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## RETROVIR® (zidovudine) Tablets

## RETROVIR® (zidovudine) Capsules

## RETROVIR® (zidovudine) Syrup

WARNING: RETROVIR (ZIDOVUDINE) MAY BE ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING GRANULOCYTOPENIA AND SEVERE ANEMIA PARTICULARLY IN PATIENTS WITH ADVANCED HIV DISEASE (SEE WARNINGS). PROLONGED USE OF RETROVIR HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY SIMILAR TO THAT PRODUCED BY HUMAN IMMUNODEFICIENCY VIRUS.

**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 (SEE WARNINGS).**

**DESCRIPTION:** RETROVIR is the brand name for zidovudine (formerly called azidothymidine [AZT]), a pyrimidine nucleoside analogue active against human immunodeficiency virus (HIV).

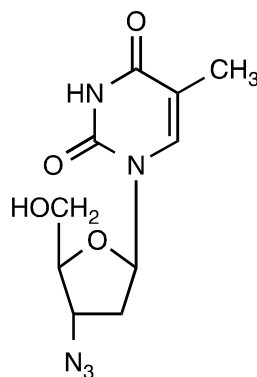
**Tablets:** RETROVIR Tablets are for oral administration. Each film-coated tablet contains 300 mg of zidovudine and the inactive ingredients hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.

**Capsules:** RETROVIR Capsules are for oral administration. Each capsule contains 100 mg of zidovudine and the inactive ingredients corn starch, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The 100-mg empty hard gelatin capsule, printed with edible black ink, consists of black iron oxide, dimethylpolysiloxane, gelatin, pharmaceutical shellac, soya lecithin, and titanium dioxide. The blue band around the capsule consists of gelatin and FD&C Blue No. 2.

**Syrup:** RETROVIR Syrup is for oral administration. Each teaspoonful (5 mL) of RETROVIR Syrup contains 50 mg of zidovudine and the inactive ingredients sodium benzoate 0.2% (added as a preservative), citric acid, flavors, glycerin, and liquid sucrose. Sodium hydroxide may be added to adjust pH.

The chemical name of zidovudine is 3'-azido-3'-deoxythymidine; it has the following structural formula:

## RETROVIR® (zidovudine) Tablets, Capsules, and Syrup



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36 Zidovudine is a white to beige, odorless, crystalline solid with a molecular weight of 267.24 and a  
37 solubility of 20.1 mg/mL in water at 25°C. The molecular formula is C<sub>10</sub>H<sub>13</sub>N<sub>5</sub>O<sub>4</sub>.

38

39 **MICROBIOLOGY: Mechanism of Action:** Zidovudine is a synthetic nucleoside analogue of the  
40 naturally occurring nucleoside, thymidine, in which the 3'-hydroxy (-OH) group is replaced by an azido  
41 (-N<sub>3</sub>) group. Within cells, zidovudine is converted to the active metabolite, zidovudine 5'-triphosphate  
42 (AztTP), by the sequential action of the cellular enzymes. Zidovudine 5'-triphosphate inhibits the  
43 activity of the HIV reverse transcriptase both by competing for utilization with the natural substrate,  
44 deoxythymidine 5'-triphosphate (dTTP), and by its incorporation into viral DNA. The lack of a 3'-OH  
45 group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester  
46 linkage essential for DNA chain elongation and, therefore, the viral DNA growth is terminated. The  
47 active metabolite AztTP is also a weak inhibitor of the cellular DNA polymerase-alpha and  
48 mitochondrial polymerase-gamma and has been reported to be incorporated into the DNA of cells in  
49 culture.

50 **In Vitro HIV Susceptibility:** The in vitro anti-HIV activity of zidovudine was assessed by infecting cell  
51 lines of lymphoblastic and monocytic origin and peripheral blood lymphocytes with laboratory and  
52 clinical isolates of HIV. The IC<sub>50</sub> and IC<sub>90</sub> values (50% and 90% inhibitory concentrations) were 0.003  
53 to 0.013 and 0.03 to 0.13 mcg/mL, respectively (1 nM = 0.27 ng/mL). The IC<sub>50</sub> and IC<sub>90</sub> values of HIV  
54 isolates recovered from 18 untreated AIDS/ARC patients were in the range of 0.003 to 0.013 mcg/mL  
55 and 0.03 to 0.3 mcg/mL, respectively. Zidovudine showed antiviral activity in all acutely infected cell  
56 lines; however, activity was substantially less in chronically infected cell lines. In drug combination  
57 studies with zalcitabine, didanosine, lamivudine, saquinavir, indinavir, ritonavir, nevirapine,  
58 delavirdine, or interferon-alpha, zidovudine showed additive to synergistic activity in cell culture. The  
59 relationship between the in vitro susceptibility of HIV to reverse transcriptase inhibitors and the  
60 inhibition of HIV replication in humans has not been established.

61 **Drug Resistance:** HIV isolates with reduced sensitivity to zidovudine have been selected in vitro and  
62 were also recovered from patients treated with RETROVIR. Genetic analysis of the isolates showed  
63 mutations which result in five amino acid substitutions (Met41→Leu, A67→Asn, Lys70→Arg,

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64 Thr215→Tyr or Phe, and Lys219→Gln) in the viral reverse transcriptase. In general, higher levels of  
65 resistance were associated with greater number of mutations with 215 mutation being the most  
66 significant.

