CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-655/S-032
19-910/S-021
20-518/S-004

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

Division of Antiviral Drug Products

REGULATORY PROJECT MANAGER (CSO) REVIEW

Application Number/Name of Drug:
NDA 19-655/SLR-032 RETROVIR® (zidovudine) Capsules
NDA 19-910/SLR-021 RETROVIR® (zidovudine) Syrup
NDA 20-518/SLR-004 RETROVIR® (zidovudine) Tablets

Sponsor: Glaxo Wellcome, Inc.

Material Reviewed

Submission Date: March 09, 1998: Supplemental Application: Labeling (SLR)

Receipt Dates: March 10, 1998: Supplemental Application: Labeling (SLR)

Background and Summary Description:

The SLRs provide for a revised draft package insert for RETROVIR® (zidovudine) Capsules, Syrup, and Tablets and were compared both manually and electronically to the RETROVIR® package insert which was approved October 1997.

The package insert for all oral RETROVIR® (zidovudine) products is updated extensively so that information contained in the label is consistent with labeling for EPIVIR® Tablets (NDA 20-564), EPIVIR® Oral Solution (NDA 20-596), and COMBIVIR® Tablets (NDA 20-857).

Review

The revisions to the **RETROVIR® package insert** are as follows:

Changes in the **BLACK BOX WARNING**:

1. Page 1, Line 6, the words "**MAY BE**" are deleted and the words "**HAS BEEN**" added.

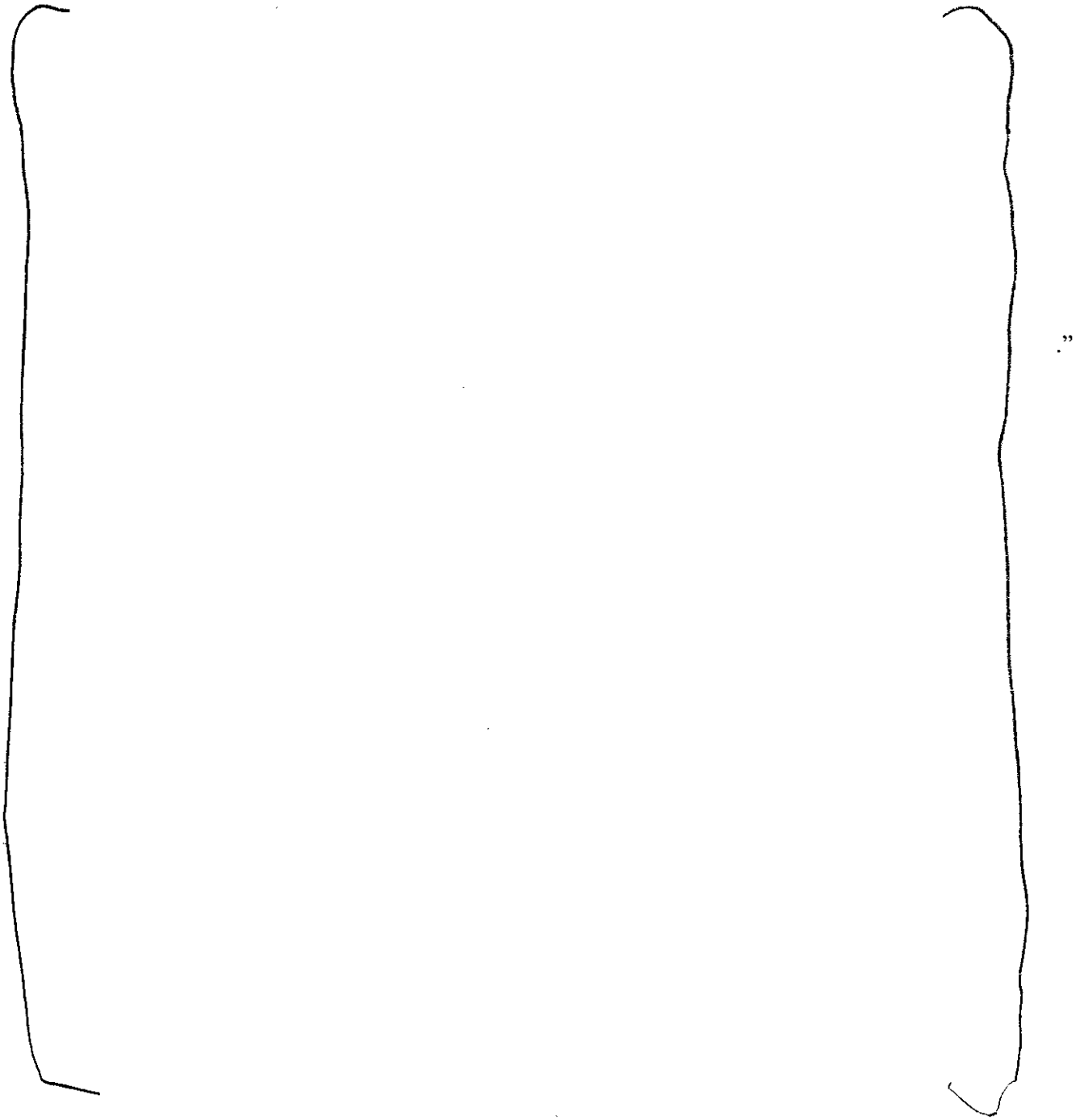
2. Page 1, Line 7, the word "**GRANULOCYTOPENIA**" is deleted and the word "**NEUTROPENIA**" added.

3. Page 1, Lines 9 and 10, the words "**SIMILAR TO THAT PRODUCED BY HUMAN IMMUNODEFICIENCY VIRUS**" are deleted.

4. Page 1, Lines 11 – 13, the following sentence: "**LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF ANTIRETROVIRAL NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING RETROVIR.**" is added.

5. Page 1, Lines 13 – 16, the following sentence is deleted: "**RARE OCCURRANCES OF POTENTIALLY FATAL LACTIC ACIDOSIS IN THE ABSENCE OF HYPOXEMIA, AND SEVERE HEPATOMEGALY WITH STEATOSIS HAVE BEEN REPORTED WITH THE USE OF CERTAIN ANTIRETROVIRAL NUCLEOSIDE ANALOGUES**"

Changes in the **MICROBIOLOGY: Mechanism of Action**:



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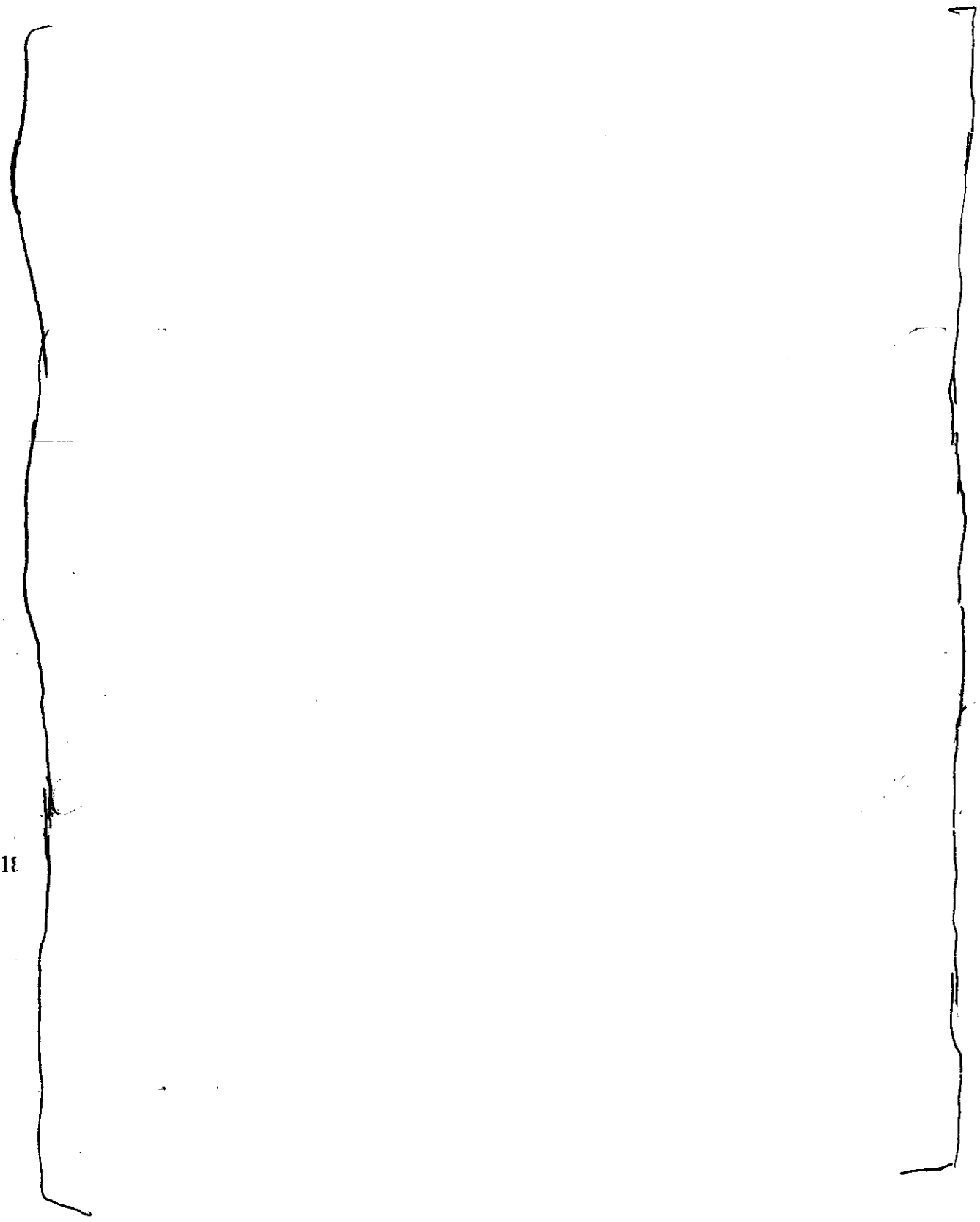

Changes in the **CLINICAL PHARMACOLOGY: Pharmacokinetics:** ***Adults:***

19. Page 4, Lines 107 – 119, the following paragraphs are added:

"The pharmacokinetic properties of zidovudine in fasting patients are summarized in Table 1. Following oral administration, zidovudine is rapidly absorbed and extensively distributed, with peak serum concentrations occurring within 0.5 to 1.5 hours. Binding to plasma protein is low.

20. Page 5, Lines 120 – 122, the following is table is added:

Table 1: Zidovudine Pharmacokinetic Parameters in Fasting Adult Patients (10)

Parameter	Mean ± SD (except where noted)
Oral bioavailability (%)	64 ± 10 (n = 5)
Apparent volume of distribution (L/kg)	1.6 ± 0.6 (n = 8)
Plasma protein binding (%)	<38
CSF:plasma ratio*	0.6 [0.04 to 2.62] (n = 39)
Systemic clearance (L/h/kg)	1.6 ± 0.6 (n = 6)
Renal clearance (L/h/kg)	0.34 ± 0.05 (n = 9)
Elimination half-life (h)†	0.5 to 3 (n = 19)

* Median [range].
† Approximate range.

21. Page 5, Lines 123 – 145, the following four paragraphs are deleted:

"The pharmacokinetics of zidovudine has been evaluated in 22 adult HIV-infected patients in a Phase 1 dose-escalation study. After oral dosing (capsules), zidovudine was rapidly absorbed from the gastrointestinal tract with peak serum concentrations occurring within 0.5 to 1.5 hours. Dose-independent kinetics was observed over the range of 2 mg/kg every 8 hours to 10 mg/kg every 4 hours. The mean zidovudine half-life was approximately 1 hour and ranged from 0.78 to 1.93 hours following oral dosing.

Zidovudine is rapidly metabolized to 3′-azido-3′-deoxy-5′-*O*-β-*D*-glucopyranuronosylthymidine (GZDV) which has an apparent elimination half-life of 1 hour (range 0.61 to 1.73 hours). Following oral administration, urinary recovery of zidovudine and GZDV accounted for 14% and 74% of the dose, respectively, and the total urinary recovery averaged 90% (range 63% to 95%), indicating a high degree of absorption. However, as a result of first-pass metabolism, the average oral capsule bioavailability of zidovudine is 65% (range 52% to 75%). A second metabolite, 3′-amino-3′-deoxythymidine (AMT), has been identified in the plasma following single-dose intravenous (IV) administration of zidovudine. AMT area-under-the-curve (AUC) was one fifth of the AUC of zidovudine and had a half-life of 2.7 ± 0.7 hours. In comparison, GZDV AUC was about threefold greater than the AUC of zidovudine.

Additional pharmacokinetic data following intravenous dosing indicated dose-independent kinetics over the range of 1 to 5 mg/kg with a mean zidovudine half-life of 1.1 hours (range 0.48 to 2.86 hours). Total body clearance averaged 1900 mL/min per 70 kg and the apparent volume of distribution was 1.6 L/kg. Renal clearance is estimated to be 400 mL/min per 70 kg, indicating glomerular filtration and active tubular secretion by the kidneys. Zidovudine plasma protein binding is 34% to 38%, indicating that drug interactions involving binding site displacement are not anticipated.

The zidovudine cerebrospinal fluid (CSF)/plasma concentration ratio was determined in 39 patients receiving chronic therapy with RETROVIR. The median ratio measured in 50 paired samples drawn 1 to 8 hours after the last dose of RETROVIR was 0.6."

Changes in the **CLINICAL PHARMACOLOGY: Pharmacokinetics:** ***Adults: Adults with Impaired Renal Function:***

22. Page 6, Lines 146 – 152 the following paragraph is added:

"Zidovudine clearance was decreased resulting in increased zidovudine and GZDV half-life and AUC in patients with impaired renal function (n = 14) following a single 200-mg oral dose (Table 2). Plasma concentrations of AMT were not determined. A dose adjustment should not be necessary for patients with creatinine clearance (CrCl) ≥ 15 mL/min."

23. Page 6, Lines 151 – 153, the following table is added:

Table 2: Zidovudine Pharmacokinetic Parameters in Patients With Severe Renal Impairment*

Parameter	Control Subjects (Normal Renal Function) (n = 6)	Patients With Renal Impairment (n = 14)
CrCl (mL/min)	120 ± 8	18 ± 2
Zidovudine AUC (ng•h/mL)	1400 ± 200	3100 ± 300
Zidovudine half-life (h)	1.0 ± 0.2	1.4 ± 0.1

*Data are expressed as mean ± standard deviation.

24. Page 6, Lines 155 – 159, the following sentences are deleted:

"The pharmacokinetics of zidovudine has been evaluated in patients with impaired renal function following a single 200-mg oral dose. In 14 patients (mean creatinine clearance 18 ± 2 mL/min) the half-life of zidovudine was 1.4 hours compared to 1.0 hour for control subjects with normal renal function; AUC values were approximately twice those of controls. Additionally, GZDV half-life in these patients was 8.0 hours (vs 0.9 hours for control) and AUC was 17 times higher than for control subjects."

25. Page 6, Line 160, the words "of zidovudine" are added immediately after the word "tolerance" and immediately before the words "were evaluated."

26. Page 6, Line 161, the words "receiving escalating doses" are added immediately after the phrase "(n = 6).

27. Page 6, Line 161, the words "Patients received escalating doses of zidovudine" are deleted.

28. Page 6, Line 163, the words "plasma levels of" are deleted immediately after the word "elevated" and immediately before the letters "GZDV."

29. Page 6, Line 163, the words "plasma concentrations" are added immediately after the letters "GZDV."

30. Page 6, Line 163, the word "zidovudine" is added immediately after the word "Apparent" and immediately before the words "oral clearance."

