events occurred in 2% of patients in the 3TC/ZDV group, 5% in the ddI group, and 4% in the ddI/ZDV group. The majority of severe or life-threatening adverse events (66%) occurred in the <3-year-old cohort across treatment groups.

Reviewer's Comment

With the exception of fever, the frequencies of common adverse events among pediatric patients on 3TC/ZDV treatment were generally lower than those reported in adults taking this combination regimen.

8.1.6.3.2. Laboratory Abnormalities

The majority of patients (> 85%) had baseline laboratory values below grade 2 toxicity levels. The baseline values were comparable across the treatment arms. The frequencies of selected marked (grade 3/4) laboratory abnormalities during the study period are summarized in Table 8.1.6.3.2 for each treatment group. Pancreatic abnormalities appeared to be comparable across all treatment arms. The frequency of marked liver function elevations was highest in the ddI/ZDV group. Patients on the ddI/ZDV arm appeared to have the highest frequencies of marked neutropenia and thrombocytopenia. However, interpretation of these results was limited by the smaller sample size.

Table 8.1.6.3.2. Frequencies of Selected Marked[1] Laboratory Abnormalities

Laboratory Test	Percentage of Patients		
	3TC/ZDV (n = 236)	ddI (n = 235)	ddI/ZDV (n = 125)
Anemia (Hb < 7 g/dL)	4	2	2
Neutropenia (ANC < 400/mm^3)	8	3	9
Thrombocytopenia (Plt < 50,000/mm^3)	1	3	7
ALT (≥ 10X ULN)	1	3	4
AST (≥ 10X ULN)	2	4	6
Bilirubin (≥ 3X ULN)	< 1	2	2
Amylase (≥ 2X ULN)	3	3	2
Lipase (≥ 2.5X ULN)	3	3	0

[1] Grade 3 or 4 using DAIDS Toxicity Table for Grading severity of Pediatric (> 3 months of age) Adverse Experiences.
(Supplemental New Drug Application; NDA 20-564/NDA 20-596, Vol. 1, Table 37, pages 262 – 267, Vol. 5; Listings 6, 7, and 8, pages 158 - 162 ; Response to FDA Request for Information, Tables 28.1, 29.1 and 30.1, pages 38 - 40)

8.1.6.3.2. Significant or Potentially Significant Adverse Events or Laboratory Toxicities

Pancreatitis, peripheral neuropathy, paresthesia, neutropenia and anemia were significant safety issues identified in the open-label studies NUCA2002 and NUCA2005. A brief review on these adverse events/laboratory abnormalities is provided below.

- Pancreatitis

There were eight cases (1%) of clinical pancreatitis documented in this study, although the proportion of patients with isolated abnormally elevated amylase and lipase levels were slightly higher (see Section 8.1.6.3.2). Five cases occurred among patients in the ddI group (three cases clinically confirmed, and two cases with laboratory abnormalities), resulting in premature treatment withdrawals in four patients. Two patients on the ZDV/ddI arm were diagnosed with pancreatitis, one occurred while the patient was on therapy which resulted in treatment discontinuation, and the other occurred eight weeks after treatment was stopped for growth failure. The applicant reported no cases of pancreatitis among patients on the 3TC/ZDV arm. However, a review of case narratives revealed the following case:

> Patient # 230932: A 12-month-old male who was originally randomized to the ddI arm was diagnosed with failure to thrive. Therapy with ddI was discontinued after 27 weeks. Subsequently he was placed on open-label 3TC, ZDV and ritonavir. He concurrently received TMP-SMX, azythromycin, prednisone, intravenous immunoglobulin and total parenteral nutrition. While on therapy, the patient developed progressive transaminase elevations. Antiretroviral therapy was again withheld. A work-up revealed severe hepatitis and pancreatitis. His hospital course was complicated by massive intra-abdominal hemorrhages which led to his demise shortly thereafter.

- Neuropathy

The frequencies of peripheral neuropathies and/or paresthesias were relatively low in this study (2 patients in the 3TC/ZDV group, three in the ddI/ZDV group, and none in the ddI group) compared to the open-label experiences. Only one patient in the ddI/ZDV group developed grade 3 neuropathy resulting in premature treatment discontinuation.

- Neutropenia

Approximately 8%, 3% and 9% of patients in the 3TC/ZDV, ddI and ddI/ZDV group, respectively, reported at least one grade 3 or 4 neutropenia (ANC < 400/mm^3) during the study period. Treatment was temporarily withheld in approximately 50% of these cases. No patient was discontinued from the study due to neutropenia.

- Anemia

Significant anemia (> grade 3 decrease of hemoglobin, i.e., < 7 g/dL) at some time point in the study was reported in nine (4%) patients in the 3TC/ZDV group, five (2%) in the ddI group and three (2%) in the ddI/ZDV group. The majority of these cases appeared to be isolated incidences requiring either no action, temporary withholding of treatment or dose reduction. One patient (3TC/ZDV group) had hemoglobin decrease to 4.2 g/dL after

24 days of treatment which necessitated blood transfusion. This patient was subsequently withdrawn from the study.

8.1.6.3.3. Treatment Discontinuation due to Adverse Events or Laboratory Toxicities

A total of 12 patients (2%) were prematurely discontinued from the study, five due to pancreatitis as described above (Section 8.1.6.3.2), and seven because of other treatment-emergent toxicities. Clinical adverse events accounted for five withdrawals (all in the ddI/ZDV group), i.e., grade 3 neuropathy (1 patient), grade 2 rash (2 patients), failure to thrive (1 patient), and drug intolerance (1 patient). Two other patients were discontinued due to laboratory abnormalities, i.e., one in the 3TC/ZDV group with grade 4 anemia requiring blood transfusion, and one in the ddI group with grade 4 transaminase elevations.

8.1.6.3.3. Death

A total of 22 patients (4%) died in this study (16 in the ddI group, 3 in the 3TC/ZDV group, and 3 in the ddI/ZDV group). All deaths occurred in patients less than two years of age. The majority of these patients (13 of 22, 59%) died of HIV-related illnesses. Five patients died of other HIV non-related infections (pneumococcal sepsis, RSV pneumonia, septic shock of unknown cause). Two patients died of "unknown" causes. The remaining case was summarized under "Pancreatitis," Section 8.1.6.3.2 above. In this case, the investigator could not attribute the cause of death to study drugs. However, the patient's private physician reported that lamivudine, zidovudine, along with other concurrent medications were possibly related to the patient's death.

8.1.6.3.5. Overdose

Ten cases of drug overdose were reported. Four cases occurred in patients on ddI treatment, and three cases each in patients on 3TC/ZDV or ddI treatment. Eight of these cases had no associated adverse events. In the remaining two cases, one patient had vomiting and diarrhea within hours of accidental ingestion of an overdose of ddI. The other patient (ddI/ZDV group) inadvertently received ddI four times daily for the first five weeks of treatment. Grade 4 neutropenia and grade 2 elevated liver function tests were noted on clinic visit. Correct ddI dosing frequency was subsequently reinitiated. No long-term adverse events were reported in these cases.

8.2. Study NUCA2002

"A phase 1/2 study of 3TC (GR109714X) in children with HIV infection"

Reviewer's Comment

An interim report of this study was previously included in the original Epivir® NDA submission (see review by Dr. H. Jolson dated 01/16/1996). This submission contains

only a safety update available at study termination (04/30/1996) which is reviewed below.

8.2.1. Synopsis

This open-label, dose-escalation study was conducted (from 04/07/1992 to 04/30/1996, under IND 37,158) to determine the safety, preliminary activity, maximally tolerated dose, and pharmacokinetic profile of 3TC monotherapy in pediatric patients with HIV infection. A total of 102 patients between the ages of 3 months and 17 years were enrolled. Among these, 18 patients were "treatment-naive" (i.e., < 6 weeks of prior antiretroviral therapy, group A), 71 were treatment-experienced, (group B), and 13 patients with active *Mycobacterium avium* complex infection were subsequently allowed to enroll on a compassionate basis (group C). The total daily 3TC dosing scheme (in BID regimen) ranged from 1 mg/Kg to 20 mg/Kg. The study was launched in 04/1992. Initially, a 24-week treatment period was planned; however, the study was later amended to extend beyond 96 weeks. The study was terminated in 04/1996. The study showed that the 8 mg/Kg/day dose of 3TC provided comparable drug exposure to that in adults receiving 4 mg/Kg/day.

Since 3TC monotherapy is no longer acceptable in current standard practice for the treatment of HIV infection, the applicant only submits an update on safety data of this study for review.

8.2.2. Results

8.2.2.1. Patient Disposition and Comparability

At the time of study termination, most (84%) of the patients were withdrawn from the study. The main reasons for early discontinuations were disease progression (23%), clinical adverse events (17%), and laboratory toxicities (15%). Thirteen patients (13%) died during the study.

The overall mean exposure to 3TC was 16.1 months for all patients in this study (21.3 months for patients in group A, 15.2 months for group B, and 13.7 months for group C). The range of exposure was quite large, between 0.9 months to 39 months. Approximately 59% of patients were exposed to greater than 12 months of study drug treatment.

Table 8.2.2.1.A provides a summary of patient demographics. Baseline disease characteristics are shown in Table 8.2.2.1.B. The majority of patients were white males over the age of 2 years. Approximately 85% of patients were treatment-experienced, and most (84%) had symptomatic HIV infection (CDC classification P-2).

Table 8.2.2.1.A. Summary of Patient Demographics

Demography	Number (%) of Patients		
	Group A (n = 18)	Group B (n = 71)	Group C (n = 13)
Gender			
- Male	6 (33)	42 (59)	10 (77)
- Female	12 (67)	29 (41)	3 (23)
Ethnicity			
- White	8 (44)	40 (56)	11 (85)
- Black	3 (17)	18 (25)	0
- Hispanic	6 (33)	9 (13)	2 (15)
- Other	1 (6)	4 (6)	0
Age (year)			
- Mean	4.0	8.2	10.8
- Range (year)	0.3 – 14.0	1.2 – 17.0	4.0 – 17.0

(Supplemental New Drug Application; NDA 20-564/NDA 20-596; Vol. 1, page 71; Vol. 7, Table 2, page 186)

Table 8.2.2.1.B. Summary of Baseline Disease Characteristics

Baseline Disease Characteristics	Number (%) of Patients		
	Group A (n = 18)	Group B (n = 71)	Group C (n = 13)
CD4 (cells/mm^3)			
- Mean	1028	200	9
- Median	787	79	4
- Range	35 - 2339	0 - 1471	0 - 57
HIV RNA (log_{10})			
- Mean	4.2	4.6	4.6
- Median	4.2	4.6	4.7
- Range	2.3 – 6.5	1.3 – 6.1	3.1 – 6.2
Disease status			
- P-0	2 (11)	0	0
- P-1	2 (67)	2 (3)	0
- P-2	4 (22)	69 (97)	13 (100)

(Supplemental New Drug Application; NDA 20-564/NDA 20-596; Vol. 7, Table 2, page 186)

Reviewer's Comment

The sponsor subsequently provided additional information on the age range of patients in Study NUCA2002 as follows:

Age Range	Number of Patients
0 to < 3 months	0
≥ 3 to < 6 months	1
≥ 6 to < 12 months	2
≥ 12 to < 36 months	15
≥ 36 months	84

(Response to FDA Request for Information [12/18/98]; page 4)

The number of patients below the age of 12 months is exceedingly small (n = 3). Therefore, adequate safety data for this age group could not be established by this study alone.

8.2.2.2. Safety Outcomes

8.2.2.2.1. Clinical Adverse Events

All patients (100%) reported at least one adverse event during the study. The majority of adverse events were fever, infections, edema, and fatigue. A number of the events reported were those commonly seen in children (ear, nose and throat disorders, skin disorders, etc.), and some were most likely associated with HIV-infection (opportunistic infections). Approximately 72% of patients experienced at least one grade 3 (64%) or grade 4 (8%) adverse event at some time during the study. A listing of the most common adverse events (reported in > 10% of patients) is presented in Table 8.2.2.2.1.

Table 8.2.2.2.1. Summary of Selected Adverse Events Occurring in > 10% of Patients

Adverse Events	Percentage of Patients			
	Group A (n = 18)	Group B (n = 71)	Group C (n = 13)	Total (n = 102)
Body as a whole				
Fever	89	85	54	81
Headache	50	66	31	59
Malaise/fatigue	22	51	23	42
Ear, nose and throat disorders				
Nasal disorders[1]	94	96	38	88
Infections	83	62	8	59
Gastrointestinal disorders				
Diarrhea	61	72	69	70
Abd. discomfort/pain	39	66	77	63
Nausea/vomiting	61	45	54	49
Oral ulceration	33	10	0	13
Skin disorders				
Rash[2]	83	63	31	63
Sweating/sebum disorders	50	51	23	47
Pruritus	17	21	15	20
Respiratory disorders				
Cough	89	87	31	80
Pneumonia	11	24	8	20
Asthma	0	18	15	15
Infection (protozoan)	0	15	15	13
Neurological disorders				
Sleep disorders	22	27	8	24
Neuropathy	6	17	5	15
Gait disorders	0	13	15	11
Musculoskeletal disorders				
Musculoskeletal pain	33	53	23	46
Arthralgia	22	21	0	19
Others				
Pancreatitis[3]	0	13	38	14
Feeding problems	61	54	15	50
Splenic disorders	67	39	15	41
Psychomotor disorders	33	17	8	19
Keratitis/conjunctivitis	22	18	0	17

[1] Unspecified signs and symptoms

[2] Inclusive of the following types: unspecified, papular, macular, and maculopapular

[3] The original data base provided by the applicant did not include three additional cases of pancreatitis in group C.

(Supplemental New Drug Application; NDA 20-564/NDA 20-596; Vol. 7, Table 3, pages 189 - 223)

Reviewer's Comments

1. *Data on adverse events were difficult to analyze due to confusing use of medical terminology. For example, under musculoskeletal disorders, the applicant provided separate listings of data on "musculoskeletal pain," "musculoskeletal discomfort," "muscle pain," and "muscle discomfort."*

2. *It is not clear whether the lower frequencies of many adverse events reported in group C (patients with advanced disease) were due to under-reporting.*

3. *The applicant did not provide data on intensities of clinical adverse events.*

8.2.2.2.2. Laboratory Abnormalities

Approximately 86% (88/102) of patients experienced at least one grade 3 or 4 (marked) laboratory abnormality; 72% (13/18) in group A, 87% (62/71) in group B, and 100% (13/13) in group C. The abnormal laboratory data are summarized in Table 8.2.2.2.3.

