

**RETROVIR® (zidovudine) IV Infusion**

**PRODUCT INFORMATION**

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**RETROVIR®**

4 **(zidovudine)**

5 **IV Infusion**

6 **FOR INTRAVENOUS INFUSION ONLY**

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

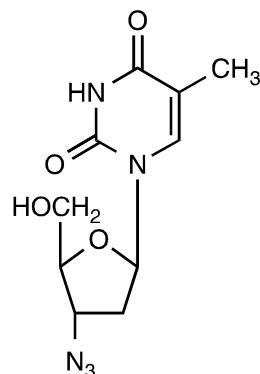
13 **RARE OCCURRENCES OF POTENTIALLY FATAL LACTIC ACIDOSIS IN THE ABSENCE OF**  
14 **HYPOXEMIA, AND SEVERE HEPATOMEGALY WITH STEATOSIS HAVE BEEN REPORTED**  
15 **WITH THE USE OF CERTAIN ANTIRETROVIRAL NUCLEOSIDE ANALOGUES (SEE**  
16 **WARNINGS).**

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18 **DESCRIPTION:** RETROVIR is the brand name for zidovudine (formerly called azidothymidine [AZT]),  
19 a pyrimidine nucleoside analogue active against human immunodeficiency virus (HIV). RETROVIR IV  
20 Infusion is a sterile solution for intravenous infusion only. Each mL contains 10 mg zidovudine in  
21 Water for Injection. Hydrochloric acid and/or sodium hydroxide may have been added to adjust the  
22 pH to approximately 5.5. RETROVIR IV Infusion contains no preservatives.

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

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28        Zidovudine is a white to beige, odorless, crystalline solid with a molecular weight of 267.24 and a  
29        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>.

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

42        **In Vitro HIV Susceptibility:** The in vitro anti-HIV activity of zidovudine was assessed by infecting cell  
43        lines of lymphoblastic and monocytic origin and peripheral blood lymphocytes with laboratory and  
44        clinical isolates of HIV. The IC<sub>50</sub> and IC<sub>90</sub> values (50% and 90% inhibitory concentrations) were 0.003  
45        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  
46        isolates recovered from 18 untreated AIDS/ARC patients were in the range of 0.003 to 0.013 mcg/mL  
47        and 0.03 to 0.3 mcg/mL, respectively. Zidovudine showed antiviral activity in all acutely infected cell  
48        lines; however, activity was substantially less in chronically infected cell lines. In drug combination  
49        studies with zalcitabine, didanosine, lamivudine, saquinavir, indinavir, ritonavir, nevirapine,  
50        delavirdine, or interferon-alpha, zidovudine showed additive to synergistic activity in cell culture. The  
51        relationship between the in vitro susceptibility of HIV to reverse transcriptase inhibitors and the  
52        inhibition of HIV replication in humans has not been established.

53        **Drug Resistance:** HIV isolates with reduced sensitivity to zidovudine have been selected in vitro and  
54        were also recovered from patients treated with RETROVIR. Genetic analysis of the isolates showed  
55        mutations which result in five amino acid substitutions (Met41→Leu, A67→Asn, Lys70→Arg,  
56        Thr215→Tyr or Phe, and Lys219→Gln) in the viral reverse transcriptase. In general, higher levels of  
57        resistance were associated with greater number of mutations with 215 mutation being the most  
58        significant.

59        **Cross-Resistance:** The potential for cross-resistance between HIV reverse transcriptase inhibitors  
60        and protease inhibitors is low because of the different enzyme targets involved. Combination therapy  
61        with zidovudine plus zalcitabine or didanosine does not appear to prevent the emergence of  
62        zidovudine-resistant isolates. Combination therapy with RETROVIR plus EPIVIR® delayed the  
63        emergence of mutations conferring resistance to zidovudine. In some patients harboring zidovudine-  
64        resistant virus, combination therapy with RETROVIR plus EPIVIR restored phenotypic sensitivity to