67 **Cross-Resistance:** The potential for cross-resistance between HIV reverse transcriptase inhibitors  
68 and protease inhibitors is low because of the different enzyme targets involved. Combination therapy  
69 with zidovudine plus zalcitabine or didanosine does not appear to prevent the emergence of  
70 zidovudine-resistant isolates. Combination therapy with RETROVIR plus EPIVIR® delayed the  
71 emergence of mutations conferring resistance to zidovudine. In some patients harboring  
72 zidovudine-resistant virus, combination therapy with RETROVIR plus EPIVIR restored phenotypic  
73 sensitivity to zidovudine by 12 weeks of treatment. HIV isolates with multidrug resistance to  
74 zidovudine, didanosine, zalcitabine, stavudine, and lamivudine were recovered from a small number  
75 of patients treated for ≥1 year with the combination of zidovudine and didanosine or zalcitabine. The  
76 pattern of resistant mutations in the combination therapy was different (Ala62→Val, Val75→Ile,  
77 Phe77→116Tyr, and Gln→151Met) from monotherapy, with mutation 151 being most significant for  
78 multidrug resistance. Site-directed mutagenesis studies showed that these mutations could also  
79 result in resistance to zalcitabine, lamivudine, and stavudine.

80

### 81 **CLINICAL PHARMACOLOGY:**

82 **Pharmacokinetics: Adults:** The pharmacokinetics of zidovudine has been evaluated in 22 adult  
83 HIV-infected patients in a Phase 1 dose-escalation study. After oral dosing (capsules), zidovudine  
84 was rapidly absorbed from the gastrointestinal tract with peak serum concentrations occurring within  
85 0.5 to 1.5 hours. Dose-independent kinetics was observed over the range of 2 mg/kg every 8 hours to  
86 10 mg/kg every 4 hours. The mean zidovudine half-life was approximately 1 hour and ranged from  
87 0.78 to 1.93 hours following oral dosing.

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

98 Additional pharmacokinetic data following intravenous dosing indicated dose-independent kinetics  
99 over the range of 1 to 5 mg/kg with a mean zidovudine half-life of 1.1 hours (range 0.48 to  
100 2.86 hours). Total body clearance averaged 1900 mL/min per 70 kg and the apparent volume of

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101 distribution was 1.6 L/kg. Renal clearance is estimated to be 400 mL/min per 70 kg, indicating  
102 glomerular filtration and active tubular secretion by the kidneys. Zidovudine plasma protein binding is  
103 34% to 38%, indicating that drug interactions involving binding site displacement are not anticipated.

104 The zidovudine cerebrospinal fluid (CSF)/plasma concentration ratio was determined in  
105 39 patients receiving chronic therapy with RETROVIR. The median ratio measured in 50 paired  
106 samples drawn 1 to 8 hours after the last dose of RETROVIR was 0.6.

107 **Adults with Impaired Renal Function:** The pharmacokinetics of zidovudine has been evaluated  
108 in patients with impaired renal function following a single 200-mg oral dose. In 14 patients (mean  
109 creatinine clearance  $18 \pm 2$  mL/min) the half-life of zidovudine was 1.4 hours compared to 1.0 hour  
110 for control subjects with normal renal function; AUC values were approximately twice those of  
111 controls. Additionally, GZDV half-life in these patients was 8.0 hours (vs 0.9 hours for control) and  
112 AUC was 17 times higher than for control subjects. The pharmacokinetics and tolerance were  
113 evaluated in a multiple-dose study in patients undergoing hemodialysis (n = 5) or peritoneal dialysis  
114 (n = 6). Patients received escalating doses of zidovudine up to 200 mg five times daily for 8 weeks.  
115 Daily doses of 500 mg or less were well tolerated despite significantly elevated plasma levels of  
116 GZDV. Apparent oral clearance of zidovudine was approximately 50% of that reported in patients with  
117 normal renal function. The plasma concentrations of AMT are not known in patients with renal  
118 insufficiency. Daily doses of 300 to 400 mg should be appropriate in HIV-infected patients with severe  
119 renal dysfunction (see DOSAGE AND ADMINISTRATION: Dose Adjustment). Hemodialysis and  
120 peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, whereas GZDV  
121 elimination is enhanced.

122 **Pediatrics:** The pharmacokinetics and bioavailability of zidovudine have been evaluated in  
123 21 HIV-infected pediatric patients, aged 6 months through 12 years, following intravenous doses  
124 administered over the range of 80 to 160 mg/m<sup>2</sup> every 6 hours, and following oral doses of the IV  
125 solution administered over the range of 90 to 240 mg/m<sup>2</sup> every 6 hours. After discontinuation of the IV  
126 infusion, zidovudine plasma concentrations decayed biexponentially, consistent with  
127 two-compartment pharmacokinetics. Proportional increases in AUC and in zidovudine concentrations  
128 were observed with increasing dose, consistent with dose-independent kinetics over the dose range  
129 studied. The mean terminal half-life and total body clearance across all dose levels administered  
130 were 1.5 hours and 30.9 mL/min per kg, respectively. These values compare to mean half-life and  
131 total body clearance in adults of 1.1 hours and 27.1 mL/min per kg.

132 The mean oral bioavailability of 65% was independent of dose. This value is the same as the  
133 bioavailability in adults. Doses of 180 mg/m<sup>2</sup> four times daily in pediatric patients produced similar  
134 systemic exposure (24-hour AUC 10.7 hr•mcg/mL) as doses of 200 mg six times daily in adult  
135 patients (10.9 hr•mcg/mL).