Table 8.2.2.2.3. Frequencies of Marked[1] Laboratory Abnormalities

Laboratory Test	Percentage of Patients			
	Group A (n = 18)	Group B (n = 71)	Group C (n = 13)	Total (n = 102)
Anemia (Hb < 8 g/dL)	6	17	15	15
Neutropenia (ANC < 750/mm^3)	17	45	54	42
Thrombocytopenia (Plt < 40,000/mm^3)	11	8	0	8
Elevated ALT (> 5X ULN)	28	14	23	18
Elevated AST (> 5X ULN)	23	22	23	23
Hyperbilirubinemia (> 5X ULN)	6	4	15	6
Amylase (> 2X ULN)	11	7	8	8
Hypocalcemia (< 7 mg/dL)	0	4	8	4

[1] Protocol-defined grade 3 or 4 toxicity

(Supplemental New Drug Application; NDA 20-564/NDA 20-596; Vol. 7, Table 9, pages 269 - 272)

Reviewer's Comments

1. *The frequencies of grade 3/4 laboratory toxicities appeared to be significantly higher than those reported in ACTG 300. This is primarily due to a different toxicity grading scale being used in this protocol. Some of the laboratory toxicities considered as grade 3 by this grading scale are equivalent to grade 2 (or less) according to the DAIDS Toxicity Table for Grading severity of Pediatric (> 3 months of age) Adverse Experiences (used in ACTG 300). Additionally, some patients also had grade 3 or 4 baseline neutropenia (9 patients) and elevated LFT (1 patient).*

2. *Using the same DAIDS Toxicity Table for Grading severity of Pediatric (> 3 months of age) Adverse Experiences, the frequencies of marked (grade 3/4) laboratory abnormalities in this study appear to be comparable to those seen in ACTG 300. Results of this exploratory analysis are included in the sponsor's Response to FDA Requests for Information submitted on 2/1/99.*

8.2.2.2.3. Significant or Potentially Significant Adverse Events or Laboratory Toxicities

- Pancreatitis

Clinical pancreatitis was reported in 14 patients (14%); nine in group B (NRTI-experienced), five in group C (advanced patients), and none in group A (treatment-naive). All cases were considered by the investigators as related to drug treatment. Seven patients (7%) discontinued 3TC treatment as a result of pancreatitis. Of the five patients who were not withdrawn, pancreatitis resolved in three patients. Two patients were reported to have clinical improvements but were subsequently withdrawn from the study for other reasons. There were three deaths which appeared related to pancreatitis (see also Section 8.2.2.2.5).

- Neuropathy

Peripheral neuropathies and/or paresthesias (pain, tingling and numbness) were reported in 15 patients (15%); one (6%) in group A, 12 (17%) in group B, and two (15%) in group C. As a result of neuropathies, three patients (3%) were withdrawn from the study. The symptoms resolved within two to three months in the majority of patients (8 of 12).

- Anemia

Anemia was reported as clinical adverse events in 34 patients (33%); five in group A, 26 in group B, and two in group C. Among these, 15 patients (15%) had grade 3 or 4 decreases in hemoglobin (<8 g/dL). Iron deficiency anemia was identified in approximately 53% of patients, and most of these cases were considered by the applicant as "unlikely" related to study drugs. Treatment was not changed in all except for temporary dose reduction in two patients.

- Neutropenia

Forty-two patients (42%) experienced at least one or more grade 3 or 4 (ANC < 750/mm^3) neutropenia events during the study. However, 14 of these patients had pre-existing baseline grade 3 or 4 neutropenia. Treatment-emergent neutropenia was identified in 33 patients (32%). Among these patients, the condition resolved to grade 2 or less in 20 patients. Treatment was prematurely discontinued in three patients due to grade 4 neutropenia.

Reviewer's Comment

Using the criteria established by DAIDS Toxicity Table for Grading Severity of Pediatric (> 3 months of age) Adverse Experiences, the frequencies of grade 3/4 neutropenia in these studies were approximately 15% (6% grade 3, 9% grade 4).

8.2.2.2.4. Treatment Discontinuation due to Adverse Events or Laboratory Toxicities

A total of 32 patients (31%); three (17%) in group A, 25 (35%) in group B, and four (31%) in group C, were prematurely withdrawn from the study. Seventeen patients (17%) were discontinued due to clinical adverse events, and fifteen patients (15%) due to laboratory toxicities. Pancreatitis was the most common clinical adverse event leading to early withdrawal in 8 patients. Elevated ALT/AST (6 patients), hyperamylasemia (4 patients), and neutropenia (3 patients) were among the most common laboratory abnormalities leading to treatment discontinuation.

8.2.2.2.4. Death

A total of 20 (20%) deaths were recorded in this study; thirteen on study, three within 30 days of premature discontinuation, and four more than 30 days after withdrawal from the study. A review of case narratives showed that the majority of deaths were secondary to complications of HIV disease progression.

Three patients (patients 2609, 2612 and 3810) were hospitalized for infections. During the course of hospitalization, these patients were found to have developed pancreatitis thought to be related to study drug. Their condition deteriorated and they subsequently died. The pancreatitis apparently remained unresolved at the time of death.

Reviewer's Comment

In this submission, the applicant reported two cases of death due to pancreatitis, i.e., patients 2612 and 3803.

8.2.2.2.5. Overdose

There were no cases of drug overdose reported in this study.

8.3. Study NUCA2005

"A phase 1/2 study to evaluate the safety, toxicity and preliminary efficacy of combinations of lamivudine (3TC), zidovudine (ZDV), and didanosine (ddI) in children with HIV infection"

Reviewer's Comment

An interim report of this study was previously included in the original Epivir® NDA submission (see review by Dr. H. Jolson dated 01/16/1996). This submission contains the final report of safety and activity data available at study termination (01/12/1997). This review will focus only on safety data since the exploratory design of this study precluded an assessment of efficacy..

8.3.1. Synopsis

This open-label study was conducted (from 01/17/1994 to 01/12/1997, under IND 37,158) to determine the safety, preliminary antiviral activity, and pharmacokinetics of combination antiretroviral regimens containing 3TC in HIV-infected pediatric patients. A total of 65 patients between 3 months and 19 years of age were enrolled and stratified by history of prior antiretroviral therapy. Group A included patients (n = 9) with no or minimal prior therapy to receive one of two triple-drug combination regimens. Group B included treatment-experienced patients (n = 56) who experienced toxicity or disease progression while on another therapy and were randomized to receive one of three combination regimens containing two or three drugs. 3TC at 4 mg/Kg BID and ddI at 135 mg/m^2 BID were used in all treatment regimens. The treatment groups are summarized as follows:

Group A:	3TC + ddI + ZDV (180 mg/m^2 QID)	(n = 5)
	3TC + ddI + ZDV (90 mg/m^2 QID)	(n = 4)
Group B:	3TC + ZDV (180 mg/m^2 QID)	(n = 18)
	3TC + ddI	(n = 7)
	3TC + ddI + ZDV (90 mg/m^2 QID)	(n = 31)

The initial treatment period was 24 weeks. However, the study was extended beyond this period for those patients who appeared to be benefiting from therapy.

8.3.2. Results

8.3.2.1. Patient Disposition and Comparability

At the time of termination, 65% (42/65) of patients were prematurely discontinued from the study (56% from group A, 66% from group B). Adverse events accounted for approximately 43% (18/42) of these cases, and treatment failure in 14% (6/42). Parental

requests, investigator discretion, noncompliance, lost to follow-up and death were the remaining reasons. Four (6%) patients died during the study.

The mean duration on therapy was approximately 16.4 months for patients in group A and 13.0 for patients in group B. Approximately 56% of patients in group A and 43% in group B had > 12 months of drug therapy.

A summary of patient demographics is provided in Table 8.3.2.1.A Baseline disease characteristics are summarized in Table 8.3.2.1.B.

Table 8.3.2.1.A. Summary of Patient Demographics

Demography	Number (%) of Patients	
	Group A (n = 9)	Group B (n = 56)
Gender		
- Male	7 (78)	38 (58)
- Female	2 (22)	27 (42)
Ethnicity		
- White	6 (67)	33 (59)
- Black	2 (22)	14 (25)
- Hispanic	1 (11)	8 (14)
- Other	0	1 (2)
Age (year)		
- Mean	7.5	9.2

(Supplemental New Drug Application; NDA 20-564/NDA 20-596; Vol. 10, Table 2, pages 168 - 171)

Table 8.2.2.1.B. Summary of Baseline Disease Characteristics

Baseline Disease Characteristics	Number (%) of Patients	
	Group A (n = 9)	Group B (n = 56)
CD4 (cells/mm^3)		
- Mean	454	142
- Median	275	68
- Range	11 - 2028	0 - 557
HIV RNA (log_{10})		
- Mean	4.3	4.8
- Median	4.7	4.9
- Range	2.7 – 6.3	2.8 – 6.1
Disease status		
- P-1	4 (44)	5 (9)
- P-2	5 (56)	51 (91)

(Supplemental New Drug Application; NDA 20-564/NDA 20-596; Vol. 10, Tables 4 and 8, pages 173 - 176 and 184 - 187)

Reviewer's Comment

The sponsor subsequently provided additional information on age range of patients in Study NUCA2005 as follows:

Age Range	Number of Patients
0 to < 3 months	0
≥ 3 to < 6 months	1
≥ 6 to < 12 months	1
≥ 12 to < 36 months	4
≥ 36 months	59
Total	65

(Response to FDA Request for Information [12/18/98]; page 4)

The number of patients less than 1 year of age is relatively small (n = 2) in this study. Therefore, adequate safety data for this age group could not be established by this study.

8.3.2.2. Safety Outcomes

8.3.2.2.1. Clinical Adverse Events

All patients (100%) reported at least one clinical adverse event during this study. Similar to those seen in study NUCA2002, a number of adverse events were commonly seen in a population of pediatric patients (ear, nose and throat disorders) and some were most likely associated with HIV-infection (opportunistic infections). According to the responses to FDA requests for information (submitted 02/01/99), approximately 65% of patients experienced at least one grade 3 (45%) or grade 4 (25%) adverse events during the study. A listing of adverse events reported in 10% or higher of patients is presented in Table 8.3.2.2.1.

Serious adverse events (defined as fatal, life-threatening, disabling adverse events requiring prolonged hospitalization, congenital anomaly, cancer or overdose) occurred in approximately 71% (46/65) of patients. The majority of these cases were fever (18%) associated with concurrent infections, neutropenia (20%), pancreatitis (11%), anemia (9%), elevated ALT/AST (9%), and abdominal pain (8%).

Table 8.3.2.2.1. Summary of Selected Adverse Events Occurring in > 10% of Patients

Adverse Events	Percentage of Patients		
	Group A (n = 9)	Group B (n = 56)	Total (n = 65)
Body as a whole			
Fever	56	55	55
Headache	22	45	42
Gastrointestinal disorders			
Abd. discomfort/pain	33	55	53
Diarrhea	44	43	43
Nausea/vomiting	44	38	38
Ear, nose, throat disorders			
Infections	78	45	49
Nasal disorders[1]	44	30	32
Sinusitis	33	20	22
Hepatobiliary disorders			
Hepatobiliary signs[2]	67	63	63
Skin disorders			
Rash[3]	55	45	44
Sweating/sebum disorders	22	25	25
Fungal infection	22	16	17
Respiratory disorders			
Cough	56	64	66
Pneumonia	0	14	12
Musculoskeletal disorders			
Musculoskeletal pain	11	23	22
Others			
Pancreatitis[4]	11	20	18
Keratitis/conjuntivitis	33	14	17

[1] Unspecified signs and symptoms
[2] Unspecified by the applicant
[3] Inclusive of the following types: unspecified, macular, papular, maculopapular, bullous, pruritic and vesicular
[4] Inclusive of "clinical" and "chemical" pancreatitis; see also Section 8.3.2.2.3.
(Supplemental New Drug Application; NDA 20-564/NDA 20-596; Vol. 10, Table 21, pages 259 – 270; Vol. 13, Listing 8, pages 202 – 207)

8.3.2.2.2. Laboratory Abnormalities

Approximately 89% (58/65) of patients experienced at least one grade 3 or grade 4 laboratory toxicity during the course of the study. The abnormal laboratory data are summarized in Table 8.3.2.2.2.

Table 8.3.2.2.2. Frequencies of Marked[1] Laboratory abnormalities

Laboratory Test	Percentage of Patients		
	Group A (n = 9)	Group B (n = 56)	Total (n = 65)
Anemia (Hb < 8 g/dL)	11	18	17
Neutropenia (ANC < 1000/mm^3)	22	62	57
Thrombocytopenia (Plt < 50,000/mm^3)	0	2	2
Elevated ALT (> 5X ULN)	33	18	20
Elevated AST (> 5X ULN)	22	24	23
Hyperbilirubinemia (> 1.5X ULN)	0	7	7
Hyperamylasemia (> 2X ULN)	11	9	9

[1] Protocol-defined grade 3 or grade 4 toxicity

(Supplemental New Drug Application; NDA 20-564/NDA 20-596; Vol. 10, Table 20, pages 256 – 258; Vol. 11, Appendix 5, pages 57 – 61)

Reviewer's Comments

1. *The frequencies of grade 3/4 laboratory toxicities, particularly neutropenia and elevated ALT/AST, appeared to be significantly higher than those reported in ACTG 300. This is primarily due to a different toxicity grading scale being used in this protocol. Some of the laboratory toxicities considered as grade 3 by this grading scale are equivalent to grade 2 (or less) according to the DAIDS Toxicity Table for Grading severity of Pediatric (> 3 months of age) Adverse Experiences used in ACTG 300.*

2. *Using the same DAIDS Toxicity Table for Grading severity of Pediatric (> 3 months of age) Adverse Experiences, the frequencies of marked (grade 3/4) laboratory abnormalities in this study appear to be comparable to those seen in ACTG 300. Results of this exploratory analysis are included in the sponsor's Response to FDA Requests for Information submitted on 2/1/99.*

8.3.2.2.3. Significant or Potentially Significant Adverse Events or Laboratory Toxicities

- Pancreatitis

Twelve patients (18%), all but one were NRTI-experienced, developed pancreatitis during the study; seven in the triple-drug (3TC/ZDV/ddI) group, three in the 3TC/ddI group, and two in the 3TC/ZDV group. In eight of these patients, pancreatitis was considered a serious adverse event by the investigators. Five patients (5 of 12, 42%) were prematurely discontinued from the study because of pancreatitis. Additionally, four other patients (4 of 12, 33%) had temporary treatment interruption.