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65 zidovudine by 12 weeks of treatment. HIV isolates with multidrug resistance to zidovudine,  
66 didanosine, zalcitabine, stavudine, and lamivudine were recovered from a small number of patients  
67 treated for  $\geq 1$  year with the combination of zidovudine and didanosine or zalcitabine. The pattern of  
68 resistant mutations in the combination therapy was different (Ala62 $\rightarrow$ Val, Val75 $\rightarrow$ Ile,  
69 Phe77 $\rightarrow$ 116Tyr, and Gln $\rightarrow$ 151Met) from monotherapy, with mutation 151 being most significant for  
70 multidrug resistance. Site-directed mutagenesis studies showed that these mutations could also  
71 result in resistance to zalcitabine, lamivudine, and stavudine.

72

73 **CLINICAL PHARMACOLOGY:**

74 **Pharmacokinetics: Adults:** The pharmacokinetics of zidovudine has been evaluated in 22 adult  
75 HIV-infected patients in a Phase 1 dose-escalation study. Following intravenous dosing,  
76 dose-independent kinetics was observed over the range of 1 to 5 mg/kg with a mean zidovudine  
77 half-life of 1.1 hours (range 0.48 to 2.86 hours). Total body clearance averaged 1900 mL/min per  
78 70 kg, and the apparent volume of distribution was 1.6 L/kg. At a dose of 7.5 mg/kg every 4 hours,  
79 total body clearance was calculated to be about 1200 mL/min per 70 kg, with no change in half-life.  
80 Renal clearance is estimated to be 400 mL/min per 70 kg, indicating glomerular filtration and active  
81 tubular secretion by the kidneys. Zidovudine plasma protein binding is 34% to 38%, indicating that  
82 drug interactions involving binding site displacement are not anticipated.

83 The mean steady-state peak and trough concentrations of zidovudine at 2.5 mg/kg every 4 hours  
84 were 1.06 and 0.12 mcg/mL, respectively.

85 The zidovudine cerebrospinal fluid (CSF)/plasma concentration ratio was determined in  
86 39 patients receiving chronic therapy with RETROVIR. The median ratio measured in 50 paired  
87 samples drawn 1 to 8 hours after the last dose of RETROVIR was 0.6.

88 Zidovudine is rapidly metabolized to GZDV which has an apparent elimination half-life of 1 hour  
89 (range 0.61 to 1.73 hours). A second metabolite, 3'-amino-3'-deoxythymidine (AMT), has been  
90 identified in the plasma following single-dose intravenous administration of zidovudine. AMT  
91 area-under-the-curve (AUC) was one fifth of the AUC of zidovudine and had a half-life of  
92  $2.7 \pm 0.7$  hours. In comparison, GZDV AUC was about threefold greater than the AUC of zidovudine.  
93 Following intravenous administration, urinary recoveries of zidovudine and GZDV accounted for 18%  
94 and 60% of the dose, respectively, and the total urinary recovery averaged 77% (range 64% to 98%).

95 **Adults with Impaired Renal Function:** The pharmacokinetics of zidovudine has been evaluated  
96 in patients with impaired renal function following a single 200-mg oral dose. In 14 patients (mean  
97 creatinine clearance  $18 \pm 2$  mL/min) the half-life of zidovudine was 1.4 hours compared to 1.0 hour  
98 for control subjects with normal renal function; AUC values were approximately twice those of  
99 controls. Additionally, GZDV half-life in these patients was 8.0 hours (versus 0.9 hours for control)  
100 and AUC was 17 times higher than for control subjects. The pharmacokinetics and tolerance were  
101 evaluated in a multiple-dose study in patients undergoing hemodialysis ( $n = 5$ ) or peritoneal dialysis

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102 (n = 6). Patients received escalating oral doses of zidovudine up to 200 mg five times daily for  
103 8 weeks. Daily oral doses of 500 mg or less were well tolerated despite significantly elevated plasma  
104 levels of GZDV. Apparent oral clearance of zidovudine was approximately 50% of that reported in  
105 patients with normal renal function. The plasma concentrations of AMT are not known in patients with  
106 renal insufficiency. Daily doses of 300 to 400 mg should be appropriate in HIV-infected patients with  
107 severe renal dysfunction (see DOSAGE AND ADMINISTRATION: Dose Adjustment). Hemodialysis  
108 and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, whereas  
109 GZDV elimination is enhanced.