136 The pharmacokinetics of zidovudine have been studied in pediatric patients from birth to 3 months  
137 of life. In one study of the pharmacokinetics of zidovudine in women during the last trimester of

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138 pregnancy, zidovudine elimination was determined immediately after birth in eight neonates who were  
139 exposed to zidovudine in utero. The half-life was  $13.0 \pm 5.8$  hours. In another study, the  
140 pharmacokinetics of zidovudine were evaluated in pediatric patients (ranging in age of 1 day to  
141 3 months) of normal birth weight for gestational age and with normal renal and hepatic function. In  
142 neonates less than or equal to 14 days old, mean  $\pm$  SD total body clearance was  $10.9 \pm 4.8$  mL/min  
143 per kg ( $n = 18$ ) and half-life was  $3.1 \pm 1.2$  hours ( $n = 21$ ). In neonates and infants greater than  
144 14 days old, total body clearance was  $19.0 \pm 4.0$  mL/min per kg ( $n = 16$ ) and half-life was  
145  $1.9 \pm 0.7$  hours ( $n = 18$ ). Bioavailability was  $89\% \pm 19\%$  ( $n = 15$ ) in the younger age group and  
146 decreased to  $61\% \pm 19\%$  ( $n = 17$ ) in patients older than 14 days.

147 Concentrations of zidovudine in cerebrospinal fluid were measured after both intermittent oral and  
148 IV drug administration in 21 pediatric patients during Phase 1 and Phase 2 studies. The mean  
149 zidovudine CSF/plasma concentration ratio measured at an average time of 2.2 hours postdose at  
150 oral doses of 120 to 240 mg/m<sup>2</sup> was  $0.52 \pm 0.44$  ( $n = 28$ ); after an IV infusion of doses of 80 to  
151 160 mg/m<sup>2</sup> over 1 hour, the mean CSF/plasma concentration ratio was  $0.87 \pm 0.66$  ( $n = 23$ ) at  
152 3.2 hours after the start of the infusion. During continuous IV infusion, mean steady-state  
153 CSF/plasma ratio was  $0.26 \pm 0.17$  ( $n = 28$ ).

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

158 **Pregnancy:** The pharmacokinetics of zidovudine have been studied in a Phase 1 study of eight  
159 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of  
160 drug accumulation. The pharmacokinetics of zidovudine were similar to that of nonpregnant adults.  
161 Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in  
162 infant plasma at birth were essentially equal to those in maternal plasma at delivery. Although data  
163 are limited, methadone maintenance therapy in five pregnant women did not appear to alter  
164 zidovudine pharmacokinetics. However, in another patient population, a potential for interaction has  
165 been identified (see PRECAUTIONS).

166 **Nursing Mothers:** The U.S. Public Health Service Centers for Disease Control and Prevention  
167 advises HIV-infected women not to breastfeed to avoid postnatal transmission of HIV to a child who  
168 may not yet be infected. After administration of a single dose of 200 mg zidovudine to 13 HIV-infected  
169 women, the mean concentration of zidovudine was similar in human milk and serum (see  
170 PRECAUTIONS: Nursing Mothers).

171 **Effect of Food on Absorption:** Administration of RETROVIR Capsules with food decreased  
172 peak plasma concentrations by greater than 50%; however, bioavailability as determined by AUC  
173 may not be affected.

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

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175       **Tablets:** In a single-dose study of 23 healthy volunteers, the mean  $\pm$  SD relative bioavailability of  
176 the RETROVIR 300-mg Tablet relative to three 100-mg RETROVIR Capsules was  $110 \pm 18\%$ . After  
177 administration of the 300-mg RETROVIR Tablet or three 100-mg RETROVIR Capsules, the mean  
178  $\pm$  SD  $C_{\max}$  values were  $1.81 \pm 0.52$  and  $1.50 \pm 0.46$  mcg/mL, respectively.

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

186

187       **INDICATIONS AND USAGE:** RETROVIR is indicated for the treatment of HIV infection when  
188 antiretroviral therapy is warranted (see Description of Clinical Studies).

189       The duration of clinical benefit from antiretroviral therapy may be limited. Alterations in  
190 antiretroviral therapy should be considered if disease progression occurs during treatment.

191       **Maternal-Fetal HIV Transmission:** RETROVIR is also indicated for the prevention of maternal-fetal  
192 HIV transmission as part of a regimen that includes oral RETROVIR beginning between 14 and  
193 34 weeks of gestation, intravenous RETROVIR during labor, and administration of RETROVIR Syrup  
194 to the neonate after birth. The efficacy of this regimen for preventing HIV transmission in women who  
195 have received RETROVIR for a prolonged period before pregnancy has not been evaluated. The  
196 safety of RETROVIR for the mother or fetus during the first trimester of pregnancy has not been  
197 assessed (see Description of Clinical Studies).

198       **Description of Clinical Studies:** Therapy with RETROVIR has been shown to prolong survival and  
199 decrease the incidence of opportunistic infections in patients with advanced HIV disease at the  
200 initiation of therapy and to delay disease progression in asymptomatic HIV-infected patients.