- Neuropathy

Paresthesia was reported in six patients (9%), four of which were on the triple-drug arms. The events were primarily tingling and numbness of distal extremities and completely resolved in four patients. No information was available on the outcome for the remaining two patients. Dosage reduction was required in one patient. However, there were no cases of premature withdrawals as a result of neuropathy.

- Anemia

Anemia was reported as clinical adverse event in 21 patients (31%), and as a serious adverse event in 6 patients (9%). Most of these cases (19 of 21) occurred in group B patients (treatment-experienced). Approximately half of these patients received 3TC/ZDV treatment, and the other half 3TC/ZDV/ddI. Laboratory analysis showed that eight patients (12%) had laboratory grade 3 anemia (Hb between 6.5 - 7.9 g/dL), and three patients (5%) with grade 4 anemia (Hb < 6.5 g/dL). Iron deficiency anemia was identified in approximately 48% of patients and was considered as "unlikely related" to treatment by the applicant. Anemia was the main or contributory cause (in conjunction with neutropenia, pancreatitis and elevated liver function tests) of premature treatment discontinuation in five patients.

- Neutropenia

A total of 37 patients (57%) had significant neutropenia in this study. Grade 3 neutropenia (ANC between 500 – 900/mm^3) was reported in 24 patients (37%), and grade 4 neutropenia (ANC < 500/mm^3) in 13 patients (20%). Most (95%) of these cases occurred in treatment-experienced patients. Approximately 46% of patients were in the 3TC/ZDV/ddI group, 32% in the 3TC/ZDV group, and 13% in the 3TC/ddI group. Neutropenia was the principal or contributory cause (in conjunction with anemia, pancreatitis and elevated liver function tests) of premature treatment withdrawal in 6 patients.

Reviewer's Comment

Using the criteria established by DAIDS Toxicity Table for Grading Severity of Pediatric (> 3 months of age) Adverse Experiences, the frequencies of marked neutropenia in these studies were approximately 13% (5% grade 3, 8% grade 4).

8.3.2.2.4. Treatment Discontinuation due to Adverse Events or Laboratory Toxicities

A total of 21 patients (32%) were discontinued from the study due to either adverse events and/or laboratory toxicities. Neutropenia, anemia, pancreatitis, and grade 3/4 elevated hepatic enzymes accounted for most of these cases (see Section 8.3.2.2.3 above). The majority of these patients were from the 3TC/ZDV/ddI group (12 of 21, 57%) and the 3TC/ZDV group (7 of 21, 33%).

8.3.2.2.5. Death

Four patients (6%) died during the study; two in the 3TC/ddI group, and one each in the 3TC/ZDV/ddI or 3TC/ZDV group. A review of case narratives revealed three deaths from respiratory failure, and one death from disseminated candidiasis and multiple organ failure. The investigator attributed acute renal failure, neurological deterioration and seizure in the last case possibly due to the use of study drugs (3TC/ZDV).

8.3.2.2.6. Overdose

There were no cases of drug overdose reported in this study.

9. REVIEWER'S CONCLUSIONS

9.1. Efficacy

- Study ACTG 300 clearly demonstrates that combination therapy with 3TC/ZDV is clinically, virologically and immunologically better than ddI monotherapy. The clinical benefit measured by death rate and time to first clinical progression appear to be more pronounced in patients less than 36 months of age.

- Study ACTG 300 enrolled a sufficient number of patients of 3 months of age and older to allow meaningful efficacy assessments in this pediatric population.

- Analyses based on the cohort of patients randomized prior to discontinuation of enrollment on the ddI/ZDV arm show that while combination therapy with either 3TC/ZDV or ddI/ZDV are better than ddI monotherapy, there is no significant difference with respect to time-to-first clinical progression event between these combination regimens.

9.2. Safety

- Treatment with 3TC, as monotherapy or in combination with an NRTI, was shown to be safe and well tolerated in three clinical trials, ACTG 300, NUCA2002 and NUCA2005. With the exception of pancreatitis, the adverse event profile and treatment-associated laboratory abnormalities in pediatric patients was similar to those seen in adult clinical trials. There were no new treatment-emergent toxicities.

- The frequencies of clinical adverse events were generally higher in the two open-label Studies NUCA2002 and NUCA 2005 than those reported in the controlled Study ACTG 300.

- A significant safety issue associated with lamivudine therapy was pancreatitis. Fourteen percent of patients in NUCA2002 and 18% in NUCA2005 developed pancreatitis while on therapy, either as asymptomatic elevations of amylase and/or lipase or confirmed by clinical signs and symptoms. Five of 14 patients (36%) who had pancreatitis in study NUCA2002 died of complications of pancreatitis. The majority of patients who experienced pancreatitis in both studies had previous exposure to other NRTIs and/or relatively advanced disease. It appears that these factors, prior NRTI-treatment experience and advanced disease, may increase the risk of developing pancreatitis with lamivudine therapy. The paucity of pancreatitis (1%) in Study ACTG 300 which enrolled treatment-naive patients with less advanced disease appears to confirm this impression. It should be noted that the incidence of pancreatitis among adults in controlled trials of lamivudine was significantly lower (< 0.5%).

- Peripheral neuropathy was reported in 15 (15%) of patients in Study NUCA2002. As a result, three (20%) patients were withdrawn from study drugs. There were six (9%) patients in Study NUCA2005 who developed treatment emergent peripheral neuropathy. None of these patients had treatment discontinuation. In Study ACTG 300, the frequencies of peripheral neuropathy across treatment arms were relatively low (<1%). The differences in treatment history between these study populations may have accounted for the variability.

- Results of these studies (ACTG 300, NUCA2002, NUCA2005) are adequate to support the safety of 3TC in combination treatment in pediatric patients 3 months of age and older. However, the pharmacokinetic profile and safety data of 3TC treatment in the age group from birth to 3 months of age are lacking. These issues have been addressed to the sponsor in a proposed pediatric study request in conjunction with the pediatric exclusivity determination.

10. LABELING REVIEW

At the time this report was prepared, Glaxo Wellcome has submitted a final draft label for approval. An addendum regarding the label approval will follow.

11. REGULATORY RECOMMENDATION

The undersigned reviewer recommends that this Supplemental Application for Treatment of HIV Infection in Pediatric Patients (NDA 20-564 and NDA 20-596) be approved under 21 CFR 314.50.

Tan T. Nguyen, MD, PhD
MO/DAVDP/CDER/ODEIV/FDA/HFD-530

Concurrence:

HFD-530/DivDir/Jolson 3/10/99
HFD-530/TL/Murray JSM 3/5/99

cc:

Orig. IND 57,465
HFD-530/Division File
HFD-530/TL/Murray
HFD-530/CSO/Crescenzi
HFD-530/MO/Nguyen
HFD-530/MO/Styrt
HFD-530/Chem/Gu
HFD-530/PharmTox/Yuen
HFD-530/Micro/Connors
HFD-530/Biopharm/Rajagopalan

Group Leader's Memorandum
March 12, 1999

NDA 20-564 Supplement 007
20-596 Supplement 007

I concur with Dr. Nguyen's clinical review and recommendation for approval of this pediatric supplement for Epivir. The supplement contains an important clinical endpoint study (ACTG 300) in pediatric patients, ages 3 months and greater. In this study, treatment with Retrovir and Epivir was associated with a decreased risk of HIV clinical progression than treatment with didanosine monotherapy. Changes in CD4 cell counts and HIV RNA levels were consistent with the treatment effects on the primary clinical endpoint. A description of this clinical study with respect to the primary clinical endpoint will be included in the revised package insert.

ACTG 300 also provided additional safety data in pediatric patients receiving Epivir. In this study, which enrolled antiretroviral naïve (<56 days) patients, Epivir was well tolerated and the frequency of pancreatitis among patients receiving Epivir was low. This data is reassuring that Epivir can be used safely in children. The higher frequency of pancreatitis observed in previous Epivir pediatric studies occurred in more advanced and treatment experienced patients. The revised package insert will retain the Warning regarding pancreatitis in children; however, emphasis is placed on factors such as, prior nucleoside experience or a history of pancreatitis, as potential risk factors for the development of pancreatitis in pediatric patients receiving Epivir.

The current package insert includes dosage recommendations for children, ages 3 months to [redacted]

In addition, the Dosage and Administration section of the label has been revised to remove the recommendation for dose reduction in adults with body weight less than 50 kg. This dose reduction scheme created somewhat of a disconnect in the consistency of dosing among children and adults, wherein older children weighing greater than 37kg would receive the standard Epivir adult dose of 150 mg bid but an adult of 49 kg (108 lbs.) would receive half dose. At the time of approval the duration of safety data was more limited; thus, such a dose reduction scheme was reasonable. However, safety data from four randomized controlled trials and an expanded access program indicate that Epivir at a dose of 300 mg bid was well tolerated and safe. In randomized controlled studies the frequency of adverse events among patients receiving either dose was similar.

In the expanded access program the total number of serious adverse events (regulatory definition) was numerically greater among the 300 mg bid dose group compared to the 150 mg bid dose, but the frequency of any particular adverse event type was relatively low among either dose group. The 300 mg bid dose group appeared to be at least as well tolerated as many of the other antiretroviral agents on the market. Furthermore patients with lower body weights taking the standard dose of Epvir would not be predicted to achieve drug concentrations approaching that of the 300 mg bid dose. Such concentrations would be more probable for patients with mild renal impairment, for which there is no dose reduction recommendation. It should also be noted that the adult clinical endpoint study (CAESAR) did not use a body weight dose reduction scheme; therefore, efficacy of a dose reduction for patients with low body weight has not been established.

The revised label will also include a statement in the Dosage and Administration section regarding dosing in pediatric patients with renal impairment. Although there is insufficient data to recommend a specific dose reduction scheme for children with renal impairment, the label states that dose reduction or increasing the dosing interval should be considered. A similar statement also appears in the label for VIDEX, a drug that is also excreted in the urine.

Jeffrey S. Murray M.D., M.P.H.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-564 / S-007
20-596 / S-007

CHEMISTRY REVIEW(S)

SUPPLEMENTAL NDA CHEMIST'S REVIEW	1. ORGANIZATION HFD-530	2. NDA NUMBER 20-564

3. NAME AND ADDRESS OF APPLICANT *(City and State)*

Glaxo Wellcome Inc.
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

4. AF NUMBER

5. SUPPLEMENT(S)

NUMBER(S)	DATE(S)
SE1-007	3/27/98

6. NAME OF DRUG
EPIVIR® Tablets and Oral solution

7. NONPROPRIETARY NAME
lamivudine tablets and oral solution

8. SUPPLEMENT(S) PROVIDES FOR:
The use of Epivir in combination with Retrovir for the treatment of HIV infection in pediatric patients — of age.

9. AMENDMENTS / REPORTS

10. PHARMACOLOGICAL CATEGORY
Anti-hepatitis B

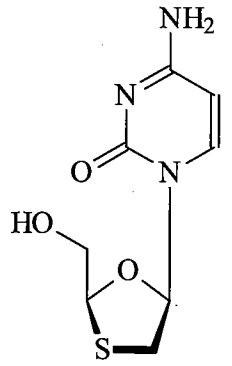
11. HOW DISPENSED
|X| Rx | | OTC

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM(S)
Film coated tablets and oral solution

14. POTENCY(IES)
150 mg and 10 mg/mL

15. CHEMICAL NAME AND STRUCTURE
(2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one



16. MEMORANDA

17. COMMENTS
This Supplement contains clinical data and details of minor labeling changes. There are no CMC changes.

18. CONCLUSIONS AND RECOMMENDATIONS
There are no CMC comments. From the CMC point of view this Supplement should be approved.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
George Lunn, Ph.D.		4/6/98

20. CONCURRENCE: HFD-530/SMiller

DISTRIBUTION						
	X	Original Jacket	X	GLunn	X	BStyrt
	X	Division File	X	SMiller	X	Perm
	X	HFD-830/CChen	X	Asocial	X	NBattula
	X	PFlyer	X	JJenkins		

STATISTICAL REVIEW AND EVALUATION

NDA#:	20-564/S-413 , 20-596
APPLICANT:	Glaxo Wellcome Inc
NAME OF DRUG:	Epivir® Tablets, Epivir® Oral Solution
INDICATION:	Treatment of HIV Infection in Pediatric Patients
TYPE OF REVIEW:	Clinical
DOCUMENTS REVIEWED:	Volumes 1, 2, 4;
MEDICAL INPUT:	Tan Nguyen, M.D. (HFD-530)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-564 / S-007
20-596 / S-007

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA#: 20-564, 20-596

1. Background

1.1 Objectives in Trial

The applicant submitted one randomized, double blind, controlled clinical trials with 3TC for this supplement. The applicant has submitted this study to provide pediatric clinical information with this drug.

The primary objective of this study was to compare the efficacy of 3TC/ZDV combination therapy with the better of ddI monotherapy and ddI/ZDV combination therapy. The primary efficacy endpoint occurrence of one or more of the following events: HIV disease progression, death, failure to achieve adequate weight growth velocity, or decline in neurophysiological assessments. The study population was HIV-1 infected children between 42 days and 15 years of age with fewer than 56 days of prior antiretroviral or immunomodulator therapy.

1.2 Summary of study design

The study, ACTG 300, was a double-blind, multi-dummy, randomized, three-arm, parallel, active-controlled multi-center trial conducted in the US. There was a planned conversion from a three-arm study to a two-arm study in the middle of the trial. The conversion was based on evidence external to this trial. The study was scheduled to provide 24 months of blinded treatment from the date of the last subject's accrual.

Study medication was discontinued after a primary endpoint was observed and subjects were then offered the best available therapy.

Subjects were randomly assigned in a 1:1:1 ratio to 3TC/ZDV, ddI, and ddI/ZDV until the results of ACTG 152 were available. On the basis of that trial, recruitment into the poorer of the two control arms was stopped. The better arm in ACTG 152 was defined by the first available of the following four criteria: 1) statistically significantly better efficacy, 2) statistically significantly better efficacy under age 30 months, 3) statistically significantly better safety, or 4) subjectively better overall cost, convenience, efficacy, safety, virology, and immunology. In fact, criterion 4 was the only one that obtained.

The stopped arm was ddI/ZDV. Subjects already enrolled in this arm remained blinded and on assigned treatment.