110 **Pediatrics:** The pharmacokinetics and bioavailability of zidovudine have been evaluated in  
111 21 HIV-infected pediatric patients, aged 6 months through 12 years, following intravenous doses  
112 administered over the range of 80 to 160 mg/m<sup>2</sup> every 6 hours, and following oral doses of the  
113 intravenous solution administered over the range of 90 to 240 mg/m<sup>2</sup> every 6 hours. After  
114 discontinuation of the IV infusion, zidovudine plasma concentrations decayed biexponentially,  
115 consistent with two-compartment pharmacokinetics. Proportional increases in AUC and in zidovudine  
116 concentrations were observed with increasing dose, consistent with dose-independent kinetics over  
117 the dose range studied. The mean terminal half-life and total body clearance across all dose levels  
118 administered were 1.5 hours and 30.9 mL/min per kg, respectively. These values compare to mean  
119 half-life and total body clearance in adults of 1.1 hours and 27.1 mL/min per kg.

120 The pharmacokinetics of zidovudine has been studied in pediatric patients from birth to 3 months  
121 of life. In one study of the pharmacokinetics of zidovudine in women during the last trimester of  
122 pregnancy, zidovudine elimination was determined immediately after birth in eight neonates who were  
123 exposed to zidovudine in utero. The half-life was 13.0 ± 5.8 hours. In another study, the  
124 pharmacokinetics of zidovudine was evaluated in pediatric patients (ranging in age of 1 day to  
125 3 months) of normal birth weight for gestational age and with normal renal and hepatic function. In  
126 neonates less than or equal to 14 days old, mean ± SD total body clearance was 10.9 ± 4.8 mL/min  
127 per kg (n = 18) and half-life was 3.1 ± 1.2 hours (n = 21). In neonates and infants greater than  
128 14 days old, total body clearance was 19.0 ± 4.0 mL/min per kg (n = 16) and half-life was  
129 1.9 ± 0.7 hours (n = 18).

130 Concentrations of zidovudine in cerebrospinal fluid were measured after both intermittent oral and  
131 IV drug administration in 21 pediatric patients during Phase 1 and Phase 2 studies. The mean  
132 zidovudine CSF/plasma concentration ratio measured at an average time of 2.2 hours postdose at  
133 oral doses of 120 to 240 mg/m<sup>2</sup> was 0.52 ± 0.44 (n = 28); after an IV infusion of doses of 80 to  
134 160 mg/m<sup>2</sup> over 1 hour, the mean CSF/plasma concentration ratio was 0.87 ± 0.66 (n = 23) at  
135 3.2 hours after the start of the infusion. During continuous IV infusion, mean steady-state  
136 CSF/plasma ratio was 0.26 ± 0.17 (n = 28).

137 As in adult patients, the major route of elimination in pediatric patients was by metabolism to  
138 GZDV. After IV dosing, about 29% of the dose was excreted in the urine unchanged and about 45%

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139 of the dose was excreted as GZDV. Overall, the pharmacokinetics of zidovudine in pediatric patients  
140 greater than 3 months of age is similar to that of zidovudine in adult patients.

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

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

154  
155     **INDICATIONS AND USAGE:** RETROVIR IV Infusion is indicated for the treatment of HIV infection  
156 when antiretroviral therapy is warranted (see Description of Clinical Studies).

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

159     **Maternal-Fetal HIV Transmission:** RETROVIR is also indicated for the prevention of maternal-fetal  
160 HIV transmission as part of a regimen that includes oral RETROVIR beginning between 14 and  
161 34 weeks of gestation, intravenous RETROVIR during labor, and administration of RETROVIR Syrup  
162 to the neonate after birth. The efficacy of this regimen for preventing HIV transmission in women who  
163 have received RETROVIR for a prolonged period before pregnancy has not been evaluated. The  
164 safety of RETROVIR for the mother or fetus during the first trimester of pregnancy has not been  
165 assessed (see Description of Clinical Studies).