31. Page 6, Lines 164 and 165, the words "of zidovudine" are deleted immediately after the words "oral clearance" and immediately before the words "was approximately".

32. Page 6, Lines 164 – 167, the following sentences are deleted:

"The plasma concentrations of AMT are not known in patients with renal insufficiency. Daily doses of 300 to 400 mg should be appropriate in HIV-infected patients with severe renal dysfunction (see DOSAGE AND ADMINISTRATION: Dose Adjustment)."

33. Page 6, Line 167, the letters "ed" are added to the word "appear".

34. Page 6, Line 168, the word "is" is deleted and the word "was" is added.

35. Page 6, Line 168 – 170, the following sentence is added:

"A dosage adjustment is recommended for patients undergoing hemodialysis or peritoneal dialysis (see DOSAGE AND ADMINISTRATION: Dose Adjustment)."

Changes in the **CLINICAL PHARMACOLOGY: Pharmacokinetics:** ***Adults:***

36. Page 6, Line 171 – 174, the following heading and paragraph are added:

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Changes in the **CLINICAL PHARMACOLOGY: Pharmacokinetics:** ***Pediatrics:***

37. Page 6, Line 175, the word "The" at the beginning of the sentence is deleted.
38. Page 6, Line 175, the word "Zidovudine" is added at the beginning of the sentence immediately before "pharmacokinetics".

39. Page 6, Line 175, the words "and bioavailability of zidovudine" immediately after the word "pharmacokinetics" is deleted.

40. Page 6, Line 176, the number "21" immediately before the words "HIV-infected pediatrics patients" is deleted.

41. Page 6, Line 176, the phrase "(Table 3)." is added immediately after the words "HIV-infected pediatrics patients".

42. Pages 6 and 7, Lines 176 – 188, the following sentences are deleted:

"...ages 6 months through 12 years, following intravenous doses administered over the range of 80 to 160 mg/m^2 every 6 hours, and following oral doses of the IV solution administered over the range of 90 to 240 mg/m^2 every 6 hours. After discontinuation of the IV infusion, zidovudine plasma concentrations decayed biexponentially, consistent with two-compartment pharmacokinetics. Proportional increases in AUC and in zidovudine concentrations were observed with increasing dose, consistent with dose-independent kinetics over the dose range studied. The mean terminal half-life and total body clearance across all dose levels administered were 1.5 hours and 30.9 mL/min per kg, respectively. These values compare to mean half-life and total body clearance in adults of 1.1 hours and 27.1 mL/min per kg.

The mean oral bioavailability of 65% was independent of dose. This value is the same as the bioavailability in adults. Doses of 180 mg/m2 four times daily in pediatric patients produced similar systemic exposure (24-hour AUC 10.7 hr• mcg/mL) as doses of 200 mg six times daily in adult patients (10.9 hr• mcg/mL)."

43. Page 7, Lines 189 – 198, the following heading and paragraph are added:

Patients From 3 Months to 12 Years of Age: Overall, zidovudine pharmacokinetics in pediatric patients greater than 3 months of age is similar to those in adult patients. Proportional increases in plasma zidovudine concentrations were observed following administration of oral solution from 90 to 240 mg/m2 every 6 hours. Oral bioavailability, terminal half-life, and oral clearance were comparable to adult values. As in adult patients, the major route of elimination was by metabolism to GZDV.

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44. Page 7, Line 199, the following heading is added: "***Patients Younger than 3 Months of Age:***"

45. Page 7, Line 199, the word "The" at the beginning of the sentence is deleted.

46. Page 7, Line 199, the word "Zidovudine" is added at the beginning of the sentence immediately before the word "pharmacokinetics".

47. Page 7, Lines 199 and 200, the words "of zidovudine have been studied" immediately after the word "pharmacokinetics" are deleted.

48. Page 7, Line 200, the words "have been evaluated" are added immediately following the word "pharmacokinetics" and immediately before the words "in pediatric patients".

49. Page 7, Line 200 and 201, the following words are deleted "In one study of the pharmacokinetics of zidovudine in women during the last trimester of pregnancy,".

50. Page 7, Line 201, the word "zidovudine" is deleted and the word "Zidovudine" is added.

51. Page 7, Line 202, the word "following" is added after the word "immediately".

52. Page 7, Line 202, the word "after" before the word "birth" is deleted.

53. Page 7, Lines 203 – 205, the following sentence is deleted:

    "In another study, the pharmacokinetics of zidovudine was evaluated in pediateic patients (ranging in age of 1 day to 3 months) of normal birth weight for gestational age and with normal renal and hepatic function."

54. Page 7, Lines 205 – 207, the following words are added immediately after the words "In neonates less than or equal to 14 days old,"

    "bioavailability was greater, total body clearance was slower, and half-life was longer than in pediatric patients greater than 14 days old. For dose recommendations for neonates see DOSAGE AND ADMINISTRATION: Neonatal Dosing."

55. Pages 7 and 8, Lines 208 – 221, the following paragraphs are deleted:

    "mean ± SD total body clearance was 10.9 ± 4.8 mL/min per kg (n = 18) and half-life was 3.1 ± 1.2 hours (n = 21). In neonates and infants greater than 14 days old, total body clearance was 19.0 ± 4.0 mL/min per kg (n = 16) and half-life was 1.9 ± 0.7 hours (n = 18). Bioavailability was 89% ± 19% (n = 15) in the younger age group and decreased to 61% ± 19% (n = 17) in patients older than 14 days.

    Concentrations of zidovudine in cerebrospinal fluid were measured after both intermittent oral and IV drug administration in 21 pediatric patients during Phase 1 and Phase 2 studies. The mean zidovudine CSF/plasma concentration ratio measured at an average time of 2.2 hours postdose at oral doses of 120 to

240 mg/m2 was 0.52 ± 0.44 (n = 28); after an IV infusion of doses of 80 to 160 mg/m^2 over 1 hour, the mean CSF/plasma concentration ratio was 0.87 ± 0.66 (n = 23) at 3.2 hours after the start of the infusion. During continuous IV infusion, mean steady-state CSF/plasma ratio was 0.26 ± 0.17 (n = 28).

As in adult patients, the major route of elimination in pediatric patients was by metabolism to GZDV. After IV dosing, about 29% of the dose was excreted in the urine unchanged and about 45% of the dose was excreted as GZDV. Overall, the pharmacokinetics of zidovudine in pediatric patients greater than 3 months of age are similar to that of zidovudine in adult patients."

56. Page 8, Lines 222 – 224, the following table is added

Table 3: Zidovudine Pharmacokinetic Parameters in Pediatric Patients*

Parameter	Birth to 14 Days of Age	14 Days to 3 Months of Age	3 Months to 12 Years of Age
Oral bioavailability (%)	89 ± 19 (n = 15)	61 ± 19 (n = 17)	65 ± 24 (n = 18)
CSF:plasma ratio	no data	no data	0.68 (0.03 to 3.25)† (n = 38)
CL (L/h/kg)	10.9 ± 4.8 (n = 18)	19.0 ± 0.4 (n = 16)	30.9 ± 7.9 (n = 20)
Elimination half-life (h)	3.1 ± 1.2 (n = 21)	1.9 ± 0.7 (n = 18)	1.5 ± 0.7 (n = 21)

*Data presented as mean ± standard deviation except where noted.
†Median [range].

Changes in the **CLINICAL PHARMACOLOGY: Pharmacokinetics:** ***Pregnancy:***

57. Page 8, Line 227, the words "The pharmacokinetics of zidovudine" are deleted and the words "Zidovudine pharmacokinetics" are added.

58. Page 8, Line 229, the words "The pharmacokinetics of zidovudine" are deleted and the words "Zidovudine pharmacokinetics" are added.

59. Page 8, Line 231, the word "infant" immediately before the word "plasma" is deleted and the word "neonatal" is added.