The target sample size was 740. Randomization was stratified by age < 3 yrs or ≥ 3 yrs and by center. The assignment used permuted blocks of size 6 (before the third arm was stopped) or of size 4 (after the third arm was stopped). A dynamic allocation procedure was used so that a maximum center imbalance of two was allowed.

Three interim analyses and one final analysis were planned. The analyses were scheduled for the end of accrual and for every 8 months thereafter. The Lan-Demets extension of the O'Brien-Fleming stopping rule was used. The trial was stopped at the first interim analysis, reported to the DSMB on June 18, 1997, and using event data through April 4, 1997, and visit data through March 12.

1.3 Patient Accounting and Baseline Characteristics

615 patients were enrolled in the trial. Of these, 18 patients never started treatment or were missing information on dispensation of treatment and one (on ddI) was ruled ineligible after starting treatment. Of the 596 eligible patients who started treatment, 125 patients were enrolled in the discontinued ddI/ZDV arm. The remaining 471 patients, 236 on 3TC/ZDV and 235 of ddI, constituted the modified ITT subset. The subjects were enrolled at 86 centers in the US.

The study population was 43% male with a median age of 2.6 years. They were 14% white, 63% black, and 22% Hispanic. Their baseline CDC clinical categories were 15% None, 47% Mild, 24% Moderate, and 14% Severe. Their baseline immunologic categories were 29% None, 41% Moderate, and 14% Severe.

The mean CD4 count at baseline was 910 cells/mm^3; the mean HIV RNA level was 5 logs.

The applicant does not provide coherent written description of patient disposition. Table 1.3 A summarizes the patient status at the time of the first interim analysis (events reported through 4-4-97, visit data through the visit scheduled between 2-

12 and 3-12). Table 1.3 B summarizes the primary reasons for discontinuation from treatment. Subjects who discontinued study treatment were nonetheless retained on study and were seen according to the regular schedule. In both these tables, the reviewer used the data from the DSMB report, not the data from volume 1 of the NDA. This disagreement concerns subject 105231, who was randomized on Aug 19, 1996, to ddI and who died on Sept 30, 1996, of B-cell lymphoma. This cancer was revealed in a baseline scan and was an inclusion/exclusion violation. The DSMB report and the following tables exclude this subject; volume 1 of the NDA includes it.

TABLE 1.3 A
PATIENT STATUS AT INTERIM ANALYSIS

	3TC+ZDV	ddI	ZDV+ddI
Randomized	244	244	127
In Modified ITT*	236	235	125
Death or Disease Progression	15	38	13
Lost to Follow-up	7	4	5
Still Observed	214	193	107

* Started treatment, met inclusion/exclusion criteria

TABLE 1.3 B
REASONS FOR TREATMENT DISCONTINUATIONS

Status and Reason	3TC+ZDV	ddI	ZDV+ddI
In Modified ITT	236	235	125
No Clinical Progression			
Still observed but off Rx			
Toxicity	1	0	4
Miscellaneous	15	13	16
Lost to Follow-up	7	4	5
Ongoing	198	180	87
Clinical Progression			
Discontinued with CP	13	32	12
Death	2	6	3
Clinical endpoints	11	19	7
Toxicity	0	1	1
Other	0	6	2
Ongoing with CP	2	6	1

1.4 Summary of Methods of Assessment

1.4.1 Schedule of Measurements

Patients were given physical exams at weeks 4, 8, 12, and every 8 weeks thereafter. HIV related symptoms, height, weight, and head circumference were measured every 4 weeks; weight growth velocity was measured every 4 weeks starting at week 24. The neurologic exam (NEC) was given every 12 weeks and more frequently if there were indications of progressive CNS disease; more comprehensive neuropsychological testing was done whenever NEC or behavioral problems reported by parents or teachers raised concerns. CD4 counts were taken at weeks 4, 8, 12, and every 12 weeks thereafter. HIV RNA was measured every 12 weeks using the

All the above measurements were repeated at the time of drug discontinuation for those stopping drug. Subjects who stopped drug due to study endpoint continued to have height, weight, and head circumference measurements and physical examinations every three months. Subjects who stopped drug due to toxicity continued to have the same measurements as those on drug until they reached a study endpoint. Then they switched to the same schedule as subjects who stopped due to study endpoint.

1.4.2 Assessment of Treatment Effects

Disease progression was defined as the time to the first of any three events: 1) development of new CDC category C diagnosis or death, 2) inadequate weight growth velocity, or 3) deterioration in neurological or neuropsychological assessments.

1.5 Summary of Statistical Analysis

Analyses in the applicant's report focus on the comparison of 3TC/ZDV to ddI because enrollment in the ZDV/ddI arm was discontinued as a result of the findings of trial ACTG 152. The protocol for this trial called for discontinuation of the poorer arm from ACTG 152 when that trial's results were available. All analyses were intent-to-treat (ITT) analyses which excluded subjects enrolled in the ddI/ZDV arm and subjects who did not receive treatment. The analyses use the visit data through 3-12-

97 (i.e. through the visit scheduled for the period 2-12 to 3-12) and events occurring through 4-4-97 and reported by 4-30-97.

Waiting time analyses used Kaplan-meier curves, log-rank tests, and Cox regressions, stratified by age category. Where all events occurred in one age stratum, stratified analyses were not done. Continuous variables were compared by the Van Elteren test and categorical variables were compared by Cochran-Mantel-Haenszel tests. Both were stratified by age stratum.
using all patients with confirmed HIV-1 infection who were assigned to a treatment. For the purposes of this supplement, the applicant regarded only the ddI and 3TC+ZDV arms as relevant and presented only the comparison between those two arms.

2. Summary of Applicant's Results

2.1 Efficacy

Enrollment in the ddI/ZDV control arm was stopped on May 16, 1996, on the basis of results from ACTG 152, using the last of the four criteria specified in the protocol. The discontinued arm showed more efficacy than did the ddI monotherapy but the increase was small and not statistically significant. The ddI monotherapy had a better cost and convenience and better, but not statistically significantly better, safety profile and was elected to continue on that basis.

The time to the earliest of progression, inadequate growth velocity, or death was statistically significantly shorter in the ddI control arm than it was in the 3TC/ZDV arm. The log rank statistic, stratified by age, for this comparison had a nominal p-value of .0005 (unadjusted for multiple looks). Table 2.1 A shows the breakdown of the various clinical endpoints by type and arm.

TABLE 2.1 A
PRIMARY ENDPOINTS
Deaths after Progression in Parentheses

	3TC/ZDV	ddI	ZDV/ddI
In Modified ITT Subset	236	235	125
Primary Endpoint	15	39	14
Death	2	12	3
Physical Growth Failure	7*	9*† (1)	5
Clinical/Neurological Deterioration	5* (1)	12* (2)	5
CDC Clinical Dx Category C	2	8† (1)	1

*,† one patient had 1st progression simultaneously in each marked category

In this table, one physical growth failure on ddI monotherapy and one neurological deterioration on ZDV/ddI occurred after 4-4-97, the cutoff point for interim analysis.

The applicant also compared the two treatment arms separately for subjects < 3 and ≥ 3 years of age. They found a statistically significantly lower risk of progression on 3TC/ZDV in the younger stratum (p=.0001) but not in the older stratum (p=.59). These p-values are unadjusted for interim looks at the data. The applicant also assessed the treatment effect adjusting for independent prognostic information, using Cox regressions with age, race, CDC immunological and clinical categories as covariates. The results of these analyses are given in table 2.1 B. Confidence levels are unadjusted for potential multiple looks at the data. The FDA statistical reviewer cannot reproduce the result including covariates.

TABLE 2.1 B
COX REGRESSIONS ON TIME TO DEATH/PROGRESSION

	Hazard	95% Confidence Limits	
Model	Ratio	Lower	Upper
Treatment only	.37	.20	.67
All Covariates	.27	.15	.50

The applicant also examined changes in CD4 count from baseline to week 36-48. There was a statistically significantly higher increase with 3TC/ZDV (mean = 113, sd = 616) than with ddI monotherapy (mean = -31, sd = 421). The unadjusted p-value for testing the difference was .012.

The applicant did notice the lack of consistency between trial ACTG 152 and the current trial. Specifically, ACTG 152 found ZDV/ddI and ddI to have comparable efficacy. The current trial showed both 3TC/ZDV and ZDV/ddI to be superior to ddI monotherapy. The applicant was unable to suggest any factor which would account for a real difference in treatment effects between trial ACTG 152 and the control arms of the current trial. They suggested only that there was sufficient uncertainty in the ACTG 152 results and in the ZDV/ddI arm of this trial that the observed differences may be mere random variation.

3. Summary of Applicant's Conclusions

The applicant concluded that 3TC/ZDV was more effective than, and at least as safe as ddI monotherapy in therapy-naive children with HIV-1. This combination therapy is also a good candidate for combination therapy with protease inhibitors.

4. Statistical Reviewer's Comments and Analyses

The study suffers from several problems. First, the applicant conducted the analyses treating subjects lost to follow-up as if they had been censored at the time of loss. The FDA has consistently advised applicants that loss to follow-up is informative censoring while standard time to event procedures such Kaplan-Meier, log-rank tests, and Cox regression require non-informative censoring. The FDA reviewer has therefore repeated the analysis treating all loss to follow-up as failures at the time of loss. Section 4.1 shows that in a two-arm trial, the trial could have legitimately been stopped with a global p-value $\approx$ .04 (after adjusting for interim analysis) at the time it actually was stopped.

Second, the FDA clinical reviewer has requested exploratory analyses of possible treatment interactions with baseline severity of disease. These analyses will be presented in section 4.2. It will be seen that there are noticeable treatment-covariate interactions. The 3TC+ZDV therapy produced much lower progression rates than did ddI monotherapy for those subjects with severe baseline CDC category or severe baseline immunological category. In the none, mild, and moderate categories, the observed difference was still favorable to 3TC+ZDV but was much less in magnitude.

Third, there are concerns about the comparison between the ddI+ZDV arm and the 3TC+ZDV arm. The former arm was stopped early in this trial on the basis of the last stopping criterion listed in the protocol. It was found to show subjectively better overall cost, convenience, and safety in ACTG 152. It was not found, in ACTG 152, to be inferior to ddI in efficacy. Section 4.3 shows the comparison in this trial of 3TC+ZDV to ddI+ZDV. It is shown there that the conclusions of trials ACTG 152 and this trial (ACTG 300) are incompatible with respect to the relative rankings of the three therapies. Specifically, the applicant concluded that ACTG 152 showed ddI monotherapy to be equivalent to ddI+ZDV on efficacy and to be superior to it on with respect to safety and convenience. In contrast, trial ACTG 300 shows ddI+ZDV to be at least as effective as 3TC+ddI and both ddI+ZDV and 3TC+ddI to be more effective than ddI monotherapy.

Fourth, the applicant used a complicated randomization scheme, which altered the assignment of subjects to prevent baseline imbalance. The applicant was unable to provide a coherent description of the randomization scheme used. The applicant did not believe that there was a center-treatment interaction, as demonstrated by their not including center as a covariate in their analyses. There was no reason for including an adjustment for center in the design.

Finally, there is an appeal to data external to the trial required to conclude that the 3TC is actually conferring a benefit. The internal evidence of this trial supports only the conclusion that 3TC+ZDV is superior to ddI monotherapy and that ddI+ZDV may be superior to ddI monotherapy as well. There is no evidence in this trial that ZDV monotherapy would not have had the same effect as 3TC+ZDV. The internal evidence is equally compatible with the conclusion that ZDV monotherapy is better than ddI monotherapy and slightly inferior to ddI+ZDV but that 3TC is completely ineffective. A conclusion that this trial has demonstrated an effect of 3TC can only be drawn from external that ZDV monotherapy is inferior to ddI monotherapy.

4.1 Alternate Handling of Loss to Follow-up:

The DSMB report states that the applicant conducted the first interim analysis based on endpoints available through 4-4-97 with corrections up to 4-30-97 and modifications from the endpoint review committee up to 5-23-97. The FDA reviewer interprets this to mean the following: 1) any endpoint occurring before 4-4-97 is counted as an event; any endpoint occurring after that up to the date of the last report is not included, 2) all times on study are to be measured as of 4-4-97, 3) subjects who had made all required visits up to 3-7-97 are considered to be still under observation. Table 4.1 A shows the status of subjects at the time of the interim analysis for this trial.

TABLE 4.1 A
CLASSIFICATION OF SUBJECTS AT TIME TO FINAL ANALYSIS

	3TC+ZDV	ddI	ddI+ZDV
Number in ITT	236	235	125
Ongoing	203	183*	99#
Missed Last Visit†	11	10	6
Lost to Contact	7	5	7
Disease Progression	15	37	13
Death	2	11	3
Phys Growth Failure	7	6	5
Clin/Neur Deterioration	4	12	4
CDC Dx Category C	2	8	1

* Subject 105193 had Phy Gr Fail on May 7, 1997
# Subject 660077 had C/N Det on April 8, 1997
† Last seen between March 3 and March 6, 1997

In the analysis reported in the DSMB report, the applicant counted 15 failures in the 3TC+ZDV arm and 38 failures in the ddI arm, incorrectly counting a failure event on ddI that occurred a month after the database was closed for the interim analysis. All other subjects were counted as censored at the time of the last visit. Using this classification, the applicant reported a log-rank test which exceeded the stopping rule for an interim analysis with an adjusted level of .05.

The applicant also committed two other bookkeeping errors. First, the DSMB report shows 14 failures on the ddI+ZDV arm by incorrectly counting a failure that occurred on May 7, 1997. This arm was not involved in the primary analysis so this did not affect actions. Second, the applicant misquoted the DSMB report and counted patient 105231 as a 39th failure on ddI. The DSMB report showed that this patient enrolled with lymphoma and was excluded from the modified ITT analysis as an entry criterion violation. The applicant's final report, by including this patient, has 236 rather than 235 patients on ddI.

It has been standard practice for the FDA to consider all lost to follow-up as failures at the time of loss, not as uninformative censoring. The FDA reviewer reanalyzed the data, using loss to follow-up as failure but with the same interim analysis schedule as the applicant. The simple failure rates for the different analyses, obtained from table 4.1 A, are given in table 4.1 B.