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

203       **Combination Therapy-Adults:** ACTG175 was a randomized, double-blind, controlled trial that  
204 compared RETROVIR 200 mg t.i.d.; didanosine 200 mg b.i.d.; RETROVIR plus didanosine; and  
205 RETROVIR plus zalcitabine 0.75 mg t.i.d. A total of 2467 HIV-infected adults with baseline CD4  
206 counts of 200 to 500 cells/mm<sup>3</sup> (mean = 352) and no prior AIDS-defining event enrolled with the  
207 following demographics: male (82%), Caucasian (70%), mean age of 35 years, asymptomatic HIV  
208 infection (81%), and prior antiretroviral use (57%, mean duration = 89.5 weeks). The overall median  
209 duration of study treatment was 118 weeks. The incidence of AIDS-defining events or death is shown  
210 in Table 1.

211

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**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%)
Naive	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%)

216

217 RETROVIR in combination with certain antiretroviral agents has been shown to be superior to  
218 monotherapy in one or more of the following: delaying death, delaying development of AIDS,  
219 increasing CD4 cell counts, and decreasing plasma HIV RNA. Use of RETROVIR in some  
220 combinations is based on surrogate marker data. The complete prescribing information for each drug  
221 should be consulted before combination therapy which includes RETROVIR is initiated.

222 ***Pregnant Women and Their Neonates:*** The utility of RETROVIR for the prevention of  
223 maternal-fetal HIV transmission was demonstrated in a randomized, double-blind, placebo-controlled  
224 trial (ACTG 076) conducted in HIV-infected pregnant women with CD4 cell counts of 200  
225 to 1818 cells/mm<sup>3</sup> (median in the treated group: 560 cells/mm<sup>3</sup>) who had little or no previous exposure  
226 to RETROVIR. Oral RETROVIR was initiated between 14 and 34 weeks of gestation (median  
227 11 weeks of therapy) followed by IV administration of RETROVIR during labor and delivery. After  
228 birth, neonates received oral RETROVIR Syrup for 6 weeks. The study showed a statistically  
229 significant difference in the incidence of HIV infection in the neonates (based on viral culture from  
230 peripheral blood) between the group receiving RETROVIR and the group receiving placebo. Of  
231 363 neonates evaluated in the study, the estimated risk of HIV infection was 7.8% in the group  
232 receiving RETROVIR and 24.9% in the placebo group, a relative reduction in transmission risk of  
233 68.7%. RETROVIR was well tolerated by mothers and infants. There was no difference in  
234 pregnancy-related adverse events between the treatment groups.

235 ***Dose-Frequency Study:*** A randomized, double-blind, dose-frequency study of RETROVIR in  
236 320 patients with AIDS or advanced ARC was conducted to assess the safety and tolerability of

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237 600 mg RETROVIR per day given as either 100 mg every 4 hours or as 300 mg every 12 hours for  
238 48 weeks. No significant difference was detected between the two dose frequencies with regard to  
239 adverse experiences or hematologic abnormalities. Although this study was not designed to  
240 determine efficacy, no differences in the frequency of or time to opportunistic infections, neoplasms,  
241 or death were noted between treatment groups. Changes in CD4 cell counts and  $\beta_2$ -microglobulin  
242 levels were similar between treatment groups.

243

244 **CONTRAINDICATIONS:** RETROVIR Tablets, Capsules, and Syrup are contraindicated for patients  
245 who have potentially life-threatening allergic reactions to any of the components of the formulations.

246

247 **WARNINGS:** Before combination therapy with RETROVIR is initiated, consult the complete  
248 prescribing information for each drug. The safety profile of RETROVIR plus other antiretroviral agents  
249 reflects the individual safety profiles of each component.

250 The incidence of adverse reactions appears to increase with disease progression, and patients  
251 should be monitored carefully, especially as disease progression occurs.

252 **Bone Marrow Suppression:** RETROVIR should be used with caution in patients who have bone  
253 marrow compromise evidenced by granulocyte count  $<1000$  cells/mm<sup>3</sup> or hemoglobin  $<9.5$  g/dL. In  
254 patients with advanced symptomatic HIV disease, anemia and neutropenia were the most significant  
255 adverse events observed (see ADVERSE REACTIONS). There have been reports of pancytopenia  
256 associated with the use of RETROVIR, which was reversible in most instances after discontinuance  
257 of the drug. However, significant anemia, in many cases requiring dose adjustment, discontinuation  
258 of RETROVIR, and/or blood transfusions has occurred during treatment with RETROVIR alone or in  
259 combination with other antiretrovirals.

260 Frequent blood counts are strongly recommended in patients with advanced HIV disease who are  
261 treated with RETROVIR. For HIV-infected individuals and patients with asymptomatic or early HIV  
262 disease, periodic blood counts are recommended. If anemia or neutropenia develops, dosage  
263 adjustments may be necessary (see DOSAGE AND ADMINISTRATION).

264 **Myopathy:** Myopathy and myositis with pathological changes, similar to that produced by HIV  
265 disease, have been associated with prolonged use of RETROVIR.