Changes in the **CLINICAL PHARMACOLOGY: Pharmacokinetics:** ***Nursing Mothers:***

60. Page 8, Lines 235 and 236, the following sentence is added:

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

61: Page 8, Lines 236 – 238, the following sentence is deleted:

"The U.S. Public Health Service Centers for Disease Control and Prevention advises HIV-infected women not to breastfeed to avoid postnatal transmission of HIV to a child who may not yet be infected."

62. Page 8, Lines 241 and 242, the following heading and sentence are added:

"***Geriatric Patients:*** Zidovudine pharmacokinetics have not been studies in patients over 65 years of age."

63. Page 9, Lines 243 – 245, the following heading and sentence are added:

"***Gender:*** A pharmacokinetic study in health male (n = 12) and female (n = 12) subjects showed no difference in zidovudine exposure (AUC) when a single dose of zidovudine was administered as the 300-mg RETROVIR Tablet."

Changes in **CLINICAL PHARMACOLOGY: Pharmacokinetics:** ***Effect of Food on absorption:***

64. Page 9, Lines 246 and 247, the following sentence is added:

"RETROVIR may be administered with or without food. The extent of zidovudine absorption (AUC) was similar when a single dose of zidovudine was administered with food."

65. Page 9, Lines 248 – 260, the following paragraphs are deleted:

"Administration of RETROVIR Capsules with food decreased peak plasma concentrations by greater than 50%; however, bioavailability as determined by AUC may not be affected.

The effect of food on the absorption of zidovudine from the tablet formulation is not known.

Tablets: In a single-dose study of 23 healthy volunteers, the mean ± SD relative bioavailability of the RETROVIR 300-mg Tablet relative to three 100-mg RETROVIR Capsules was 110 ± 18%. After administration of the 300-mg RETROVIR Tablet or three 100-mg RETROVIR Capsules, the mean ± SD Cmax values were 1.81 ± 0.52 and 1.50 ± 0.46 mcg/mL, respectively.

Syrup: In a multiple-dose bioavailability study conducted in 12 HIV-infected adults receiving doses of 100 or 200 mg every 4 hours, RETROVIR Syrup was demonstrated to be bioequivalent to RETROVIR Capsules with respect to area under the zidovudine plasma concentration-time curve (AUC). The rate of absorption of RETROVIR Syrup was greater than that of RETROVIR Capsules, as indicated by mean times to peak concentration of 0.5 and 0.8 hours, respectively. Mean values for steady-state peak concentration (dose-normalized to 200 mg) were 1.5 and 1.2 mcg/mL for syrup and capsules, respectively."

66. Page 9, Lines 261 – 264, The following words, heading, and sentence are added:

"**Drug Interactions:** See PRECAUTIONS: Drug Interactions.

Zidovudine Plus Lamivudine: 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 every 12 hours)."

67. Page 10, Lines 266 – 273, the following table is added:

Table 4: Effect of Coadministered Drugs on Zidovudine AUC*

Note: ROUTINE DOSE MODIFICATION OF ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.

Coadministered Drug and Dose	Zidovudine Dose	N	Zidovudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Atovaquone 750 mg q 12 h with food	200 mg q 8 h	14	↑ AUC 31%	Range 23% to 78%**	↔
Fluconazole 400 mg daily	200 mg q 8 h	12	↑ AUC 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 h	9	↑ AUC 43%	Range 16% to 64%**	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 200 mg	11	↓ AUC 35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 h x 2 days	2 mg/kg q 8 h x 3 days	3	↑ AUC 106%	Range 100% to 170%**	Not Assessed
Ritonavir 300 mg q 6 h x 4 days	200 mg q 8 h x 4 days	9	↓ AUC 25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg q 8 h x 4 days	100 mg q 8 h x 4 days	6	↑ AUC 80%	Range 64% to 130%**	Not Assessed

↑ = Increase; ↓ = Decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.

* This table is not all inclusive.

** Estimated range of percent difference.

Changes to the **INDICATIONS AND USAGE:**

68. Page 10, Lines 275 – 276, the words "in adults and pediatric patients, when antiretroviral therapy is warranted" are deleted immediately after the words "HIV infection."

69. Page 10, Lines 276 – 281, the following sentences are added:

[redacted]

70. Page 11, Lines 294 and 295, the following sentence is deleted:

"Other randomized studies suggest that the duration of the clinical benefit of monotherapy with RETROVIR is time-limited."

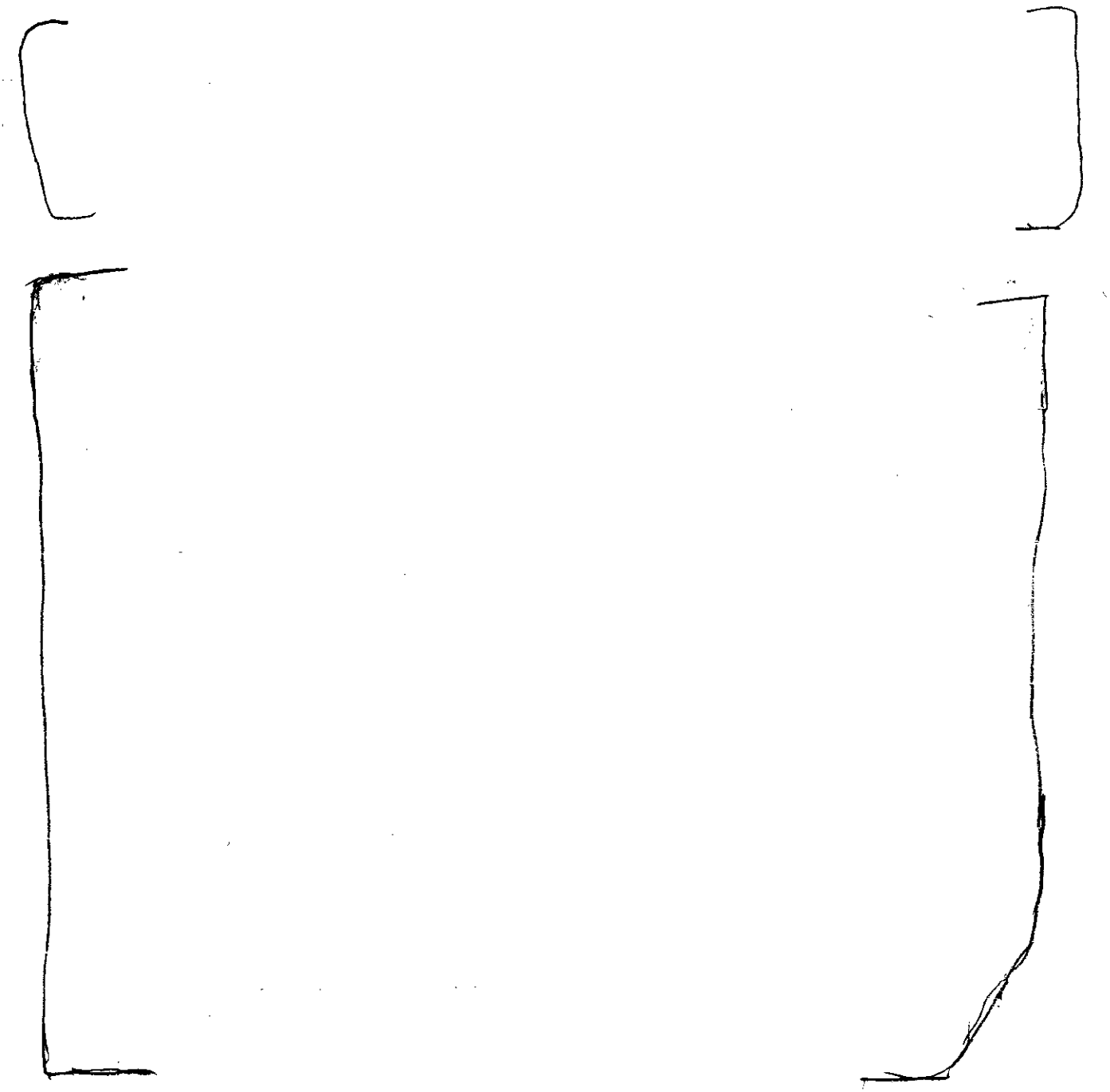
71. Page 11, Lines 296 – 307, the following heading and table are deleted:

"***Combination Therapy-Adults:*** ACTG175 was a randomized, double-blind, controlled trial that compared RETROVIR 200 mg t.i.d.; didanosine 200 mg b.i.d.; RETROVIR plus didanosine; and RETROVIR plus zalcitabine 0.75 mg t.i.d. A total of 2467 HIV-infected adults with baseline CD4 counts of 200 to 500 cells/mm3 (mean = 352) and no prior AIDS-defining event enrolled with the following demographics: male (82%), Caucasian (70%), mean age of 35 years, asymptomatic HIV infection (81%), and prior antiretroviral use (57%, mean duration = 89.5 weeks). The overall median duration of study treatment was 118 weeks. The incidence of AIDS-defining events or death is shown in Table 1

Table 1
First AIDS-Defining Event or Death and Death Only
by Study Arm and Antiretroviral Experience

Treatment Antiretroviral Experience	Event	RETROVIR	Didanosine	RETROVIR Plus Didanosine	RETROVIR plus Zalcitabine
Overall	No. of Patients	619	620	613	615
	AIDS/Death	96 (16%)	71 (11%)	66 (11%)	76 (12%)
	Death Only	54 (9%)	29 (5%)	31 (5%)	40 (7%)
Naïve	No. of Patients	269	268	263	267
	AIDS/Death	32 (12%)	23 (9%)	20 (8%)	16 (6%)
	Death Only	18 (7%)	11 (4%)	11 (4%)	9 (3%)
Experienced	No. of Patients	350	352	350	348
	AIDS/Death	64 (18%)	48 (14%)	45 (13%)	60 (17%)
	Death Only	36 (10%)	18 (5%)	20 (6%)	31 (9%)

72. Pages 11 and 12, Lines 308 – 332, the following heading, paragraphs, and two tables are added:



73. Page 12, Lines 334 – 338, the following paragraph is deleted:

"RETROVIR in combination with certain antiretroviral agents has been shown to be superior to monotherapy in one or more of the following: delaying death, delaying development of AIDS, increasing

CD4 cell counts, and decreasing plasma HIV RNA. Use of RETROVIR in some combinations is based on surrogate marker data. The complete prescribing information for each drug should be consulted before combination therapy which includes RETROVIR is initiated."

Changes in **INDICATIONS AND USAGE:** ***Pregnant Women and Their Neonates:***

74. Page 13, Line 343, the letters "IV" are deleted and the word " ——— is added.

75. Page 13, Line 344, the word "After" is deleted and the word "Following" is added.

Changes in **WARNINGS:**

76. Page 13, Lines 364 and 365, the following sentence is added as the third sentence in the paragraph:

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Changes in **WARNINGS: Bone Marrow Suppression:**

76. Page 13, Line 369, the number "1" immediately following the words "granulocyte count < is deleted and the numbers "1000" are added.

Changes in **WARNINGS: Lactic Acidosis/Severe Hepatomegaly with Steatosis:**

77. Page 14, Lines 381 – 392, the following paragraph is deleted:

"Rare occurrences of potentially fatal lactic acidosis in the absence of hypoxemia, and severe hepatomegaly with steatosis have been reported with the use of certain antiretroviral nucleoside analogues. Lactic acidosis should be considered whenever a patient receiving therapy with RETROVIR develops unexplained tachypnea, dyspnea, or fall in serum bicarbonate level. Under these circumstances, therapy with RETROVIR should be suspended until the diagnosis of lactic acidosis has been excluded. Caution should be exercised when administering RETROVIR to any patient, particularly obese women, with hepatomegaly, hepatitis, or other known risk factor for liver disease. These patients should be followed closely while on therapy with RETROVIR. The significance of elevated aminotransferase levels suggesting hepatic injury in HIV-infected patients prior to starting RETROVIR or while on RETROVIR is unclear. Treatment with RETROVIR should be suspended in the setting of rapidly elevating aminotransferase levels, progressive hepatomegaly, or metabolic/lactic acidosis of unknown etiology.

78. Page 14, Lines 392 – 397, the following paragraph is added:

"Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination, including zidovudine. A majority of these cases have been in women. Obesity and prolonged exposure to antiretroviral nucleoside analogues may be risk factors. Particular caution should be exercised when administering RETROVIR 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 RETROVIR should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity."

Changes in **WARNINGS: Other Serious Adverse Reactions:**

79. Page 14, Lines 398 – 402, the following heading and paragraph are deleted:

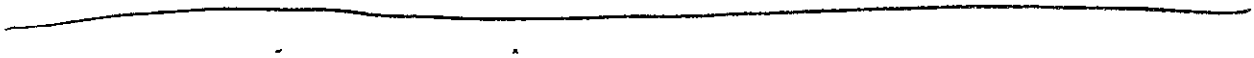
"**Other Serious Adverse Reactions:** Several serious adverse events have been reported with use of RETROVIR in clinical practice. Reports of pancreatitis, sensitization reactions (including anaphylaxis in one patient), vasculitis, and seizures have been rare. These adverse events, except for sensitization, have also been associated with HIV disease. Changes in skin and nail pigmentation have been associated with the use of RETROVIR."

Changes in **PRECAUTIONS: General:**

80. Page 14, Lines 406 and 407, the value "CrCl<15 mL/min" is added immediately after the words "renal function" and immediately before ", dosage". A period is added immediately after the word " recommended" at the end of the first sentence.

81. Page 14, Lines 407 and 408, the following words are deleted:

"(see CLINICAL PHARMACOLOGY: Pharmacokinetics and DOSAGE AND ADMINISTRATION). Although very little data are available,"

82. 

83. Page 14, Line 409, the word "which" is added immediately after the word "function" and immediately after the word "may".

84. Page 14, Line 409, the words "be at greater" are deleted immediately after the word "may".

85. Page 14, Line 409, the words "increase the" are added immediately after the word "may".

86. Page 14, Line 409, the word "hematologic" is added immediately before the word "toxicity" and immediately after the words "risk of".

87. Page 14, Line 410, the words "(see CLINICAL PHARMACOLOGY: Pharmacokinetics and DOSAGE AND ADMINISTRATION)." are added to the end of the second sentence immediately following the word "toxicity".

Changes in **PRECAUTIONS: Information for Patients:**

88. Page 15, Line 419, the words "dose modifications including possible" immediately after the words "transfusions or" are deleted.

89. Page 15, Line 419, the word "drug" is added immediately after the words "transfusions or" and immediately before the word "discontinuation."

Changes in **PRECAUTIONS: Drug Interactions:**

90. Page 15, Lines 438 – 441, the following paragraph is added immediately after the heading "**Drug Interactions:**"

[ ]

91. Pages 15 – 17, Lines 442 – 501, the following headings and paragraphs are deleted:

"***Ganciclovir:*** Use of RETROVIR in combination with ganciclovir increases the risk of hematologic toxicities in some patients with advanced HIV disease. Should the use of this combination become necessary in the treatment of patients with HIV disease, dose reduction or interruption of one or both agents may be necessary to minimize hematologic toxicity. Hematologic parameters, including hemoglobin, hematocrit, and white blood cell count with differential, should be monitored frequently in all patients receiving this combination.

Interferon-alpha: Hematologic toxicities have also been seen when RETROVIR is used concomitantly with interferon-alpha. As with the concomitant use of RETROVIR and ganciclovir, dose reduction or interruption of one or both agents may be necessary, and hematologic parameters should be monitored frequently.

Bone Marrow Suppressive Agents/Cytotoxic Agents: Coadministration of RETROVIR with drugs that are cytotoxic or which interfere with RBC/WBC number or function (e.g., dapsone, flucytosine, vincristine, vinblastine, or adriamycin) may increase the risk of hematologic toxicity.