TABLE 4.1 B
SIMPLE FAILURE RATES AT TIME TO FINAL ANALYSIS

	3TC+ZDV	ddI	ddI+ZDV
Number in ITT	236	235	125
Applicant's Analysis	15 (6%)	38 (16%)*	14 (11%)*
FDA Analysis 1	22 (9%)	42 (18%)†	20 (16%)†
FDA Analysis 2	33 (14%)	52 (22%)†	26 (21%)†
FDA Sensitivity Analysis	22 (9%)	37 (16%)†	13 (10%)†

* Failures include misclassified 105193 and 660077
† Failures exclude 105193 and 660077

In the first FDA analysis, all the loss to follow-up is counted as failures (and the two subjects with failures after interim analysis are re-classified as censored at the interim analysis date). In the second FDA analysis, the 11+10+6 subjects who did not have a report from the visit scheduled in the 28 day period from March 7 to April 4 are also counted as failures. As noted in the footnote to table 4.1 A, all of these subjects were seen between March 3 and March 6. The FDA sensitivity analysis classified only the loss to follow-up on 3TC+ZDV as failures; the loss to follow-up on the other arms were counted as censored. This analysis also counted 11 subjects who missed only their visit between March 7 and April 4 as censored. The results of these analyses are summarized in table 4.1 C. These results are based on age stratified log-rank tests, adjusted for 4 possible analyses (3 interim and 1 final). The p-values in this table have been adjusted for potential multiple looks at the data and thus may be interpreted in the usual way. (Mathematical details of the adjustment are given in appendix 1.)

TABLE 4.1 C
INTERIM ANALYSIS CONCLUSIONS FOR VARIOUS ASSUMPTIONS

	Failure Rates		
	3TC+ZDV	ddI	Adjusted P-values
Applicant's Analysis	6%	16%	.021
FDA Analysis 1	9%	18%	.025
FDA Analysis 2	14%	22%	.032
FDA Sensitivity Analysis	9%	16%	>.25

It can be seen from these analyses that the applicant's conclusion of statistically significant differences between the 3TC+ZDV arm and the ddI arm is supported even if subjects who are lost to follow-up or missed their last scheduled visit are

counted as failures. The analysis which assumes a differential failure rate among subjects lost to follow-up does not produce statistically significant results. This reflects that half as many subjects were lost as had events in the 3TC+ZDV arm. This suggests that the estimate of risk of progression in the 3TC+ZDV arm is not robust; it could vary by as much as 50% depending on assumptions about the unobserved fate of the lost subjects.

One may also consider changes in the Kaplan-Meier curves under various methods of handling the loss to follow-up. Figures 4.1 i and ii show the Kaplan-Meier survival curves for all three arms with loss treated as censoring and as failure, respectively. Figures 4.1 iii and iv show the (non-simultaneious) 95% confidence limits for the difference between the survival curves of 3TC/ZDV - ddI under the same two assumptions. One can see that the results do not change dramatically from one figure to the next.

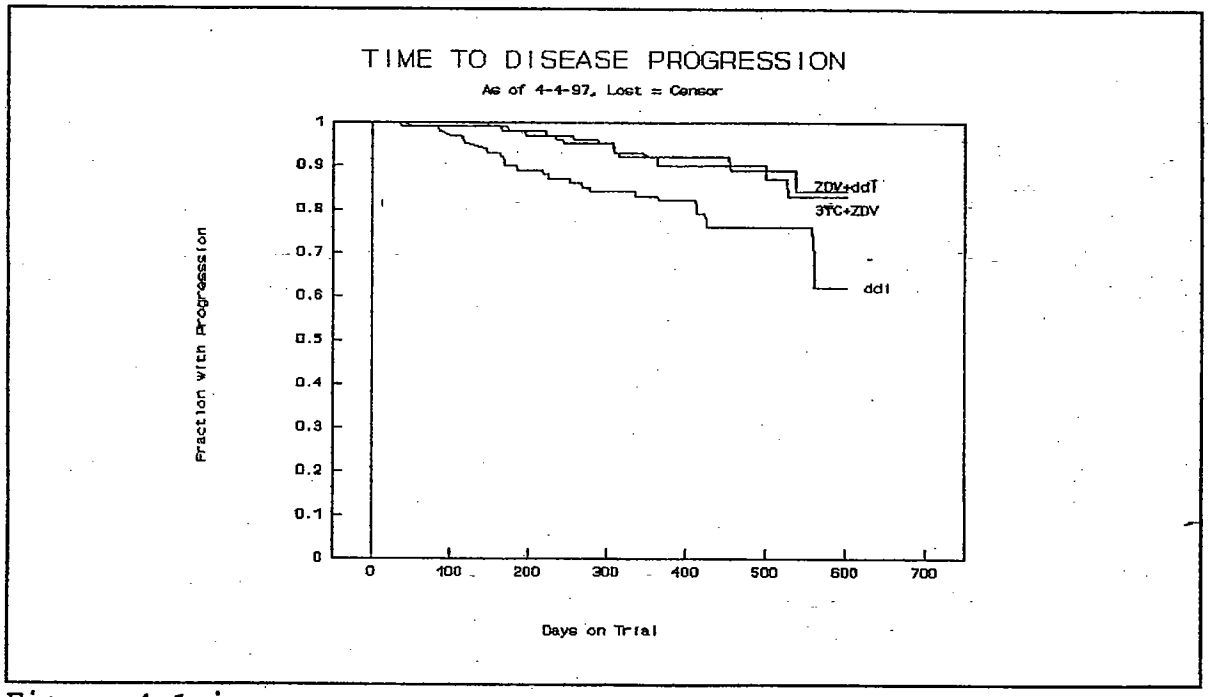


Figure 4.1 i

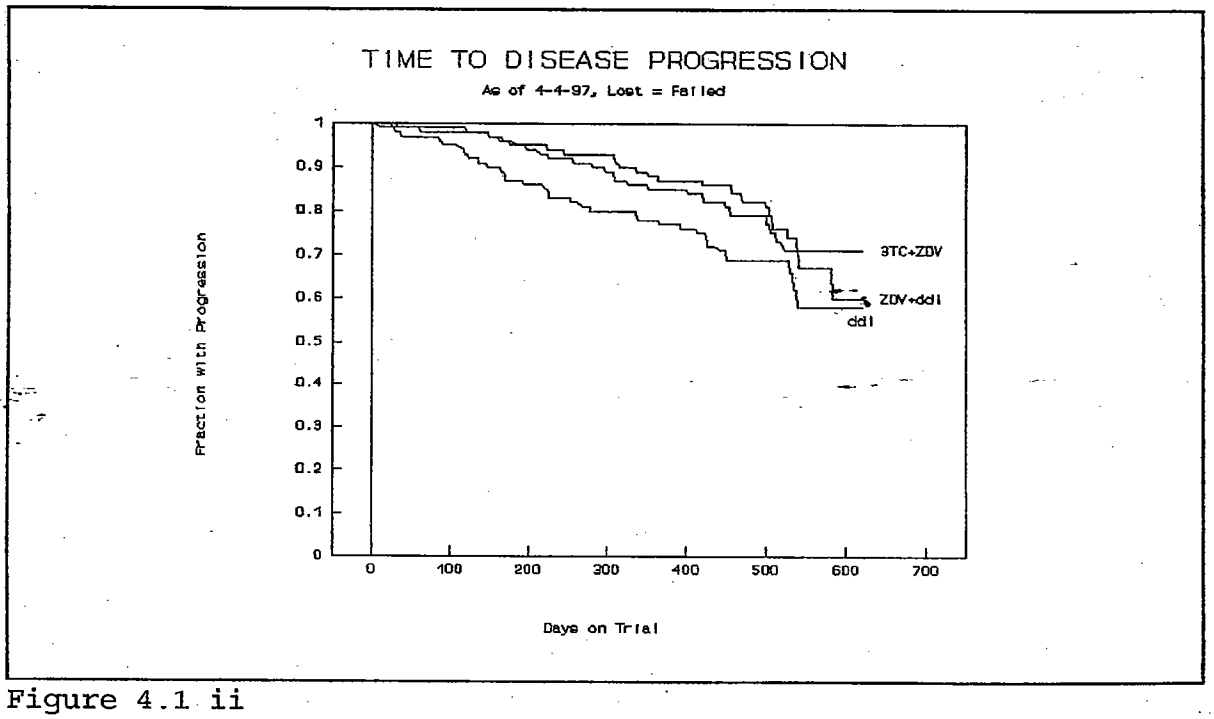


Figure 4.1 ii

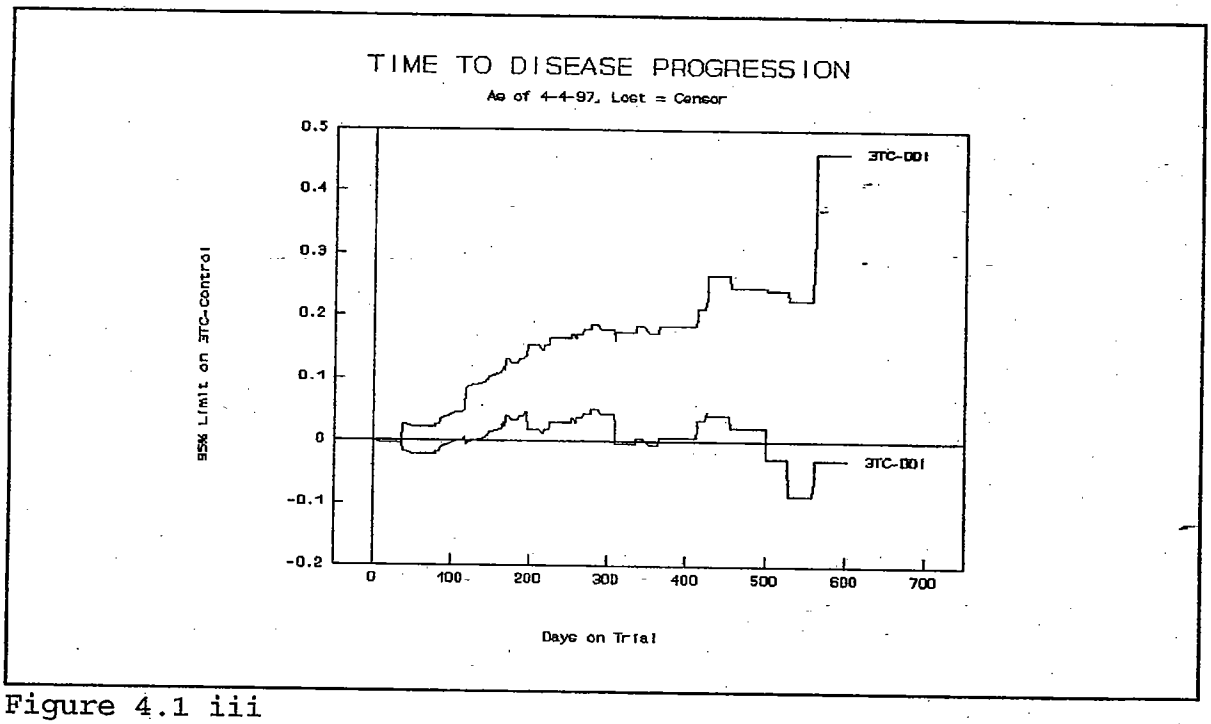


Figure 4.1 iii

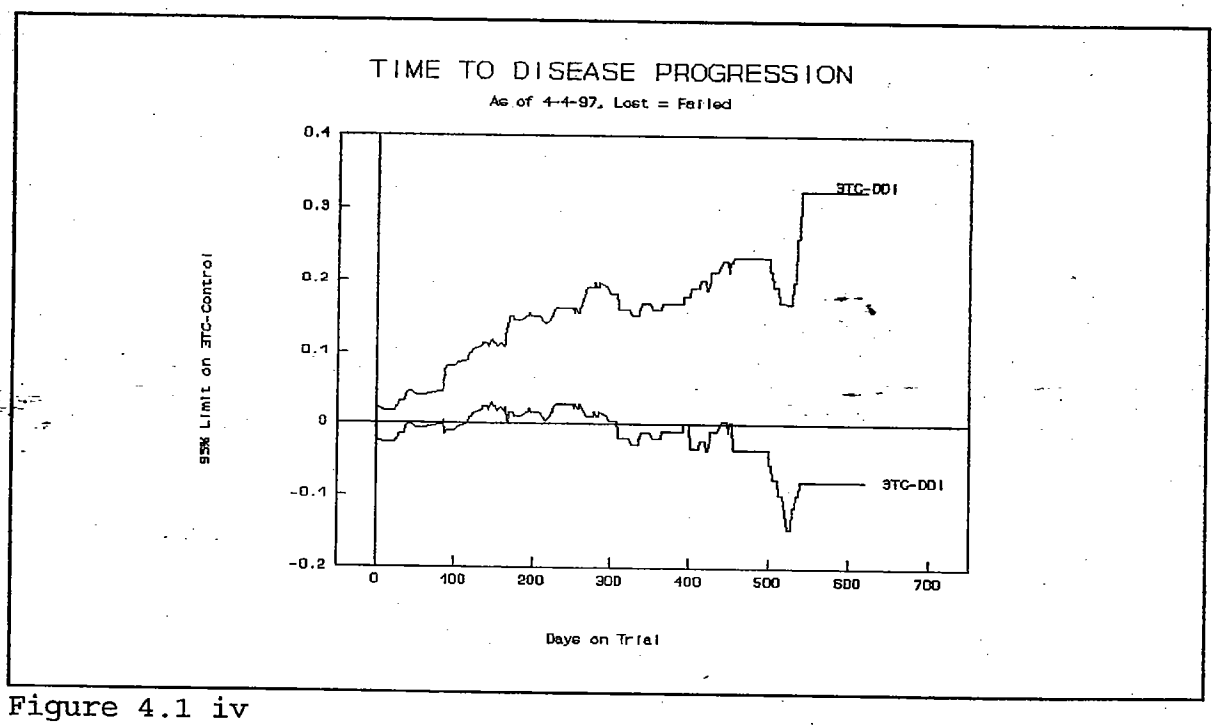


Figure 4.1 iv

4.2 Treatment Interactions with Baseline Covariates

The FDA clinical reviewer identified two baseline covariates as potentially having important interactions with treatment. These covariates were baseline levels of CDC disease category and of immunological suppression (CDCCAT and IMMCAT). Figure 4.2 i shows the histograms of these two baseline covariates across the two primary treatment arms.