266 **Lactic Acidosis/Severe Hepatomegaly with Steatosis:** Rare occurrences of potentially fatal lactic  
267 acidosis in the absence of hypoxemia, and severe hepatomegaly with steatosis have been reported  
268 with the use of certain antiretroviral nucleoside analogues. Lactic acidosis should be considered  
269 whenever a patient receiving therapy with RETROVIR develops unexplained tachypnea, dyspnea, or  
270 fall in serum bicarbonate level. Under these circumstances, therapy with RETROVIR should be  
271 suspended until the diagnosis of lactic acidosis has been excluded. Caution should be exercised  
272 when administering RETROVIR to any patient, particularly obese women, with hepatomegaly,  
273 hepatitis, or other known risk factor for liver disease. These patients should be followed closely while



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274 on therapy with RETROVIR. The significance of elevated aminotransferase levels suggesting hepatic  
275 injury in HIV-infected patients prior to starting RETROVIR or while on RETROVIR is unclear.

276 Treatment with RETROVIR should be suspended in the setting of rapidly elevating aminotransferase  
277 levels, progressive hepatomegaly, or metabolic/lactic acidosis of unknown etiology.

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

283

### 284 **PRECAUTIONS:**

285 **General:** Zidovudine is eliminated from the body primarily by renal excretion following metabolism in  
286 the liver (glucuronidation). In patients with severely impaired renal function, dosage reduction is  
287 recommended (see CLINICAL PHARMACOLOGY: Pharmacokinetics and DOSAGE AND  
288 ADMINISTRATION). Although very little data are available, patients with severely impaired hepatic  
289 function may be at greater risk of toxicity.

290 **Information for Patients:** RETROVIR is not a cure for HIV infection, and patients may continue to  
291 acquire illnesses associated with HIV infection, including opportunistic infections. Therefore, patients  
292 should be advised to seek medical care for any significant change in their health status.

293 The safety and efficacy of RETROVIR in women, intravenous drug users, and racial minorities is  
294 not significantly different than that observed in white males.

295 Patients should be informed that the major toxicities of RETROVIR are neutropenia and/or  
296 anemia. The frequency and severity of these toxicities are greater in patients with more advanced  
297 disease and in those who initiate therapy later in the course of their infection. They should be told that  
298 if toxicity develops, they may require transfusions or dose modifications including possible  
299 discontinuation. They should be told of the extreme importance of having their blood counts followed  
300 closely while on therapy, especially for patients with advanced symptomatic HIV disease. They  
301 should be cautioned about the use of other medications, including ganciclovir and interferon-alpha,  
302 that may exacerbate the toxicity of RETROVIR (see PRECAUTIONS: Drug Interactions). Patients  
303 should be informed that other adverse effects of RETROVIR include nausea and vomiting. Patients  
304 should also be encouraged to contact their physician if they experience muscle weakness, shortness  
305 of breath, symptoms of hepatitis or pancreatitis, or any other unexpected adverse events while being  
306 treated with RETROVIR.

307 RETROVIR Tablets, Capsules, and Syrup are for oral ingestion only. Patients should be told of the  
308 importance of taking RETROVIR exactly as prescribed. They should be told not to share medication  
309 and not to exceed the recommended dose. Patients should be told that the long-term effects of  
310 RETROVIR are unknown at this time.

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311 Pregnant women considering the use of RETROVIR during pregnancy for prevention of  
312 HIV-transmission to their infants should be advised that transmission may still occur in some cases  
313 despite therapy. The long-term consequences of in utero and infant exposure to RETROVIR are  
314 unknown, including the possible risk of cancer.

315 HIV-infected pregnant women should be advised not to breastfeed to avoid postnatal transmission  
316 of HIV to a child who may not yet be infected.

317 Patients should be advised that therapy with RETROVIR has not been shown to reduce the risk of  
318 transmission of HIV to others through sexual contact or blood contamination.

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

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

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

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

336 ***Phenytoin*:** Phenytoin plasma levels have been reported to be low in some patients receiving  
337 RETROVIR, while in one case a high level was documented. However, in a pharmacokinetic  
338 interaction study in which 12 HIV-positive volunteers received a single 300-mg phenytoin dose alone  
339 and during steady-state zidovudine conditions (200 mg every 4 hours), no change in phenytoin  
340 kinetics was observed. Although not designed to optimally assess the effect of phenytoin on  
341 zidovudine kinetics, a 30% decrease in oral zidovudine clearance was observed with phenytoin.

342 ***Methadone*:** In a pharmacokinetic study of nine HIV-positive patients receiving  
343 methadone-maintenance (30 to 90 mg daily) concurrent with 200 mg of RETROVIR every 4 hours,  
344 no changes were observed in the pharmacokinetics of methadone upon initiation of therapy with  
345 RETROVIR and after 14 days of treatment with RETROVIR. No adjustments in  
346 methadone-maintenance requirements were reported. For four patients, the mean zidovudine AUC

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347 was elevated twofold, while for five patients, the value was equal to that of control patients. The exact  
348 mechanism and clinical significance of these data are unknown.

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

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

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

371 **Lamivudine:** RETROVIR and lamivudine were coadministered to 12 asymptomatic HIV-positive  
372 patients in a single-center, open-label, randomized, crossover study. No significant differences were  
373 observed in AUC<sub>∞</sub> or total clearance for lamivudine or zidovudine when the two drugs were  
374 administered together. Coadministration of RETROVIR with lamivudine resulted in an increase of  
375 39% ± 62% (mean ± SD) in C<sub>max</sub> of zidovudine.

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

382 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Zidovudine was administered orally at  
383 three dosage levels to separate groups of mice and rats (60 females and 60 males in each group).

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384 Initial single daily doses were 30, 60, and 120 mg/kg per day in mice and 80, 220, and 600 mg/kg per  
385 day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg per day after day 90 because of  
386 treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg per day on  
387 day 91 and then to 300 mg/kg per day on day 279.