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

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

171     **Pregnant Women and Their Neonates:** The utility of RETROVIR for the prevention of  
172 maternal-fetal HIV transmission was demonstrated in a randomized, double-blind, placebo-controlled  
173 trial (ACTG 076) conducted in HIV-infected pregnant women with CD4 cell counts of 200 to 1818  
174 cells/mm<sup>3</sup> (median in the treated group: 560 cells/mm<sup>3</sup>) who had little or no previous exposure to  
175 RETROVIR. Oral RETROVIR was initiated between 14 and 34 weeks of gestation (median 11 weeks

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176 of therapy) followed by intravenous administration of RETROVIR during labor and delivery. After  
177 birth, neonates received oral RETROVIR Syrup for 6 weeks. The study showed a statistically  
178 significant difference in the incidence of HIV infection in the neonates (based on viral culture from  
179 peripheral blood) between the group receiving RETROVIR and the group receiving placebo. Of  
180 363 neonates evaluated in the study, the estimated risk of HIV infection was 7.8% in the group  
181 receiving RETROVIR and 24.9% in the placebo group, a relative reduction in transmission risk of  
182 68.7%. RETROVIR was well tolerated by mothers and infants. There was no difference in  
183 pregnancy-related adverse events between the treatment groups.

184

185 **CONTRAINdications:** RETROVIR IV Infusion is contraindicated for patients who have potentially  
186 life-threatening allergic reactions to any of the components of the formulation.

187

188 **WARNINGS:** The incidence of adverse reactions appears to increase with disease progression, and  
189 patients should be monitored carefully, especially as disease progression occurs.

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

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

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

204 **Lactic Acidosis/Severe Hepatomegaly with Steatosis:** Rare occurrences of potentially fatal lactic  
205 acidosis in the absence of hypoxemia, and severe hepatomegaly with steatosis have been reported  
206 with the use of certain antiretroviral nucleoside analogues. Lactic acidosis should be considered  
207 whenever a patient receiving therapy with RETROVIR develops unexplained tachypnea, dyspnea, or  
208 fall in serum bicarbonate level. Under these circumstances, therapy with RETROVIR should be  
209 suspended until the diagnosis of lactic acidosis has been excluded. Caution should be exercised  
210 when administering RETROVIR to any patient, particularly obese women, with hepatomegaly,  
211 hepatitis, or other known risk factor for liver disease. These patients should be followed closely while  
212 on therapy with RETROVIR. The significance of elevated aminotransferase levels suggesting hepatic

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213 injury in HIV-infected patients prior to starting RETROVIR or while on RETROVIR is unclear.  
214 Treatment with RETROVIR should be suspended in the setting of rapidly elevating aminotransferase  
215 levels, progressive hepatomegaly, or metabolic/lactic acidosis of unknown etiology.  
216 **Other Serious Adverse Reactions:** Several serious adverse events have been reported with use of  
217 RETROVIR in clinical practice. Reports of pancreatitis, sensitization reactions (including anaphylaxis  
218 in one patient), vasculitis, and seizures have been rare. These adverse events, except for  
219 sensitization, have also been associated with HIV disease. Changes in skin and nail pigmentation  
220 have been associated with the use of RETROVIR.

221

222 **PRECAUTIONS:**

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

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

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

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

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

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

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

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

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

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

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

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

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

283 **Fluconazole:** The coadministration of fluconazole with RETROVIR has been reported to interfere  
284 with the oral clearance and metabolism of RETROVIR. In a pharmacokinetic interaction study in  
285 which 12 HIV-positive men received RETROVIR 200 mg every 8 hours alone and in combination with

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286 fluconazole 400 mg daily, fluconazole increased the zidovudine AUC (74%; range 28% to 173%) and  
287 the zidovudine half-life (128%; range -4% to 189%) at steady state. The clinical significance of this  
288 interaction is unknown.