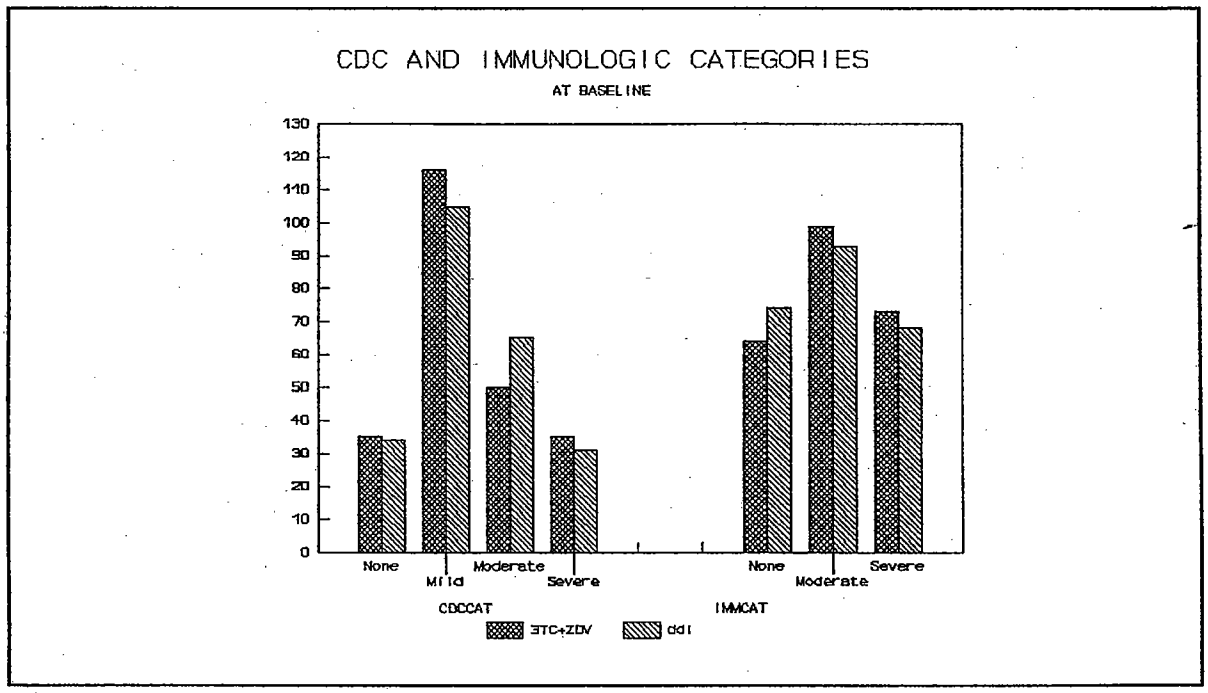


Figure 4.2 i

The FDA statistical reviewer compared both the risk of ever having progression and the Cox modelled hazard ratio for time to progression between the ddI and 3TC/ZDV arms in each of the seven levels of these two covariates. Both covariates showed a conspicuous interaction with treatment. For both covariates, the 3TC/ZDV arm was estimated to be slightly superior to the ddI arm in all categories. However, the 3TC/ZDV arm had a much larger estimated superiority over the ddI arm in the severe category of each covariate than it did in the none, mild, or moderate categories. This pattern was consistent for both occurrence of progression and for time to progression, and both with lost subjects treated as censored and with lost subjects treated as failed.

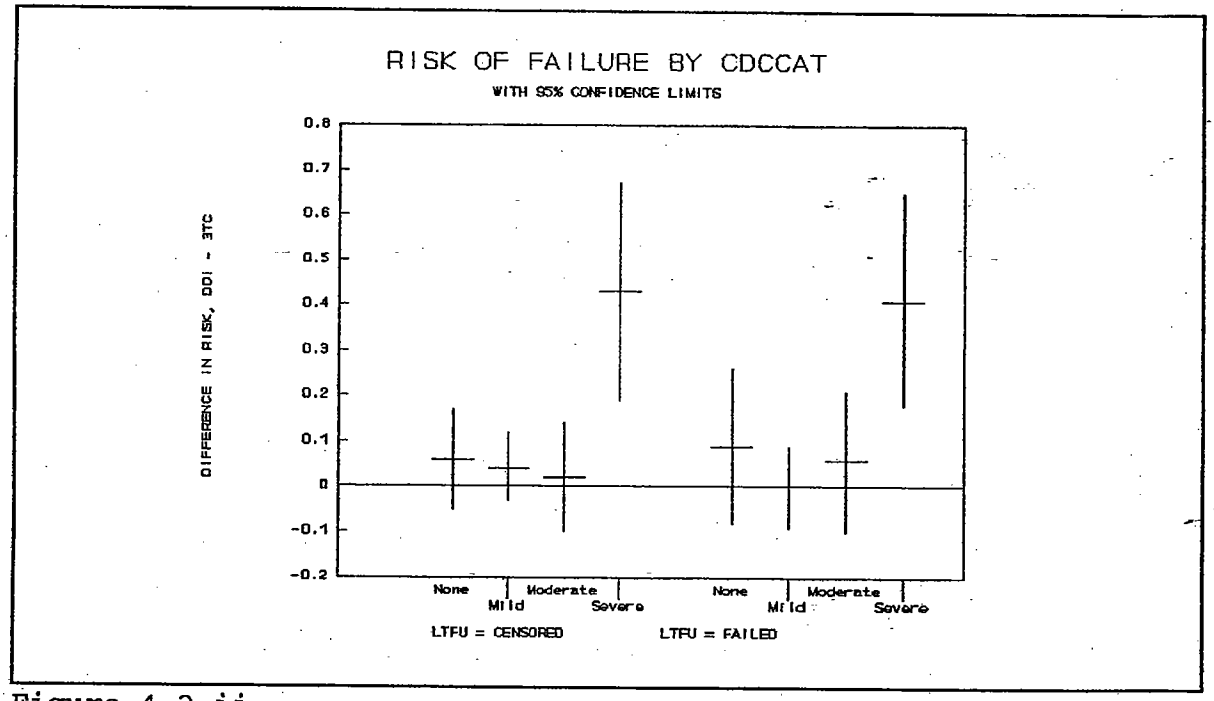
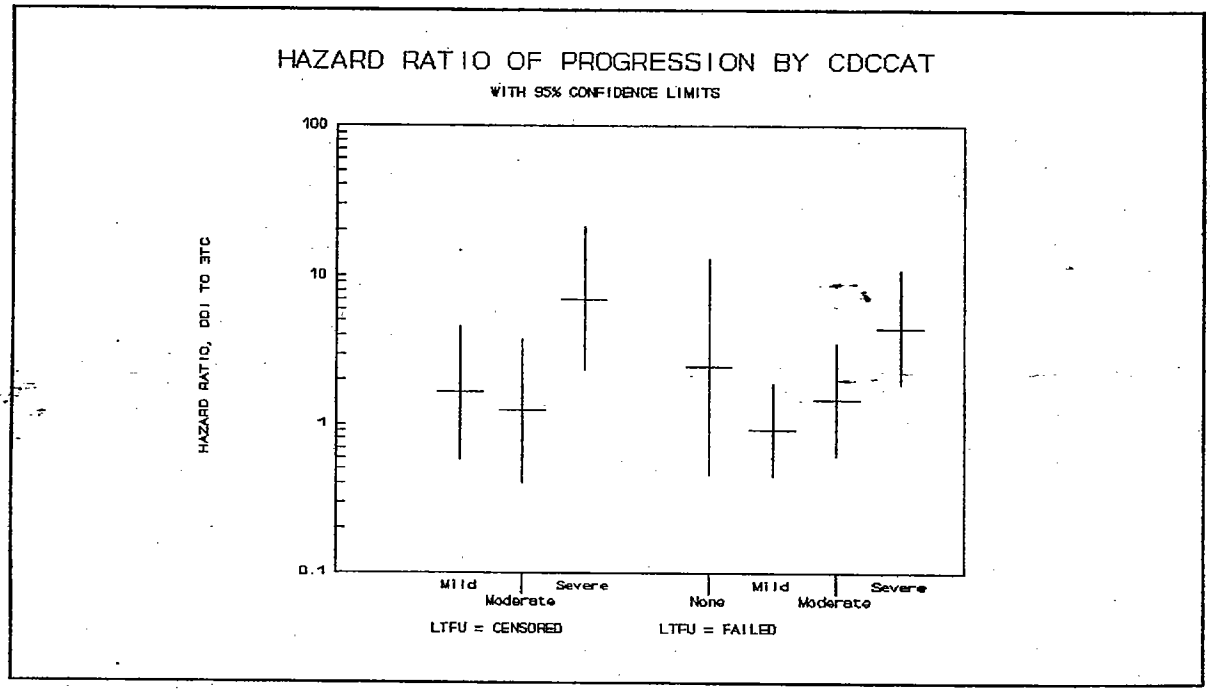

RISK OF FAILURE BY CDCCAT
WITH 95% CONFIDENCE LIMITS
DIFFERENCE IN RISK, DDI - 3TC
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
None
Mild
Moderate
Severe
None
Mild
Moderate
Severe
LTFU = CENSORED
LTFU = FAILED

Figure 4.2 ii


HAZARD RATIO OF PROGRESSION BY CDCCAT
WITH 95% CONFIDENCE LIMITS
HAZARD RATIO, DDI TO 3TC
100
10
1
0.1
Mild
Moderate
Severe
None
Mild
Moderate
Severe
LTFU = CENSORED
LTFU = FAILED

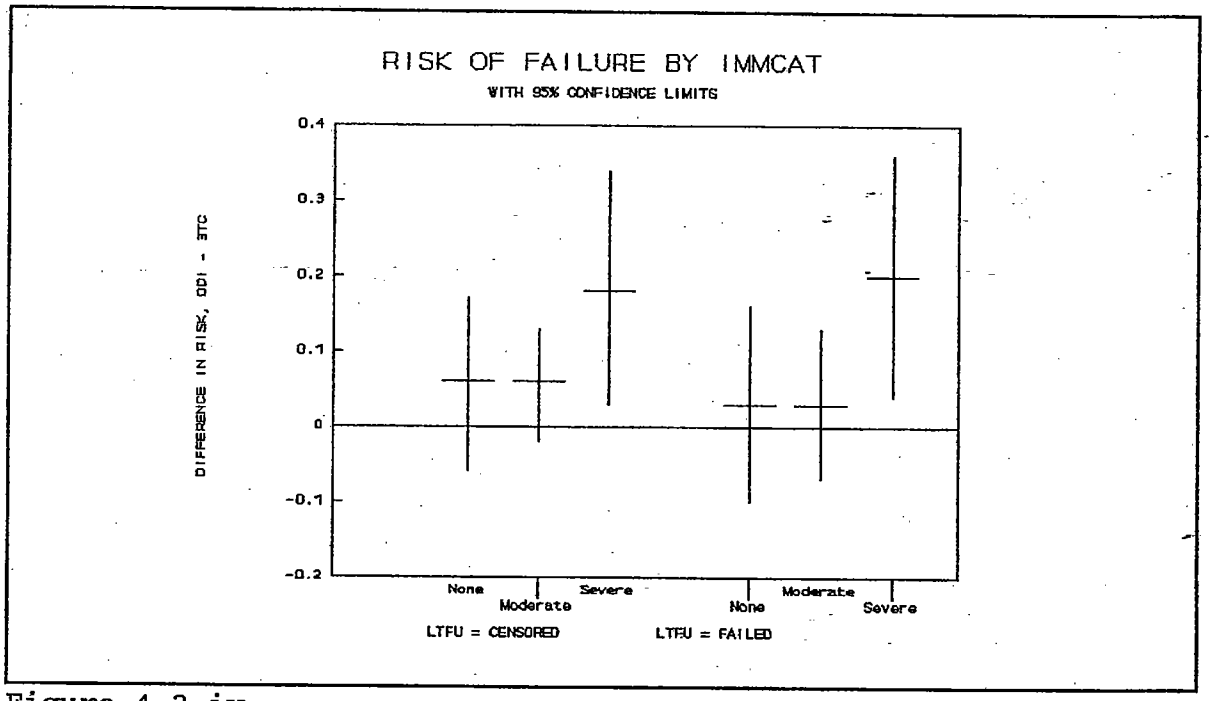


Figure 4.2 iv

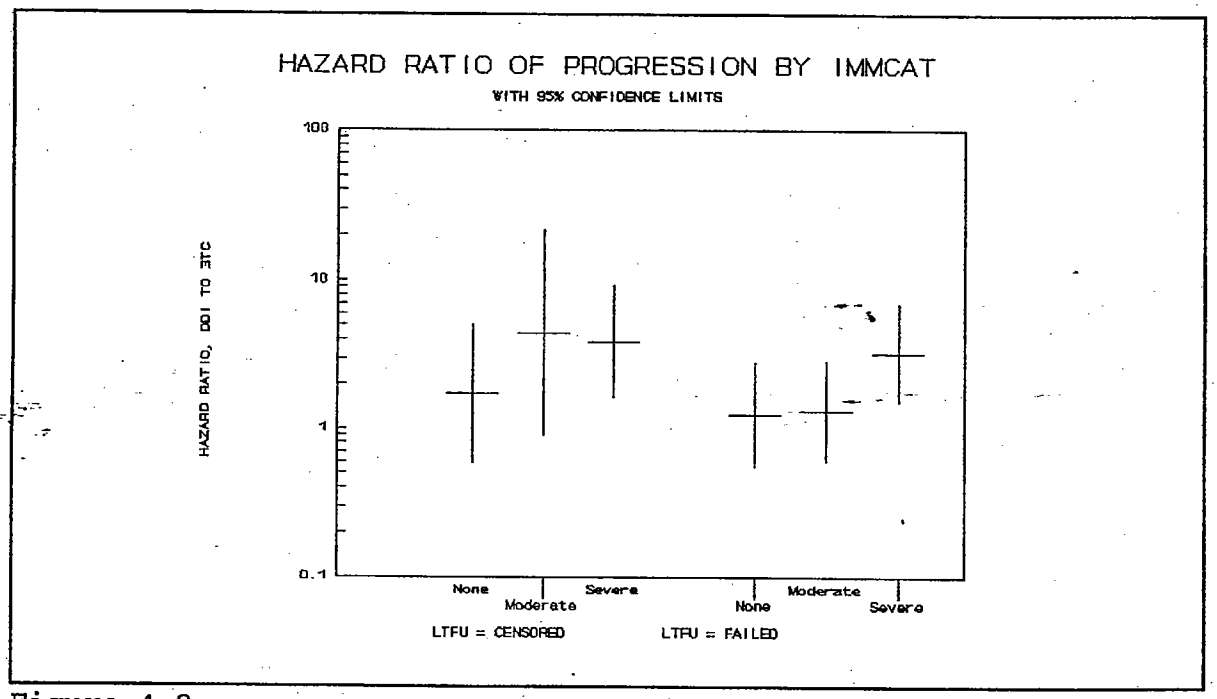


Figure 4.2 v

Figure 4.2 ii show the point estimates and 95% confidence intervals for the difference in risk of progression between ddI and 3TC/ZDV in each baseline CDC category, for lost treated as both censored and failed. Figure 4.2 iii shows the same thing for the hazard ratio of progression, estimated by Cox modelling, for ddI relative to 3TC/ZDV in the same groups. (Note that the vertical scale here is logarithmic.) With respect to this latter figure, one should note that, when lost subjects were treated as censored, the 3TC/ZDV arm had no progressions with baseline CDC category = None. Consequently, there is no finite estimate of the hazard ratio in this category.