388 In mice, seven late-appearing (after 19 months) vaginal neoplasms (five nonmetastasizing  
389 squamous cell carcinomas, one squamous cell papilloma, and one squamous polyp) occurred in  
390 animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina  
391 of a middle-dose animal. No vaginal tumors were found at the lowest dose.

392 In rats, two late-appearing (after 20 months), nonmetastasizing vaginal squamous cell carcinomas  
393 occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in  
394 rats. No other drug-related tumors were observed in either sex of either species.

395 At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by  
396 AUC) was approximately three times (mouse) and 24 times (rat) the estimated human exposure at  
397 the recommended therapeutic dose of 100 mg every 4 hours.

398 Two transplacental carcinogenicity studies were conducted in mice. One study administered  
399 zidovudine at doses of 20 mg/kg per day or 40 mg/kg per day from gestation day 10 through  
400 parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of  
401 zidovudine employed in this study produced zidovudine exposures approximately three times the  
402 estimated human exposure at recommended doses. After 24 months, an increase in incidence of  
403 vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either  
404 gender. These findings are consistent with results of the standard oral carcinogenicity study in mice,  
405 as described earlier. A second study administered zidovudine at maximum tolerated doses of  
406 12.5 mg/day or 25 mg/day (~1000 mg/kg nonpregnant body weight or ~450 mg/kg of term body  
407 weight) to pregnant mice from days 12 through 18 of gestation. There was an increase in the number  
408 of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher  
409 dose level of zidovudine.

410 It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

411 Zidovudine was mutagenic in a 5178Y/TK<sup>+/-</sup> mouse lymphoma assay, positive in an in vitro cell  
412 transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and  
413 positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic  
414 study in rats given a single dose.

415 Zidovudine, administered to male and female rats at doses up to seven times the usual adult dose  
416 based on body surface area considerations, had no effect on fertility judged by conception rates.

417 **Pregnancy:** Pregnancy Category C. Oral teratology studies in the rat and in the rabbit at doses up to  
418 500 mg/kg per day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment  
419 resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in  
420 rats given 150 or 450 mg/kg per day and rabbits given 500 mg/kg per day. The doses used in the

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421 teratology studies resulted in peak zidovudine plasma concentrations (after one half of the daily dose)  
422 in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma  
423 concentrations (after one sixth of the daily dose) achieved with the recommended daily dose (100 mg  
424 every 4 hours). In an in vitro experiment with fertilized mouse oocytes, zidovudine exposure resulted  
425 in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose  
426 of 3000 mg/kg per day (very near the oral median lethal dose in rats of 3683 mg/kg) caused marked  
427 maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak  
428 zidovudine plasma concentrations 350 times peak human plasma concentrations. (Estimated  
429 area-under-the-curve [AUC] in rats at this dose level was 300 times the daily AUC in humans given  
430 600 mg per day.) No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg  
431 per day or less.

432 Two rodent transplacental carcinogenicity studies were conducted (see Carcinogenesis,  
433 Mutagenesis, Impairment of Fertility).

434 A randomized, double-blind, placebo-controlled trial was conducted in HIV-infected pregnant  
435 women to determine the utility of RETROVIR for the prevention of maternal-fetal HIV-transmission  
436 (see INDICATIONS AND USAGE: Description of Clinical Studies). Congenital abnormalities occurred  
437 with similar frequency between neonates born to mothers who received RETROVIR and neonates  
438 born to mothers who received placebo. Abnormalities were either problems in embryogenesis (prior  
439 to 14 weeks) or were recognized on ultrasound before or immediately after initiation of study drug.

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

443 **Nursing Mothers:** The U.S. Public Health Service Centers for Disease Control and Prevention  
444 advises HIV-infected women not to breastfeed to avoid postnatal transmission of HIV to a child who  
445 may not yet be infected. Zidovudine is excreted in human milk (see Pharmacokinetics).

446 **Pediatric Use:** RETROVIR has been studied in HIV-infected pediatric patients over 3 months of age  
447 who have HIV-related symptoms or who are asymptomatic with abnormal laboratory values indicating  
448 significant HIV-related immunosuppression (see ADVERSE REACTIONS, DOSAGE AND  
449 ADMINISTRATION, and INDICATIONS AND USAGE: Description of Clinical Studies, and  
450 Pharmacokinetics).

451 **Geriatric Use:** Clinical studies of RETROVIR did not include sufficient numbers of subjects aged 65  
452 and over to determine whether they respond differently from younger subjects. Other reported clinical  
453 experience has not identified differences in responses between the elderly and younger patients. In  
454 general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of  
455 decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

456

457 **ADVERSE REACTIONS:**

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458 **Monotherapy: Adults:** The frequency and severity of adverse events associated with the use of  
 459 RETROVIR in adults are greater in patients with more advanced infection at the time of initiation of  
 460 therapy. The following table summarizes the relative incidence of hematologic adverse events  
 461 observed in clinical studies by severity of HIV disease present at the start of treatment:

462

463

464

**Table 2**

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

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

466 † Not statistically significant compared to placebo.

467 ‡ Anemia = Hgb <7.5 g/dL.