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

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

305      **Lamivudine:** RETROVIR and lamivudine were coadministered to 12 asymptomatic HIV-positive  
306 patients in a single-center, open-label, randomized, crossover study. No significant differences were  
307 observed in  $AUC_{\infty}$  or total clearance for lamivudine or zidovudine when the two drugs were  
308 administered together. Coadministration of RETROVIR with lamivudine resulted in an increase of  
309  $39\% \pm 62\%$  (mean  $\pm$  SD) in  $C_{max}$  of zidovudine.

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

316      **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Zidovudine was administered orally at  
317 three dosage levels to separate groups of mice and rats (60 females and 60 males in each group).  
318 Initial single daily doses were 30, 60, and 120 mg/kg per day in mice and 80, 220, and 600 mg/kg per  
319 day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg per day after day 90 because of  
320 treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg per day on  
321 day 91, and then to 300 mg/kg per day on day 279.

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

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

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

332        Two transplacental carcinogenicity studies were conducted in mice. One study administered  
333        zidovudine at doses of 20 mg/kg per day or 40 mg/kg per day from gestation day 10 through  
334        parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of  
335        zidovudine employed in this study produced zidovudine exposures approximately three times the  
336        estimated human exposure at recommended doses. After 24 months, an increase in incidence of  
337        vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either  
338        gender. These findings are consistent with results of the standard oral carcinogenicity study in mice,  
339        as described earlier. A second study administered zidovudine at maximum tolerated doses of  
340        12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or ~450 mg/kg of term body  
341        weight) to pregnant mice from days 12 through 18 of gestation. There was an increase in the number  
342        of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher  
343        dose level of zidovudine. It is not known how predictive the results of rodent carcinogenicity studies  
344        may be for humans.

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

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

351        **Pregnancy:** Pregnancy Category C. Oral teratology studies in the rat and in the rabbit at doses up to  
352        500 mg/kg per day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment  
353        resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in  
354        rats given 150 or 450 mg/kg per day and rabbits given 500 mg/kg per day. The doses used in the  
355        teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the daily dose)  
356        in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma  
357        concentrations (after one-sixth of the daily dose) achieved with the recommended daily dose (100 mg  
358        every 4 hours). In an in vitro experiment with fertilized mouse oocytes, zidovudine exposure resulted

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359 in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose  
360 of 3000 mg/kg per day (very near the oral median lethal dose in rats of 3683 mg/kg) caused marked  
361 maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak  
362 zidovudine plasma concentrations 350 times peak human plasma concentrations. (Estimated  
363 area-under-the-curve [AUC] in rats at this dose level was 300 times the daily AUC in humans given  
364 600 mg per day.) No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg  
365 per day or less.

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

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

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

377 **Nursing Mothers:** The US Public Health Service Centers for Disease Control and Prevention  
378 advises HIV-infected women not to breastfeed to avoid postnatal transmission of HIV to a child who  
379 may not yet be infected.

380 Zidovudine is excreted in human milk (see Pharmacokinetics).

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

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

391  
392 **ADVERSE REACTIONS:** The adverse events reported during intravenous administration of  
393 RETROVIR IV Infusion are similar to those reported with oral administration; neutropenia and anemia  
394 were reported most frequently. Long-term intravenous administration beyond 2 to 4 weeks has not

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395 been studied in adults and may enhance hematologic adverse events. Local reaction, pain, and slight  
396 irritation during intravenous administration occur infrequently.

397 **Adults:** The frequency and severity of adverse events associated with the use of oral RETROVIR in  
398 adults are greater in patients with more advanced infection at the time of initiation of therapy. Table 1  
399 summarizes the relative incidence of hematologic adverse events observed in clinical studies by  
400 severity of HIV disease present at the start of treatment with oral RETROVIR:

401

402

**Table 1**

403

Stage of Disease	RETROVIR Daily Dose* (mg)	Neutropenia (<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%‡

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

405 † Not statistically significant compared to placebo.

406 ‡ Anemia = Hgb <7.5 g/dL.