Figures 4.2 iv and v are the same as figures 4.2 ii and iii, except that baseline Immunologic category is now used instead of baseline CDC disease category.

In all four figures, one can see the same pattern: the severe category shows a large treatment effect (in favor of 3TC/ZDV); the other categories show a much smaller effect. This estimated effect is always positive but never convincingly so. Formal testing in each subgroup is problematic because of multiple inference and lack of power but the pattern is nonetheless strongly suggestive of the treatment effect being confined to the most severely ill group of subjects.

Because of the unorthodox randomization used by the applicant, it becomes necessary to guard against potential confounding with covariates. The FDA statistical reviewer has re-analyzed the data, using log-rank tests stratified by both age and baseline severity as stratum variables. The results are given in table 4.2 A with technical details in appendix A.1.

TABLE 4.2 A

LOG-RANK TESTS STRATIFIED BY AGE AND BASELINE SEVERITY

Analysis	P-values (Adjusted for Interim Analysis)	
Stratified by Age and	CDCCAT	IMMCAT
Applicant's Analysis	.03	.03
FDA Analysis 1	.048	.04
FDA Analysis 2	.048	.052

One can see that the overall finding is not an artifact of confounding with either of these two baseline covariates. There remains a statistically significant difference, even after

adjusting for either of the baseline health variable, for loss to follow-up, and for the use of an interim analysis.

The FDA statistical reviewer also conducted analyses using sex and race/ethnicity as the second covariate. Briefly, no evidence of treatment interaction with either of these covariates was found.

4.3 Comparison of the 3TC-ZDV arm to the ddI-ZDV arm

The applicant concluded, on the basis of ACTG 152, that ddI monotherapy was as effective as ddI-ZDV combination therapy and more convenient. Therefore, the ddI-ZDV arm was discontinued early in this trial and not analyzed further. The FDA reviewers note that this arm was continued until accrual was half over and that, consequently, enough subjects were recruited to this arm to permit meaningful comparisons to be made even if they were not intended in the protocol. In particular, the FDA reviewer notes that the ddI-ZDV arm in this trial appears to be superior in efficacy, not equivalent to the ddI monotherapy. If one conducts a formal comparison of the two control therapies by log-rank test, one finds that the ddI-ZDV arm was superior to the ddI monotherapy arm with a p-value of .095, adjusted for interim analysis and treating loss to follow-up as failure. (See appendix A.1 for technical details of this computation.)

Furthermore, the ddI-ZDV arm appeared to be as effective as, and possibly superior to, the 3TC-ZDV arm. One can see this in figures 4.3 i and ii. Figure 4.3 i shows the Kaplan-Meier curves for time to loss, disease progression, or death for the first 350 days on trial of the two arms; figure 4.3 ii shows the (non-simultaneous) 95% confidence limits for the survival rate on 3TC-ZDV minus the rate on ddI-ZDV. One can see in figure i that the 3TC-ZDV is consistently estimated to be slightly inferior to ddI-ZDV on percent surviving. In figure ii one can see that, with 95% confidence at each time point, the 3TC-ZDV is never more than 6% better than ddI-ZDV on percent surviving and may be as much as 12% worse.

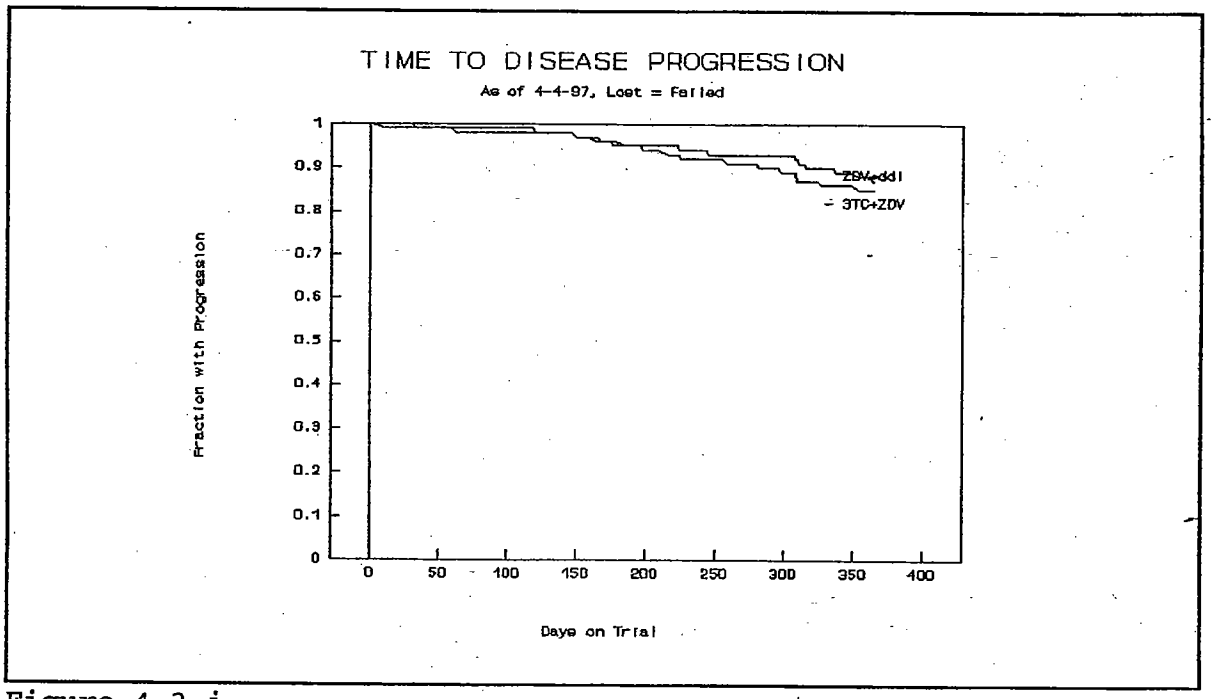


Figure 4.3 i

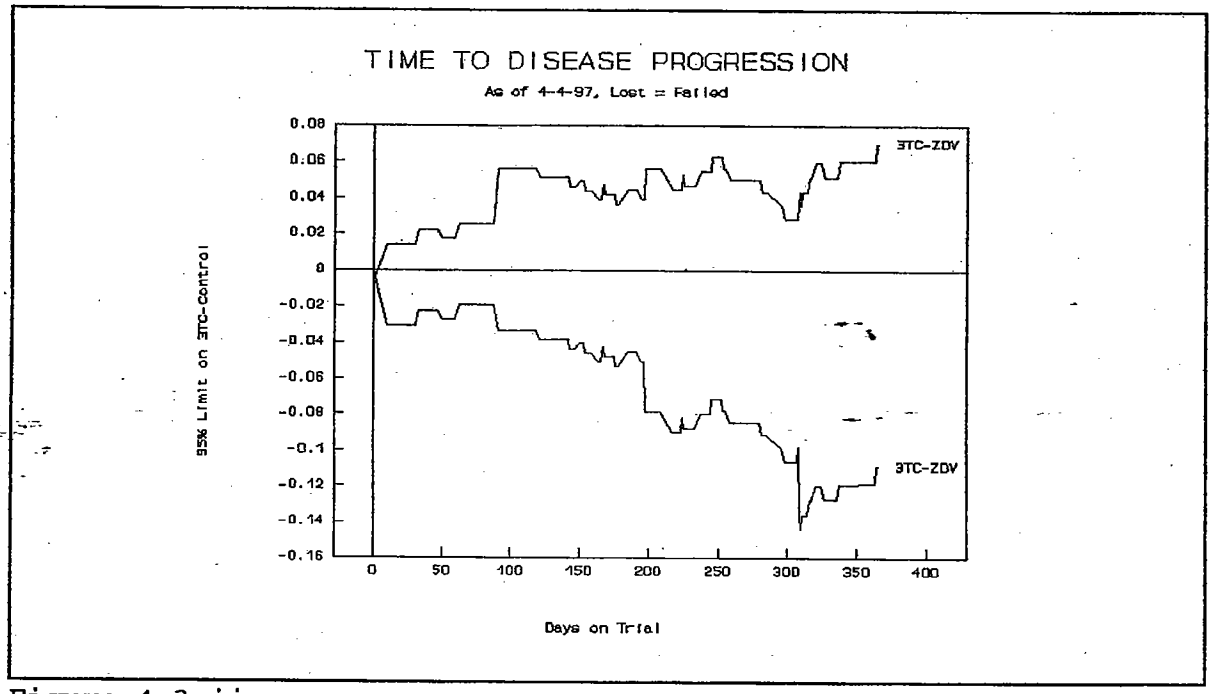


Figure 4.3 ii

4.4 Re-randomization Tests

The applicant used an unnecessarily cumbersome method for assigning subjects to trials. This method resulted in more subjects having assignments which were determined entirely by assignments of earlier recruits rather than by new random coin tosses than would be the case in a simple randomized block design. The added complexity of the applicant's assignment scheme was intended to achieve only an unnecessary degree of balance among the arms within each investigator.

The consequence of the applicant's non-standard assignment scheme is that standard approximations for the p-value cannot be trusted to be valid. The applicant's use of the log-rank test implicitly assumes that responses of subjects on the same arm and in the same age stratum are identically distributed random variables. There is no satisfactory method to verify this assumption.

There is a gold standard technique that may be applied to such assignment schemes without requiring untestable assumptions of identically distributed responses. This method is to repeat the limited random assignment many (10,000) times, each time getting a different assignment of responses to the two arms. The p-value is the proportion of such new assignments that yield a larger value of the log-rank statistic than did the observed assignment. The results of such re-assignments are given in table 4.4 A. The p-values here are, as in previous tables, already adjusted for the effects of interim looks at the data. Details of how this was done are in appendix A.1.

TABLE 4.4 A
COMPARISON OF P-VALUES: MODEL BASED/ RERANDOMIZATION

	P-values (Adjusted for Interim Analysis)	
	Model-based	Re-Randomization
Applicant's Analysis	.021	.06
FDA Analysis 1	.025	.048
FDA Analysis 2	.032	.031

One can see from this table that the finding that the 3TC+ZDV arm was statistically significantly superior to the ddI control after adjusting for interim looks remains valid after adjustment for the non-standard assignment scheme as well. The strength of the conclusion is slightly weaker: the adjusted p-value for the most credible analysis (FDA analysis 1, loss to follow-up = failure) is .048 rather .025.

5. Statistical Reviewer's Summary

The data presented by the applicant support the claim that 3TC+ZDV combination therapy is statistically significantly superior to ddI monotherapy in children. This claim is robust to adjustments for interim looks at the data, for loss to follow-up, and for the use of a non-standard randomization scheme.

The improvement in duration of progression-free survival is found mainly in subjects with poorer conditions at baseline, specifically with severe immunologic suppression and/or severe signs/symptoms on the CDC disease scale. The estimated treatment effect in less severely ill baseline groups is smaller, and compatible with a zero effect, but the estimated effect is never less for 3TC+ZDV than for ddI in any subgroup.

The data presented do not support the claim that 3TC+ZDV is superior to ddI+ZDV therapy. If anything, the data are compatible with a one-year progression free survival rate that is 12% higher on ddI+ZDV than on 3TC+ZDV. One should note that this finding is partially contradictory to the finding in trial ACTG 152 that ddI monotherapy and ddI+ZDV were equivalent in efficacy.

As mentioned at the beginning of section 4, this trial presents no direct evidence that 3TC provides any benefit. External evidence that ZDV monotherapy is inferior to ddI monotherapy is needed to conclude that this trial supports 3TC efficacy.

Finally, this trial presents no direct evidence on the possible contribution of 3TC to a therapy including ddI plus a protease inhibitor and/or a non-nucleoside analogue. The applicant's conclusion that 3TC is a good candidate for inclusion in such a regimen is a speculation.

Thomas Hammerstrom

Thomas Hammerstrom, Ph.D.
Mathematical Statistician

Concur: Dr. Flyer OF 3/16/99

cc:
Archival NDA #20-564, #20-596
HFD-530
HFD-530/Dr. Jolson
HFD-530/Dr. Birnkrant
HFD-530/Dr. Dempsey
HFD-530/Dr. Crescenzi
HFD-530/Dr. Murray
HFD-530/Dr. Nguyen
HFD-725/Dr. Flyer
HFD-725/Dr. Hammerstrom
HFD-725/Dr. Huque
HFD-725/Ms. Shores

APPENDIX 1

CALCULATION OF P-VALUES ADJUSTED FOR INTERIM ANALYSIS

The interim analyses reported in sections 2.1 and 4.1 use the Lan-De Mets modification of the O'Brien Fleming boundaries. These boundaries are calculated by assuming a specified level (two-sided .05), a specified maximum number of failures and a specified number of looks at the data. The boundaries are given in the form of unadjusted p-values. The experiment stops when the log-rank test has nominal p-value greater than the boundary p-value. The nominal p-value at the time of stopping is not adjusted for interim looks and cannot be interpreted in the same way as the single p-value obtained at the end of a study with no interim analyses. The adjusted p-value, which does have the same interpretation as the single p-value in a study without interim looks (= the probability of data at least as favorable to the test arm as that actually seen, given the null hypothesis is true) is computed as follows.

If the nominal p-value at the time of stopping is exactly equal to the boundary value, then the adjusted p-value is exactly equal to the level of the procedure, .05. If the nominal p-value at the time of stopping is smaller than the boundary value, then one finds the level of the test whose boundary value exactly equals the nominal p-value observed, keeping all other parameters in the design fixed. The level of this test is the correct p-value of the data, adjusted for potential multiple looks at the data. The levels of the tests whose boundaries correspond to the observed nominal p-values have to be found by trial and error. Table A.1 A gives the results needed to compute the adjusted p-values given in table 4.1 C above.