Probenecid: Limited data suggest that probenecid may increase zidovudine levels by inhibiting glucuronidation and/or by reducing renal excretion of zidovudine. Some patients who have used RETROVIR concomitantly with probenecid have developed flu-like symptoms consisting of myalgia, malaise, and/or fever and maculopapular rash.

Phenytoin: Phenytoin plasma levels have been reported to be low in some patients receiving RETROVIR, while in one case a high level was documented. However, in a pharmacokinetic interaction study in which 12 HIV-positive volunteers received a single 300-mg phenytoin dose alone and during steady-state

zidovudine conditions (200 mg every 4 hours), no change in phenytoin kinetics was observed. Although not designed to optimally assess the effect of phenytoin on zidovudine kinetics, a 30% decrease in oral zidovudine clearance was observed with phenytoin.

Methadone: In a pharmacokinetic study of nine HIV-positive patients receiving methadone-maintenance (30 to 90 mg daily) concurrent with 200 mg of RETROVIR every 4 hours, no changes were observed in the pharmacokinetics of methadone upon initiation of therapy with RETROVIR and after 14 days of treatment with RETROVIR. No adjustments in methadone-maintenance requirements were reported. For four patients, the mean zidovudine AUC was elevated twofold, while for five patients, the value was equal to that of control patients. The exact mechanism and clinical significance of these data are unknown.

Fluconazole: The coadministration of fluconazole with RETROVIR has been reported to interfere with the oral clearance and metabolism of RETROVIR. In a pharmacokinetic interaction study in which 12 HIV-positive men received RETROVIR 200 mg every 8 hours alone and in combination with fluconazole 400 mg daily, fluconazole increased the zidovudine AUC (74%; range 28% to 173%) and the zidovudine half-life (128%; range -4% to 189%) at steady state. The clinical significance of this interaction is unknown.

Atovaquone: Data from 14 HIV-infected volunteers who were given atovaquone tablets 750 mg every 12 hours with zidovudine 200 mg every 8 hours showed a 24% ± 12% decrease in zidovudine oral clearance, leading to a 35% ± 23% increase in plasma zidovudine AUC. The glucuronide metabolite:parent ratio decreased from a mean of 4.5 when zidovudine was administered alone to 3.1 when zidovudine was administered with atovaquone tablets. Zidovudine had no effect on atovaquone pharmacokinetics.

Valproic Acid: The concomitant administration of valproic acid 250 mg (n = 5) or 500 mg (n = 1) every 8 hours and zidovudine 100 mg orally every 8 hours for 4 days to six HIV-infected, asymptomatic male volunteers resulted in a 79% ± 61% (mean ± SD) increase in the plasma zidovudine AUC and a 22% ± 10% decrease in the plasma GZDV AUC as compared to the administration of zidovudine in the absence of valproic acid. The GZDV/zidovudine urinary excretion ratio decreased 58% ± 12%. Because no change in the zidovudine plasma half-life occurred, these results suggest that valproic acid may increase the oral bioavailability of zidovudine through inhibition of first-pass metabolism. Although the clinical significance of this interaction is unknown, patients should be monitored more closely for a possible increase in zidovudine-related adverse effects. The effect of zidovudine on the pharmacokinetics of valproic acid was not evaluated.

Lamivudine: RETROVIR and lamivudine were coadministered to 12 asymptomatic HIV-positive patients in a single-center, open-label, randomized, crossover study. No significant differences were observed in AUC• or total clearance for lamivudine or zidovudine when the two drugs were administered together. Coadministration of RETROVIR with lamivudine resulted in an increase of 39% ± 62% (mean ± SD) in C_{max} of zidovudine.

Other Agents: Preliminary data from a drug interaction study (n = 10) suggest that coadministration of 200 mg RETROVIR and 600 mg rifampin decreases the area under the plasma concentration curve by an average of 48% ± 34%. However, the effect of once-daily dosing of rifampin on multiple daily doses of RETROVIR is unknown. Some nucleoside analogues affecting DNA replication, such as ribavirin, antagonize the in vitro antiviral activity of RETROVIR against HIV; concomitant use of such drugs should be avoided."

Changes in **PRECAUTIONS: Pregnancy:** ***Antiretroviral Pregnancy Registry:***

92. Page 19, Line 565, the telephone number of the Antiretroviral Pregnancy Registry "(800) 722-9292, ext. 39437" is deleted and the phone number "1-800-258-4263" is added.

Changes in **PRECAUTIONS: Nursing Mothers:**

93. Page 19, Lines 566 – 568, the following sentence is deleted:

    "The U.S. Public Health Service Centers for Disease Control and Prevention advises HIV-infected women not to breastfeed to avoid postnatal transmission of HIV to a child who may not yet be infected. Zidovudine is excreted in human milk."

94. Page 19, Lines 568 – 569, the following sentence is added:

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

95. Page 19, Line 570, the words "CLINICAL PHARMACOLOGY:" are added immediately after "(see" and immediately before "Pharmacokinetics)."

Changes in **PRECAUTIONS: Pediatric Use:**

96. Page 19, Line 573, the words "RETROVIR has also been studies in neonates perinatally exposed to HIV" are added immediately after "immunosuppression." and immediately before the words "(see ADVERSE REACTIONS,"

97. Page 19, Line 574, the word "and" is deleted immediately after the word "ADMINISTRATION," and immediately before "INDICATIONS".

98. Page 19, Line 575, the words "CLINICAL PHARMACOLOGY:" are added immediately after the words "Description of Clinical Studies, and" and immediately before the word "Pharmacokinetics)."

Changes in **ADVERSE REACTIONS:**

99. Page 19, Line 578, the heading "**Adults:** ——— is added to the first sentence immediately prior to the sentence beginning "The frequency and severity".

100. Page 19, Line 578, the heading "**Monotherapy:** ***Adults:*** " is deleted from the first sentence immediately prior to the sentence beginning "The frequency and severity".

101. Page 19, Line 579, the words "in adults" are deleted immediately after the word "RETROVIR" and immediately before the words "are greater".

102. Page 19., Lines 580 – 580, the following sentence is deleted:

"The following table sumerizes the relative incidence of hematologic adverse events observed in clinical studies by severity of HIV disease present at the start of treatment:"

103. Page 19, Lines 581 – 583, the following sentence is added:

104. Page 20, Lines 585 – 587, the following table is added:

105. Pages 20 and 21, Lines 589 – 599, the following sentence and table are added:

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106. Page 21, Lines 601 – 605, the following table is deleted:

Table 2

Stage of Disease	RETROVIR Daily Dose* (mg)	Granulocytopenia (<750 cells/mm^3)	Anemia (Hgb <8.0 g/dL)
Asymptomatic			
ACTG 019	500	1.8%†	1.1%†
Early HIV Disease (CD4 >200 cells/mm^3)			
ACTG 016	1200	4%	4%
Advanced HIV Disease (CD4 >200 cells/mm^3)			
BW 02	1500	10%†	3%†‡
(CD4 ≤200 cells/mm^3)			
ACTG 002	600	37%	29%
BW 02	1500	47%	29%‡

* The currently recommended dose is 500 to 600 mg daily.
† Not statistically significant compared to placebo.
‡ Anemia = Hgb <7.5 g/dL.

107. Pages 21 and 22, Lines 607 – 620, the following paragraphs are deleted:

"The anemia reported in patients with advanced HIV disease receiving RETROVIR appeared to be the result of impaired erythrocyte maturation as evidenced by macrocytosis while on drug. Although mean platelet counts in patients receiving RETROVIR were significantly increased compared to mean baseline values, thrombocytopenia did occur in some of these patients with advanced disease. Twelve percent of patients receiving RETROVIR compared to 5% of patients receiving placebo had >50% decreases from baseline platelet count. Mild drug-associated elevations in total bilirubin levels have been reported as an uncommon occurrence in patients treated for asymptomatic HIV infection.