407

408       The anemia reported in patients with advanced HIV disease receiving RETROVIR appeared to be  
409 the result of impaired erythrocyte maturation as evidenced by macrocytosis while on drug. Although  
410 mean platelet counts in patients receiving RETROVIR were significantly increased compared to  
411 mean baseline values, thrombocytopenia did occur in some of these patients with advanced disease.  
412 Twelve percent of patients receiving RETROVIR compared to 5% of patients receiving placebo had  
413 >50% decreases from baseline platelet count. Mild drug-associated elevations in total bilirubin levels  
414 have been reported as an uncommon occurrence in patients treated for asymptomatic HIV infection.

415       The HIV-infected adults participating in these clinical trials often had baseline symptoms and signs  
416 of HIV disease and/or experienced adverse events at some time during study. It was often difficult to

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417 distinguish adverse events possibly associated with administration of RETROVIR from underlying  
418 signs of HIV disease or intercurrent illnesses. Table 2 summarizes clinical adverse events or  
419 symptoms which occurred in at least 5% of all patients with advanced HIV disease treated with  
420 1500 mg/day of oral RETROVIR in the original placebo-controlled study. Of the items listed in the  
421 table, only severe headache, nausea, insomnia, and myalgia were reported at a significantly greater  
422 rate in patients receiving RETROVIR.

423

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**Table 2: Percentage (%) of Patients with Adverse Events  
in Advanced HIV Disease (BW 02)**

425

426

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

427

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

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432

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

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433 the underlying disease. Tables 3 and 4 summarize all those events reported at a statistically  
434 significant greater incidence for patients receiving RETROVIR in these studies:

435

436 **Table 3: Percentage (%) of Patients with Adverse Events  
437 in Early HIV Disease (ACTG 016)**

438

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

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

440

441 **Table 4: Percentage (%) of Patients with Adverse Events\*  
442 in Asymptomatic HIV Infection (ACTG 019)**

443

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
Constipation	6.4†	3.5
Nausea	51.4	29.9
Vomiting	17.2	9.8
NERVOUS		
Dizziness	17.9†	15.2

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

445 † Not statistically significant versus placebo.

446

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

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

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

460        ***Cardiovascular:*** Syncope, vasodilation.

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

463        ***Hemic and Lymphatic:*** Lymphadenopathy.

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

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

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

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

469        ***Special Senses:*** Amblyopia, hearing loss, photophobia, taste perversion.

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

471        ***Pediatrics:*** Anemia and neutropenia among pediatric patients with advanced HIV disease receiving  
472        RETROVIR occurred with similar incidence to that reported for adults with AIDS or advanced ARC  
473        (see above). Management of neutropenia and anemia included, in some cases, dose modification  
474        and/or blood product transfusions. In the open-label studies, 17% had their dose modified (generally  
475        a reduction in dose by 30%) due to anemia and 25% had their dose modified (temporary  
476        discontinuation or dose reduction by 30%) for neutropenia. Four pediatric patients had RETROVIR  
477        permanently discontinued for neutropenia. Table 5 summarizes the occurrence of anemia (Hgb  
478        <7.5 g/dL) and neutropenia (<750 cells/mm<sup>3</sup>) among 124 pediatric patients receiving oral RETROVIR  
479        for a mean of 267 days (range 3 to 855 days):

480

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482

**Table 5**

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

483 \* Twenty-two pediatric patients received one or more transfusions due to a decline in hemoglobin to  
484 <7.5 g/dL; an additional 15 pediatric patients were transfused for hemoglobin levels >7.5 g/dL.  
485 Fifty-nine percent of the patients transfused had a prestudy history of anemia or transfusion  
486 requirement.

487

488 Macrocytosis was observed among the majority of pediatric patients enrolled in the studies.  
489 In the open-label studies involving 124 pediatric patients, 16 clinical adverse events were reported  
490 by 24 pediatric patients. No event was reported by more than 5.6% of the study populations. Due to  
491 the open-label design of the studies, it was difficult to determine possible events related to the use of  
492 RETROVIR versus disease-related events. Therefore, all clinical events reported as associated with  
493 therapy with RETROVIR or of unknown relationship to therapy with RETROVIR are presented in  
494 Table 6:  
495

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**Table 6: Percentage (%) of Pediatric Patients  
with Clinical Events in Open-Label Studies**

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

499

\* Peripheral vein IV catheter site.