TABLE A.1 A

CALCULATIONS OF P-VALUES ADJUSTED FOR INTERIM LOOKS

Analysis	Failures Observed	Level of Test	P-values Boundary	Observed P-value SAS	SXACT	Rerandom
Applicant's	52	.01	.00014	.0005	.0006	.0039
		.02	.00053			
		.03	.00113			
		.05	.0029			
		.06	.0041			
FDA 1	64	.02	.0018	.0021	.0029	.0078
		.025	.0026			
		.03	.0034			
		.04	.0054			
		.045	.0065			
		.05	.0077			
		.09	.0193			
		.10	.0228			
FDA 2	85	.03	.0123	.0123	.0133	.0125
		.032	.0133			
		.035	.0148			
		.045	.0203			
		.05	.0231			
		.055	.0260			
Sensitivity	76	.15	.068	.1399	.1637	Not Done
		.25	.136			
		.05	.0153			

In this table, it was always assumed that 109 was the maximum number of failures and that there would be 4 looks with O!Brien-Fleming boundaries. The 109 maximum was the same value used in the applicant's design and is calculated to give 80% power to detect a difference in median time to failure between 74.5 on control and 130.15 on test, using four looks at level .05 and a maximum of 620 subjects recruited at the rate of 35 per unit time.

The computations of Lan-DeMets boundaries was done using the EAST program. The computation of observed nominal p-values was done using the Log-rank test, Monte Carlo option, of the Statxact program and by a re-randomization algorithm due to Paul Flyer,

Yulan Li, and Tom Hammerstrom of the FDA. Nominal p-values as computed by the PROC LIFETEST of SAS 6.12 are also given in the table. The nominal and adjusted p-values using SAS are slightly smaller than those using Statxact but not consequentially so. Both SAS LIFETEST and Statxact give results based on the assumption of identically distributed responses in each arm * age stratum. The SAS algorithm uses an asymptotic distribution based on assuming the responses are exponentially distributed; the Statxact algorithm merely assumes they all have the same unspecified distribution. The re-randomization algorithm makes no assumption at all about the distribution of the responses but rather assumes that the randomness of the final test statistic comes from the randomness of the assignments.

The Lan-DeMets boundaries depend only on the random distribution of the final test statistic and are the same, regardless of how that distribution is derived. One may notice that the boundaries become less stringent as the number of observed failures at the time of the first look gets larger. This is responsible for the somewhat paradoxical result that the adjusted p-values in table 4.4 A get smaller as one goes from the applicant's analysis (loss to follow-up = censored) to the FDA analysis 1 (loss to follow-up = failed) to the FDA analysis 2 (loss to follow-up plus missing or late last visit = failed), even though the relative risk of failure for 3TC+ZDV gets larger relative to ddI. One can see from table A.1 A that the nominal p-values at the time of the first look get larger with relative risk increasing toward unity but that this is offset by the decreasing stringent borders used for adjustment as the total number of failures increases toward the limit of 109.

In section 4.2, the FDA reviewer reported the results of log-rank tests stratified by age category crossed with either baseline CDC disease category or baseline Immunologic category. The nominal p-values, computed from Statxact using these two possible strata, are given in table A.1 B.

TABLE A.1 B

LOGRANK TEST Two-sided p-value: Asymptotic / Monte Carlo

Stratum	Applicant	FDA 1	FDA 2
AGECDC	.0012	.0091	.0235
	.0010	.0074	.0215
AGEIMM	.0008	.0062	.0231
	.0013	.0056	.0246

The adjusted p-values reported in section 4.2, table 4.2 A, were obtained by using the Monte Carlo nominal p-value estimates from this table and comparing them with the levels of the tests in table A.1 A.

The results of log-rank tests comparing the ddI monotherapy arm to the ddI-ZDV arm are given in table A.1 C. These are the nominal p-values from SAS PROC LIFETEST. Adjusted p-values, as cited in section 4.3, are obtained from these values and the levels in table A.1 A.

TABLE A.1 C

NOMINAL P-VALUES, ddI vs ddI-ZDV

Method	Log-rank p-value
Applicant's (LTFU = censored)	.0031
FDA 1 (LTFU= failed)	.0219

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-564 / S-007
20-596 / S-007

MICROBIOLOGY REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

MEMORAMDUM

Food and Drug Administration
Rockville MD 20857

NDA: 20-564/S-007
20-596/ S-007

Drug: Epivir® Tablets

Sponsor: Glaxo Wellcome

The changes made to the microbiology section of the label are acceptable.

Narayana Battula

Narayana Battula, Ph.D.
Microbiologist

Concurrence:
HFD-530/Assoc. Dir. N. Dempsey Signature 3/16/99 Date
HFD-530/TLmicro N. Battula Signature 3/15/99 Date
Distribution:
HFD-530/Original IND
HFD-530/Division File
HFD-530/MO
HFD-530/Pharm
HFD-530/Chem
HFD-530/TLMicro
HFD-530/Reviewer Micro
HFD-530/CSO, Crescenzi, T

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-564 / S-007
20-596 / S-007

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA : 20564
TYPE : Supplement SE1-007
DRUG : Lamivudine
APPLICANT: GlaxoWellcome

Reviewer: Prabhu Rajagopalan, Ph. D.
SUBMISSION DATE : 03-30-98
DATE RECEIVED : 04-02-98
DRAFT REVIEW : 03-17-99
FINAL REVIEW : 03-18-99

This supplement primarily deals with the addition of pediatric information in the Indications and Usage section of the label.

The Sponsor has submitted one study (NUCA2005) to Section 6 of the NDA. In this study, the safety, toxicity and efficacy of combinations of lamivudine, zidovudine and didanosine were examined in pediatric HIV-infected patients. This clinical trial and another trial (NUCA2002) in which pediatric patients were studied have been reviewed by Dr. Davit under the original NDA submission. In the current submission, the Applicant has proposed to move the relevant information from the *Precautions: Pediatric use* to the *Clinical Pharmacology* section of the label. Other minor changes proposed by the Applicant are consistent with the label for Combivir®. These changes are acceptable.

The following sentence has been added regarding the dose for pediatric patients with renal impairment: "Although there are insufficient data to recommend a specific dose adjustment of EPIVIR in pediatric patients with renal impairment, a reduction in the dose and / or an increase in the dosing interval should be considered." This is acceptable.

R. Prabhu 3/18/99

Prabhu Rajagopalan, Ph. D.
Reviewer, Pharmacokinetics
Division of Pharmaceutical Evaluation III, OCPB

Concurrence: Kellie S. Reynolds 3/18/99
Kellie S. Reynolds, Pharm. D.
Team Leader, Antiviral Drug Products Section
Division of Pharmaceutical Evaluation III, OCPB

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-564 / S-007
20-596 / S-007

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

ITEM 13 PATENT INFORMATION
pursuant to 21 USC Section 355
for
Epivir® Tablets in Pediatric Patients -- NDA 20-564

Active Ingredient:	Lamivudine
Dosage Form:	Tablets
Strength of Drug Product:	150mg of lamivudine per tablet
Route of Administration:	Oral
Applicant Firm Name:	Glaxo Wellcome Inc.
Patent Number:	**5,047,407**
Owner	**BioChem Pharma (IAF Biochem International, Inc.) License owned by Glaxo Wellcome Inc.**
Coverage:	Lamivudine per se, formulations and methods of use
Issue Date:	September 10, 1991
Expiration Date:	February 8, 2009

The Undersigned certifies to the best of his knowledge and belief the above listed patent is valid, claiming lamivudine, the subject of a Supplemental New Drug Application.

12/04/97
Date

Charles E. Dadswell
Registered Patent Attorney
United States Registration No. 35,851

ITEM 13 PATENT INFORMATION
pursuant to 21 USC Section 355
for
Epivir® Oral Solution in Pediatric Patients -- NDA 20-596

Active Ingredient:	Lamivudine
Dosage Form:	Solution
Strength of Drug Product:	10mg/mL
Route of Administration:	Oral
Applicant Firm Name:	Glaxo Wellcome Inc.
Patent Number:	**5,047,407**
Owner	**BioChem Pharma (IAF Biochem International, Inc.) License owned by Glaxo Wellcome Inc.**
Coverage:	Lamivudine per se, formulations and methods of use
Issue Date:	September 10, 1991
Expiration Date:	February 8, 2009

The Undersigned certifies to the best of his knowledge and belief the above listed patent is valid, claiming lamivudine, the subject of a Supplemental New Drug Application.

12/04/97
Date

Charles E. Dadswell
Registered Patent Attorney
United States Registration No. 35,851

EXCLUSIVITY SUMMARY FOR NDA # 20-564/20-596/SE1-007

Trade Name **EPIVIR®** Generic Name lamivudine tablets and oral solution
Applicant Name **Glaxo Wellcome Inc** HFD # 530
Approval Date If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /__/ NO /_X_/

b) Is it an effectiveness supplement?

YES /_X_/ NO /__/

If yes, what type? (SE1, SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no").

YES /_X_/ NO /__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES / X / NO / __ /

If the answer to (d) is "yes", how many years of exclusivity did the applicant request?

3 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES / X / NO / __ /

If yes, NDA # 20-564/20-596 Drug Name **Epivir (lamivudine)**

IF THE ANSWER TO QUESTION 2 IS "YES", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / __ / NO / __ /

IF THE ANSWER TO QUESTION 3 IS "YES", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / __ / NO / __ /

If "yes", identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one-never-before-approved active moiety and one previously approved active moiety, answer "yes". (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved).

YES /__/ NO /__/

If "yes", identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES", GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant". This section should be completed only if the answer to PART II, Question 1 or 2 was "yes".

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies). If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes", then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__/ NO /___/

If "no", state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__/ NO /___/

(1) If the answer to 2(b) is "yes", do you personally know of any reason to disagree with the applicant's conclusion?

YES /__/ NO /__/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no", are you aware of published studies not conducted or sponsored by the applicant or other publicly available date that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /__/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no", identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval", has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no").

Investigation #1 YES /__/ NO /__/ Investigation #3 YES /___/ NO /___/

Investigation #2 YES /__/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /__/ Investigation #3 YES /___/ NO /___/

Investigation #2 YES /___/ NO /__/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are "no", identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /__/ NO /__/ Explain: _____

Investigation #2

IND # _____ YES /__/ NO /__/ Explain: _____

Investigation #3

IND # _____ YES /__/ NO /__/ Explain: _____

b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /__/ Explain _____ NO /__/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /__/ Explain _____ NO /__/ Explain _____

_____ _____

_____ _____

(c) Not withstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest)

YES /__/ NO /__/

If yes, explain: _____

_____

_____ 3/19/99

Signature of Project Manager — Date

_____ 3/19/99

Signature of Division Director — Date

cc: Orig NDA Div File HFD-85

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-564/20-596 Supplement # 007 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-530 Trade and generic names/dosage form: Epivir (lamivudine tablets and oral solution)
Action: AP AE NA

Applicant Glaxo Wellcome Inc Therapeutic Class 7030241 NRTI

Indication(s) previously approved N/A

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate X

Indication in this application Treatment of HIV infection in combination with other antiretrovirals (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

X 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

X c. The applicant has committed to doing such studies as will be required.
- X (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

Regulatory Management Officer 3/5/99

Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 20-564/20-596
Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NDA 20-564 - Epivir® Tablets (lamivudine tablets)

NDA 20-596 - Epivir® Oral Solution (lamivudine oral solution)

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that to the best of its knowledge and belief, it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

17-DEC 97

Charles E. Mueller
Head, International Compliance Services
World Wide Compliance

Date

.....

The list of Glaxo Wellcome Principal Investigators for the above titled submission has been compared with the 12Nov97 Food and Drug Administration Debarment List and the 22Aug97 Disqualified, Restricted, and Given Assurances lists.

Jeanne Kistler 17-Dec-97

Jeanne Kistler
Compliance Standards & Information Administrator
World Wide Compliance

Date

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-564
NDA 20-596

MAR 11 1999

GlaxoWellcome, Inc.
Attention: David M. Cocchetto, Ph.D.
Five Moore Drive
Research Triangle Park, NC 27709

Dear Dr. Cocchetto:

Reference is made to your Proposed Pediatric Study Request submitted on August 14, 1998 for Epivir® (lamivudine) to IND 37,158 (Serial No. 468)

To obtain needed pediatric information on lamivudine, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following study:

Type of study:

Multiple-dose pharmacokinetics and safety study of lamivudine in combination with other antiretroviral drugs in HIV-infected infants and HIV-exposed neonates (born to HIV-infected mothers).

Age group in which study will be performed:

HIV-infected infants up to three months of age and HIV-exposed neonates (born to HIV-infected mothers).

Drug information:

Dosage form: oral solution
Route of administration: oral
Regimen: to be determined by development program.

Drug specific safety concerns:

Pancreatitis and lactic acidosis.

Statistical information, including power of study and statistical assessments:

Descriptive analyses of multiple-dose pharmacokinetic and safety data in HIV-infected infants and HIV-exposed neonates (born to HIV-infected mothers).

Studies should include an adequate number of patients to characterize pharmacokinetics over the age range studied, taking into account intersubject and intrasubject variability. The number of subjects should be uniformly distributed across the age range studied.

Clinical endpoints and timing of assessments, including primary efficacy endpoints:

Pharmacokinetic
Parameters such as C_{max}, C_{min}, $t_{1/2}$, AUC

Safety and tolerability
HIV-exposed neonates (born to HIV-infected mothers) and HIV-infected pediatric patients should be followed for safety for a minimum of six months. In addition, please also submit plans for long term safety monitoring in HIV-exposed neonates (born to HIV-infected mothers) and HIV-infected pediatric patients who have received lamivudine.

Labeling that may result from the study:

Information regarding dosing and safety in HIV-infected infants up to 3 months of age and HIV-exposed neonates (born to HIV-infected mothers).

Format of reports to be submitted:

Full study report not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. Please include other information as appropriate.

Timeframe for submitting reports of the study:

Reports of the above studies must be submitted to the Agency on or before June 30, 2000. Please keep in mind that pediatric exclusivity only extends existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Reports of the study should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of

Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, please contact Terrie L. Crescenzi, R.Ph., Regulatory Management Officer, at (301) 827-2335.

Sincerely yours,

Sandra L. Kweder, M.D. for
Acting Director

M. Dianne Murphy, M.D.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research