468

469 The anemia reported in patients with advanced HIV disease receiving RETROVIR appeared to be  
 470 the result of impaired erythrocyte maturation as evidenced by macrocytosis while on drug. Although  
 471 mean platelet counts in patients receiving RETROVIR were significantly increased compared to  
 472 mean baseline values, thrombocytopenia did occur in some of these patients with advanced disease.  
 473 Twelve percent of patients receiving RETROVIR compared to 5% of patients receiving placebo had  
 474 >50% decreases from baseline platelet count. Mild drug-associated elevations in total bilirubin levels  
 475 have been reported as an uncommon occurrence in patients treated for asymptomatic HIV infection.

476 The HIV-infected adults participating in these clinical trials often had baseline symptoms and signs  
 477 of HIV disease and/or experienced adverse events at some time during study. It was often difficult to  
 478 distinguish adverse events possibly associated with administration of RETROVIR from underlying  
 479 signs of HIV disease or intercurrent illnesses. The following table summarizes clinical adverse events  
 480 or symptoms which occurred in at least 5% of all patients with advanced HIV disease treated with  
 481 1500 mg/day of RETROVIR in the original placebo-controlled study. Of the items listed in the table,

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482 only severe headache, nausea, insomnia, and myalgia were reported at a significantly greater rate in  
 483 patients receiving RETROVIR.

484

485

**Table 3**

486

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

487

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

488

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

489

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

496

497

**Table 4**

498

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

499

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

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

501



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502 **Table 5**  
 503 **Percentage (%) of Patients with Adverse Events\* in Asymptomatic HIV Infection (ACTG**  
 504 **019)**  
 505

Adverse Event	RETROVIR 500 mg/day (n = 453) %	Placebo (n = 428) %
<b>BODY AS A WHOLE</b>		
Asthenia	8.6†	5.8
Headache	62.5	52.6
Malaise	53.2	44.9
<b>GASTROINTESTINAL</b>		
Anorexia	20.1	10.5
Constipation	6.4†	3.5
Nausea	51.4	29.9
Vomiting	17.2	9.8
<b>NERVOUS</b>		
Dizziness	17.9†	15.2

506 \* Reported in ≥5% of study population.

507 † Not statistically significant versus placebo.

508

509 Several serious adverse events have been reported with the use of RETROVIR in clinical practice.  
 510 Myopathy and myositis with pathological changes, similar to that produced by HIV disease, have  
 511 been associated with prolonged use of RETROVIR. Reports of hepatomegaly with steatosis,  
 512 hepatitis, pancreatitis, lactic acidosis, sensitization reactions (including anaphylaxis in one patient),  
 513 hyperbilirubinemia, vasculitis, and seizures have been rare. These adverse events, except for  
 514 sensitization, have also been associated with HIV disease. A single case of macular edema has been  
 515 reported with the use of RETROVIR.

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

520 **Body as a Whole:** Abdominal pain, back pain, body odor, chest pain, chills, edema of the lip,  
 521 fever, flu syndrome, hyperalgesia.

522 **Cardiovascular:** Syncope, vasodilation.

523 **Gastrointestinal:** Bleeding gums, constipation, diarrhea, dysphagia, edema of the tongue,  
 524 eructation, flatulence, mouth ulcer, rectal hemorrhage.

525 **Hemic and Lymphatic:** Lymphadenopathy.

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526 **Musculoskeletal:** Arthralgia, muscle spasm, tremor, twitch.

527 **Nervous:** Anxiety, confusion, depression, dizziness, emotional lability, loss of mental acuity,  
528 nervousness, paresthesia, somnolence, vertigo.

529 **Respiratory:** Cough, dyspnea, epistaxis, hoarseness, pharyngitis, rhinitis, sinusitis.

530 **Skin:** Acne, changes in skin and nail pigmentation, pruritus, rash, sweat, urticaria.

531 **Special senses:** Amblyopia, hearing loss, photophobia, taste perversion.

532 **Urogenital:** Dysuria, polyuria, urinary frequency, urinary hesitancy.

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

542

543 **Table 6**

544

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

545 \* Twenty-two pediatric patients received one or more transfusions due to a decline in hemoglobin to  
546 <7.5 g/dL; an additional 15 pediatric patients were transfused for hemoglobin levels >7.5 g/dL.  
547 Fifty-nine percent of the patients transfused had a prestudy history of anemia or transfusion  
548 requirement.

549

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

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

557

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558

Table 7

559

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

560

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

561

\* Peripheral vein IV catheter site.

562

563

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

565

**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<sup>3</sup>). Anemia occurred in 22% of the neonates who received RETROVIR and in 12% of

570

## RETROVIR® (zidovudine) Tablets, Capsules, and Syrup

571 the neonates who received placebo. The mean difference in hemoglobin values was less than  
572 1.0 g/dL for neonates receiving RETROVIR compared to neonates receiving placebo. No neonates  
573 with anemia required transfusion and all hemoglobin values spontaneously returned to normal within  
574 6 weeks after completion of therapy with RETROVIR. Neutropenia was reported with similar  
575 frequency in the group that received RETROVIR (21%) and in the group that received placebo (27%).  
576 The long-term consequences of in utero and infant exposure to RETROVIR are unknown.