500

501

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

503

504

505

506

507

508

**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

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509 the neonates who received placebo. The mean difference in hemoglobin values was less than  
510 1.0 g/dL for neonates receiving RETROVIR compared to neonates receiving placebo. No neonates  
511 with anemia required transfusion, and all hemoglobin values spontaneously returned to normal within  
512 6 weeks after completion of therapy with RETROVIR. Neutropenia was reported with similar  
513 frequency in the group that received RETROVIR (21%) and in the group that received placebo (27%).  
514 The long-term consequences of in utero and neonatal exposure to RETROVIR are unknown.

515

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

525

526 **DOSAGE AND ADMINISTRATION:**

527 **Adults:** The recommended intravenous dose is 1 mg/kg infused over 1 hour. This dose should be  
528 administered five to six times daily (5 to 6 mg/kg daily). The effectiveness of this dose compared to  
529 higher dosing regimens in improving the neurologic dysfunction associated with HIV disease is  
530 unknown. A small randomized study found a greater effect of higher doses of RETROVIR on  
531 improvement of neurological symptoms in patients with pre-existing neurological disease.

532 Patients should receive RETROVIR IV Infusion only until oral therapy can be administered. The  
533 intravenous dosing regimen equivalent to the oral administration of 100 mg every 4 hours is  
534 approximately 1 mg/kg intravenously every 4 hours.

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

537 **Maternal Dosing:** 100 mg orally five times per day until the start of labor. During labor and  
538 delivery, intravenous RETROVIR should be administered at 2 mg/kg (total body weight) over  
539 1 hour followed by a continuous intravenous infusion of 1 mg/kg per hour (total body weight) until  
540 clamping of the umbilical cord.

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

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

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

558       In end-stage renal disease patients maintained on hemodialysis or peritoneal dialysis,  
559 recommended dosing is 1 mg/kg every 6 to 8 hours (see CLINICAL PHARMACOLOGY:  
560 Pharmacokinetics).

561       There are insufficient data to recommend dose adjustment of zidovudine in patients with impaired  
562 hepatic function.

563 **Method of Preparation:** RETROVIR IV Infusion must be diluted prior to administration. The  
564 calculated dose should be removed from the 20-mL vial and added to 5% Dextrose Injection solution  
565 to achieve a concentration no greater than 4 mg/mL. Admixture in biologic or colloidal fluids (e.g.,  
566 blood products, protein solutions, etc.) is not recommended.

567       After dilution, the solution is physically and chemically stable for 24 hours at room temperature  
568 and 48 hours if refrigerated at 2° to 8°C (36° to 46°F). Care should be taken during admixture to  
569 prevent inadvertent contamination. As an additional precaution, the diluted solution should be  
570 administered within 8 hours if stored at 25°C (77°F) or 24 hours if refrigerated at 2° to 8°C to  
571 minimize potential administration of a microbially contaminated solution.

572       Parenteral drug products should be inspected visually for particulate matter and discoloration prior  
573 to administration whenever solution and container permit. Should either be observed, the solution  
574 should be discarded and fresh solution prepared.

575 **Administration:** RETROVIR IV Infusion is administered intravenously at a constant rate over one  
576 hour. Rapid infusion or bolus injection should be avoided. RETROVIR IV Infusion should not be  
577 given intramuscularly.

578

579 **HOW SUPPLIED:** RETROVIR IV Infusion, 10 mg zidovudine in each mL. 20-mL Single-Use Vial,  
580 Tray of 10 (NDC 0173-0107-93).

581       **Store vials at 15° to 25°C (59° to 77°F) and protect from light.**

**RETROVIR® (zidovudine) IV Infusion**

582  
583 US Patent Nos. 4,818,538 (Product Patent)  
584 4,724,232; 4,833,130; and 4,837,208 (Use Patents)

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586

587 **GlaxoWellcome**

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