The HIV-infected adults participating in these clinical trials often had baseline symptoms and signs of HIV disease and/or experienced adverse events at some time during study. It was often difficult to distinguish adverse events possibly associated with administration of RETROVIR from underlying signs of HIV disease or intercurrent illnesses. The following table summarizes clinical adverse events or symptoms which occurred in at least 5% of all patients with advanced HIV disease treated with 1500 mg/day of RETROVIR in the original placebo-controlled study. Of the items listed in the table, only severe headache, nausea, insomnia, and myalgia were reported at a significantly greater rate in patients receiving RETROVIR."

108. Page 22, Lines 622 – 625, the following table is deleted:

Table 3
Percentage (%) of Patients with Clinical Events in Advanced HIV Disease (BW 02)

Adverse Event	RETROVIR 1500 mg/day* (n = 144) %	Placebo (n = 137) %
BODY AS A WHOLE		
Asthenia	19	18
Diaphoresis	5	4
Fever	16	12
Headache	42	37
Malaise	8	7
GASTROINTESTINAL		
Anorexia	11	8
Diarrhea	12	18
Dyspepsia	5	4
GI Pain	20	19
Nausea	46	18
Vomiting	6	3
MUSCULOSKELETAL		
Myalgia	8	2
NERVOUS		
Dizziness	6	4
Insomnia	5	1
Paresthesia	6	3
Somnolence	8	9
RESPIRATORY		
Dyspnea	5	3
SKIN		
Rash	17	15
SPECIAL SENSES		
Taste Perversion	5	8

* The currently recommended dose is 500 to 600 mg daily.

109. Page 22, Lines 627 – 632, the following paragraph is deleted:

"All events of a severe or life-threatening nature were monitored for adults in the placebo-controlled studies in early HIV disease and asymptomatic HIV infection. Data concerning the occurrence of additional signs or symptoms were also collected. No distinction was made in reporting events between those possibly associated with the administration of the study medication and those due to the underlying disease. The following tables summarize all those events reported at a statistically significant greater incidence for patients receiving RETROVIR in these studies:"

110. Page 23, Lines 634 – 636, the following table is deleted:

Table 4
Percentage (%) of Patients with Adverse Events in Early HIV Disease (ACTG 016)

Adverse Event	RETROVIR 1200 mg/day* (n = 361) %	Placebo (n = 352) %
BODY AS A WHOLE		
Asthenia	69	62
GASTROINTESTINAL		
Dyspepsia	6	1
Nausea	61	41
Vomiting	25	13

* The currently recommended dose is 500 to 600 mg daily.

Changes in **ADVERSE REACTIONS: Adults:** ***Monotherapy:***

111. Page 23, Lines 637 – 639, the following heading and sentence are added:

[ ]

112. Page 23, Lines 640 – 643, the following table is added:

Table 8: Percentage (%) of Patients with Adverse Events* in Asymptomatic HIV Infection (ACTG 019)

Adverse Event	RETROVIR 500 mg/day (n = 453) %	Placebo (n = 428) %
Body as a whole		
Asthenia	8.6†	5.8
Headache	62.5	52.6
Malaise	53.2	44.9
Gastrointestinal		
Anorexia	20.1	10.5
Nausea	51.4	29.9
Vomiting	17.2	9.8

* Reported in ≥5% of study population.
† Not statistically significant versus placebo.

113. Page 23, Lines 645 – 655, the following paragraphs are deleted:

"Several serious adverse events have been reported with the use of RETROVIR in clinical practice. Myopathy and myositis with pathological changes, similar to that produced by HIV disease, have been

associated with prolonged use of RETROVIR. Reports of hepatomegaly with steatosis, hepatitis, pancreatitis, lactic acidosis, sensitization reactions (including anaphylaxis in one patient), hyperbilirubinemia, vasculitis, and seizures have been rare. These adverse events, except for sensitization, have also been associated with HIV disease. A single case of macular edema has been reported with the use of RETROVIR.

Additional adverse events reported in clinical trials at a rate not significantly different from placebo are listed below. Selected events from post-marketing clinical experience with RETROVIR are also included. Many of these events may also occur as part of HIV disease. The clinical significance of the association between treatment with RETROVIR and these events is unknown."

Changes in **ADVERSE REACTIONS: Pediatrics:**

114. Pages 23 and 24, Lines 656 – 663, the following heading and paragraphs are added:

[redacted]

115. Page 24, Lines 671 – 676, the following paragraphs are added:

[redacted]

116. Page 25, Lines 678 – 680, the following table is added:

117. Page 25, Lines 682 and 683, the following sentence is added:

"The clinical adverse events reported among adult recipients of RETROVIR may also occur in pediatric patients."

Changes in **ADVERSE REACTIONS: Use for the Prevention of Maternal-Fetal Transmission of HIV:**

118. Page 25, Lines 684 – 695, the following heading and paragraph are added:

Use for the Prevention of Maternal-Fetal Transmission of HIV: In a randomized, double-blind, placebo-controlled trial in HIV-infected women and their neonates conducted to determine the utility of RETROVIR for the prevention of maternal-fetal HIV transmission, RETROVIR Syrup at 2 mg/kg was administered every 6 hours for 6 weeks to neonates beginning within 12 hours after birth. The most commonly reported adverse experiences were anemia (hemoglobin <9.0 g/dL) and neutropenia (<1000 cells/mm^3). Anemia occurred in

22% of the neonates who received RETROVIR and in 12% of the neonates who received placebo. The mean difference in hemoglobin values was less than 1.0 g/dL for neonates receiving RETROVIR compared to neonates receiving placebo. No neonates with anemia required transfusion and all hemoglobin values spontaneously returned to normal within 6 weeks after completion of therapy with RETROVIR. Neutropenia was reported with similar frequency in the group that received RETROVIR (21%) and in the group that received placebo (27%). The long-term consequences of in utero and infant exposure to RETROVIR are unknown."

Change in **ADVERSE REACTIONS: Observed During Clinical Practice:**

119. Pages 25 and 26, Lines 696 – 700, the following heading and paragraph are added:

"**Observed During Clinical Practice:** In addition to adverse events reported from clinical trials, the following events have been identified during use of RETROVIR in clinical practice. 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 either their seriousness, frequency of reporting, potential causal connection to RETROVIR, or a combination of these factors."

120. Page 26, Lines 701 and 702, the following words are deleted: "Abdominal pain, body odor, chills, edema of the lip, fever, hyperalgesia and the word "like" is added to the word "flu"

121. Page 26, Line 703, the word "vasodilation" is deleted and the word "Cardiomyopathy" added.

122. Page 26, Line 704, the following heading is added: "***Eye:*** Macular edema."

123. Page 26, Lines 705 and 706, the following words are deleted: "bleeding gums, diarrhea, edema of the tongue, eructation, rectal hemorrhage."

124: Page 26, Line 707, the following heading is added: "***General:*** Sensitization reactions including anaphylaxis and angioedema, vasculitis."

125. Page 26, Lines 708 and 709, the following words are added: "Aplastic anemia, hemolytic anemia, leukopenia, pancytopenia with marrow hypoplasia"

126. Page 26, Lines 710 and 711, the following heading is added: "***Hepatobiliary Tract and Pancreas:*** Hepatitis, hepatomegaly with steatosis, juandice, lactic acidosis, pancreatitis."

127. Page 26, Lines 712 – 714, the following words are deleted: "Arthralgia, twitch." The following words are added: "Increased CPK, increased LDH, muscle spasm, myopathy and myositis with pathological changes (similar to that produced by HIV disease), rhabdomyolysis, tremor."

128. Page 26, Lines 715 and 716, the following words are deleted: "emotional lability, nervousness" and the following words are added: "mania, seizures".

129. Page 26, Line717, the following words are deleted: "epistaxis, hoarseness, pharyngitis".

130. Page 26, Lines 718 and 719, the word "Acne" is deleted and the words "Stevens-Johnson syndrome, toxic epidermal necrosis" are added.