577

578 **OVERDOSAGE:** Cases of acute overdoses in both pediatric patients and adults have been reported  
579 with doses up to 50 grams. None were fatal. The only consistent finding in these cases of overdose  
580 was spontaneous or induced nausea and vomiting. Hematologic changes were transient and not  
581 severe. Some patients experienced nonspecific CNS symptoms such as headache, dizziness,  
582 drowsiness, lethargy, and confusion. One report of a grand mal seizure possibly attributable to  
583 RETROVIR occurred in a 35-year-old male 3 hours after ingesting 36 grams of RETROVIR. No other  
584 cause could be identified. All patients recovered without permanent sequelae. Hemodialysis and  
585 peritoneal dialysis appear to have a negligible effect on the removal of zidovudine while elimination of  
586 its primary metabolite, GZDV, is enhanced.

587

### 588 **DOSAGE AND ADMINISTRATION:**

589 **Adults:** The recommended total oral daily dose of RETROVIR is 600 mg per day in divided doses in  
590 combination with other antiretroviral agents and 500 mg (100 mg every 4 hours while awake) or  
591 600 mg per day in divided doses for monotherapy. The effectiveness of this dose compared to higher  
592 dosing regimens in improving the neurologic dysfunction associated with HIV disease is unknown. A  
593 small randomized study found a greater effect of higher doses of RETROVIR on improvement of  
594 neurological symptoms in patients with pre-existing neurological disease.

595 **Pediatrics:** The recommended dose in pediatric patients 3 months to 12 years of age is 180 mg/m<sup>2</sup>  
596 every 6 hours (720 mg/m<sup>2</sup> per day), not to exceed 200 mg every 6 hours.

597 **Maternal-Fetal HIV Transmission:** The recommended dosing regimen for administration to  
598 pregnant women (>14 weeks of pregnancy) and their neonates is:

599 **Maternal Dosing:** 100 mg orally five times per day until the start of labor (see INDICATIONS AND  
600 USAGE: Description of Clinical Studies). During labor and delivery, intravenous RETROVIR  
601 should be administered at 2 mg/kg (total body weight) over 1 hour followed by a continuous  
602 intravenous infusion of 1 mg/kg per hour (total body weight) until clamping of the umbilical cord.

603 **Neonatal Dosing:** 2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing  
604 through 6 weeks of age. Neonates unable to receive oral dosing may be administered RETROVIR  
605 intravenously at 1.5 mg/kg, infused over 30 minutes, every 6 hours. (See PRECAUTIONS if  
606 hepatic disease or renal insufficiency is present.)

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607 **Monitoring of Patients:** Hematologic toxicities appear to be related to pretreatment bone marrow  
608 reserve and to dose and duration of therapy. In patients with poor bone marrow reserve, particularly  
609 in patients with advanced symptomatic HIV disease, frequent monitoring of hematologic indices is  
610 recommended to detect serious anemia or neutropenia (see WARNINGS). In patients who  
611 experience hematologic toxicity, reduction in hemoglobin may occur as early as 2 to 4 weeks, and  
612 neutropenia usually occurs after 6 to 8 weeks.

613 **Dose Adjustment:** Significant anemia (hemoglobin of <7.5 g/dL or reduction of >25% of baseline)  
614 and/or significant neutropenia (granulocyte count of <750 cells/mm<sup>3</sup> or reduction of >50% from  
615 baseline) may require a dose interruption until evidence of marrow recovery is observed (see  
616 WARNINGS). For less severe anemia or neutropenia, a reduction in daily dose may be adequate. In  
617 patients who develop significant anemia, dose modification does not necessarily eliminate the need  
618 for transfusion. If marrow recovery occurs following dose modification, gradual increases in dose may  
619 be appropriate depending on hematologic indices and patient tolerance.

620 In end-stage renal disease patients maintained on hemodialysis or peritoneal dialysis,  
621 recommended dosing is 100 mg every 6 to 8 hours (see CLINICAL PHARMACOLOGY:  
622 Pharmacokinetics).

623 There are insufficient data to recommend dose adjustment of RETROVIR in patients with  
624 impaired hepatic function.

625

626 **HOW SUPPLIED:** RETROVIR Tablets 300 mg (biconvex, white, round, film-coated) containing  
627 300 mg zidovudine, one side engraved "GX CW3" and "300" on the other side. Bottle of 60 (NDC  
628 0173-0501-00).

629 **Store at 15° to 25°C (59° to 77°F).**

630

631 RETROVIR Capsules 100 mg (white, opaque cap and body with a dark blue band) containing  
632 100 mg zidovudine and printed with "Wellcome" and unicorn logo on cap and "Y9C" and "100" on  
633 body. Bottles of 100 (NDC 0173-0108-55) and Unit Dose Pack of 100 (NDC 0173-0108-56).

634 **Store at 15° to 25°C (59° to 77°F) and protect from moisture.**

635

636 RETROVIR Syrup (colorless to pale yellow, strawberry-flavored) containing 50 mg zidovudine in  
637 each teaspoonful (5 mL). Bottle of 240 mL (NDC 0173-0113-18) with child-resistant cap.

638 **Store at 15° to 25°C (59° to 77°F).**

639

640 US Patent Nos. 4,818,538 and 4,828,838 (Product Patents); 4,724,232; 4,833,130; and 4,837,208  
641 (Use Patents)

642

643

**RETROVIR® (zidovudine) Tablets, Capsules, and Syrup**

644 ***GlaxoWellcome***

645 Glaxo Wellcome Inc.

646 Research Triangle Park, NC 27709

647

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650 Date of Issue

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/s/

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Debra Birnkrant  
10/5/01 03:55:05 PM  
NDA 19-910 SLR 024