131. Page 26, Line 721, the words "Dysuria, polyurea" are deleted.

132. Page 26, Line 722 – 730, the following heading and paragraph are deleted:

"***Pediatrics:*** Anemia and granulocytopenia among pediatric patients with advanced HIV disease receiving RETROVIR occurred with similar incidence to that reported for adults with AIDS or advanced ARC (see above). Management of neutropenia and anemia included, in some cases, dose modification and/or blood product transfusions. In the open-label studies, 17% had their dose modified (generally a reduction in dose by 30%) due to anemia and 25% had their dose modified (temporary discontinuation or dose reduction by 30%) for neutropenia. Four pediatric patients had RETROVIR permanently discontinued for neutropenia. The following table summarizes the occurrence of anemia (Hgb <7.5 g/dL) and granulocytopenia (<750 cells/mm3) among 124 pediatric patients receiving RETROVIR for a mean of 267 days (range 3 to 855 days):"

133. Page 27, Lines 732 – 735, the following table is deleted:

Table 6

Advanced Pediatric HIV Disease (n = 124)	Granulocytopenia (<750 cells/m m^3)		Anemia (Hgb <7.5 g/dL)	
	n	%	n	%
	48	39	28*	23

* Twenty-two pediatric patients received one or more transfusions due to a decline in hemoglobin to < 7.5 g/dL; an additional 15 pediatric patients were transfused for hemoglobin levels >7.5 g/dL. Fifty-nine percent of the patients transfused had a prestudy history of anemia or transfusion requirement.

134. Page 27, Lines 737 – 742, the following paragraphs are deleted:

" Macrocytosis was observed among the majority of pediatric patients enrolled in the studies.

In the open-label studies involving 124 pediatric patients, 16 clinical adverse events were reported by 24 pediatric patients. No event was reported by more than 5.6% of the study populations. Due to the open-label design of the studies, it was difficult to determine possible events related to the use of RETROVIR versus disease-related events. Therefore, all clinical events reported as associated with therapy with RETROVIR or of unknown relationship to therapy with RETROVIR are presented in the following table:"

135. Page 27, Lines 744 – 746, the following table is deleted:

Table 7
Percentage (%) of Pediatric Patients with Clinical Events in Open-Label Studies

Adverse Event	n	%
BODY AS A WHOLE		
Fever	4	3.2
Phlebitis*/Bacteremia	2	1.6
Headache	2	1.6
GASTROINTESTINAL		
Nausea	1	0.8
Vomiting	6	4.8
Abdominal Pain	4	3.2
Diarrhea	1	0.8
Weight Loss	1	0.8
NERVOUS		
Insomnia	3	2.4
Nervousness/Irritability	2	1.6
Decreased Reflexes	7	5.6
Seizure	1	0.8
CARDIOVASCULAR		
Left Ventricular Dilation	1	0.8
Cardiomyopathy	1	0.8
S_3 Gallop	1	0.8
Congestive Heart Failure	1	0.8
Generalized Edema	1	0.8
ECG Abnormality	3	2.4
UROGENITAL		
Hematuria/Viral Cystitis	1	0.8

* Peripheral vein IV catheter site.

136. Page 28, Lines 748 – 761, the following paragraphs and heading are deleted:

"The clinical adverse events reported among adult recipients of RETROVIR may also occur in pediatric patients.

Use for the Prevention of Maternal-Fetal Transmission of HIV: In a randomized, double-blind, placebo-controlled trial in HIV-infected women and their neonates conducted to determine the utility of RETROVIR for the prevention of maternal-fetal HIV transmission, RETROVIR Syrup at 2 mg/kg was administered every 6 hours for 6 weeks to neonates beginning within 12 hours after birth. The most commonly reported adverse experiences were anemia (hemoglobin <9.0 g/dL) and neutropenia (<1000 cells/mm3). Anemia occurred in 22% of the neonates who received RETROVIR and in 12% of the neonates who received placebo. The mean difference in hemoglobin values was less than 1.0 g/dL for neonates receiving RETROVIR compared to neonates receiving placebo. No neonates with anemia required transfusion and all hemoglobin values spontaneously returned to normal within 6 weeks after completion of therapy with RETROVIR. Neutropenia was reported with similar frequency in the group that received RETROVIR (21%) and in the group that

received placebo (27%). The long-term consequences of in utero and infant exposure to RETROVIR are unknown."

Changes in **OVERDOSAGE:**

137. Page 28, Line 763, the words "Cases of a" at the beginning of the section are deleted and the letter "A" is added to form the word "Acute".

138. Page 28, Line 763, the words "of zidovudine have been reported" is added immediately after the word "overdoses".

139. Page 28, Line 763 and 764, the word "both" immediately before the word "pediatric" is deleted. The words "have been reported" immediately after the word "adults" are deleted. The word "doses" immediately before the words "up to 50 grams." is deleted.

140. Page 28, Line 764 – 766, the words "These involved exposures" immediately before the words "up to 50 grams." are added. The following sentence is added immediately after the words "up to 50 grams.": "No specific symptoms or signs have been identified following acute overdosage with zidovudine apart from those listed as adverse events such as fatigue, headache, vomiting, and occasional reports of hematological disturbances."

141. Page 28, Lines 766 – 771, the following sentences are deleted:

"None were fatal. The only consistent finding in these cases of overdose was spontaneous or induced nausea and vomiting. Hematologic changes were transient and not severe. Some patients experienced nonspecific CNS symptoms such as headache, dizziness, drowsiness, lethargy, and confusion. One report of a grand mal seizure possibly attributable to RETROVIR occurred in a 35-year-old male 3 hours after ingesting 36 grams of RETROVIR. No other cause could be identified."

Changes in **DOSAGE AND ADMINISTRATION: Adults:**

142. Page 28, Line 776, The word "total" immediately after the word "recommended" and immediately before the word "oral" is deleted. The word "daily" immediately after the word "oral" and immediately before the word "dose" is deleted.

143. Page 28, Lines 777 and 778, a period is added immediately after the word "agents" at the end of the first sentence. The following words "and 500 mg (100 mg every 4 hours while awake) or 600 mg per day in divided doses for monotherapy." are deleted from the first sentence immediately after the word "agents.".

144. _____

Changes in **DOSAGE AND ADMINISTRATION: Dose Adjustment: *Anemia:***

145. Page 29, Line 801, The heading "***Anemia:*** is added immediately following the heading "**Dose Adjustment:**" and immediately before the first sentence of the section.

146. Page 29, Lines 803 – 804, the following sentence is deleted: "For less severe anemia or neutropenia, a reduction in daily dose may be adequate."

147. Page 29, Line 808, the heading "***End-stage Renal Disease:***" is added immediately after the ***Anemia:*** section and the words "end-stage renal disease" are deleted from the first sentence immediately after the word "In".

148. Page 29, Line 811, the following heading and first sentence "***Hepatic Impairment:*** are added immediately after the heading "***End-stage Renal Disease:***".

149. Page 29, Lines 812 and 813. The words Mild to moderate are added immediately after the words "in patients with" and immediately after the words "impaired hepatic function. The words "(see CLINICAL PHARMACOLOGY: Pharmacokinetics."

150. Page 30, Line 828, the letters "U.S." are deleted and the letters "US" are added immediately before the words (Patent Nos."

151. Page 30, Line 838, the date and numbers "October 1997 RL 493" are deleted.

152. Page 30, Line 839, Date of Issue and RL no. will be added when final printed labeling is approved.

Conclusions

All of the changes noted in the labeling review were acceptable. An approval letter will be sent to the sponsor and they will be asked to submit a final printed labeling identical to the draft labeling submitted March 9, 1998 and the RETROVIR package insert.

/s/ Marsha S. Holloman, BS Pharm, JD — October 10, 2000

Regulatory Project Manager (Consumer Safety Officer) — Date