

1 PRESCRIBING INFORMATION

2  
3 **RETROVIR<sup>®</sup>**  
4 **(zidovudine)**  
5 **IV Infusion**

6  
7 **FOR INTRAVENOUS INFUSION ONLY**

8 **WARNING**

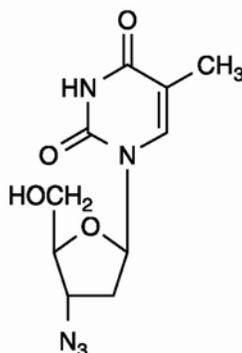
9 **RETROVIR (ZIDOVUDINE) HAS BEEN ASSOCIATED WITH HEMATOLOGIC**  
10 **TOXICITY, INCLUDING NEUTROPENIA AND SEVERE ANEMIA, PARTICULARLY**  
11 **IN PATIENTS WITH ADVANCED HUMAN IMMUNODEFICIENCY VIRUS (HIV)**  
12 **DISEASE (SEE WARNINGS). PROLONGED USE OF RETROVIR HAS BEEN**  
13 **ASSOCIATED WITH SYMPTOMATIC MYOPATHY.**

14 **LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS,**  
15 **INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF**  
16 **NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING**  
17 **RETROVIR AND OTHER ANTIRETROVIRALS (SEE WARNINGS).**

18 **DESCRIPTION**

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

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



27  
28  
29 Zidovudine is a white to beige, odorless, crystalline solid with a molecular weight of 267.24  
30 and a 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>.

31 **MICROBIOLOGY**

32 **Mechanism of Action:** Zidovudine is a synthetic nucleoside analogue. Intracellularly,  
33 zidovudine is phosphorylated to its active 5'-triphosphate metabolite, zidovudine triphosphate  
34 (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of reverse transcriptase (RT)  
35 via DNA chain termination after incorporation of the nucleotide analogue. ZDV-TP is a weak  
36 inhibitor of the cellular DNA polymerases  $\alpha$  and  $\gamma$  and has been reported to be incorporated into  
37 the DNA of cells in culture.

38 **Antiviral Activity:** Activity of zidovudine against HIV-1 was assessed in a number of cell lines  
39 (including monocytes and fresh human peripheral blood lymphocytes). The EC<sub>50</sub> and EC<sub>90</sub>  
40 values for zidovudine were 0.01 to 0.49  $\mu$ M (1  $\mu$ M = 0.27 mcg/mL) and 0.1 to 9  $\mu$ M,  
41 respectively. HIV from therapy-naïve subjects with no mutations associated with resistance gave  
42 median EC<sub>50</sub> values of 0.011  $\mu$ M (range: 0.005 to 0.110  $\mu$ M) from Virco (n = 93 baseline  
43 samples from COLA40263) and 0.02  $\mu$ M (0.01 to 0.03  $\mu$ M) from Monogram Biosciences  
44 (n = 135 baseline samples from ESS30009). The EC<sub>50</sub> values of zidovudine against different  
45 HIV-1 clades (A-G) ranged from 0.00018 to 0.02  $\mu$ M, and against HIV-2 isolates from 0.00049  
46 to 0.004  $\mu$ M. In cell culture drug combination studies, zidovudine demonstrates synergistic  
47 activity with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir, didanosine,  
48 lamivudine, and zalcitabine; the non-nucleoside reverse transcriptase inhibitors (NNRTIs)  
49 delavirdine and nevirapine; and the protease inhibitors (PIs) indinavir, nelfinavir, ritonavir, and  
50 saquinavir; and additive activity with interferon alfa. Ribavirin has been found to inhibit the  
51 phosphorylation of zidovudine in cell culture.

52 **Resistance:** Genotypic analyses of the isolates selected in cell culture and recovered from  
53 zidovudine-treated patients showed mutations in the HIV-1 RT gene resulting in 6 amino acid  
54 substitutions (M41L, D67N, K70R, L210W, T215Y or F, and K219Q) that confer zidovudine  
55 resistance. In general, higher levels of resistance were associated with greater number of  
56 mutations. In some patients harboring zidovudine-resistant virus at baseline, phenotypic  
57 sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine.  
58 Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations  
59 conferring resistance to zidovudine.

60 **Cross-Resistance:** In a study of 167 HIV-infected patients, isolates (n = 2) with multi-drug  
61 resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were recovered from  
62 patients treated for  $\geq$ 1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The  
63 pattern of resistance-associated mutations with such combination therapies was different (A62V,  
64 V75I, F77L, F116Y, Q151M) from the pattern with zidovudine monotherapy, with the  
65 Q151M mutation being most commonly associated with multi-drug resistance. The mutation at  
66 codon 151 in combination with mutations at 62, 75, 77, and 116 results in a virus with reduced  
67 susceptibility to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine. Thymidine  
68 analogue mutations (TAMs) are selected by zidovudine and confer cross-resistance to abacavir,  
69 didanosine, stavudine, tenofovir, and zalcitabine.

70 **CLINICAL PHARMACOLOGY**

71 **Pharmacokinetics: Adults:** The pharmacokinetics of zidovudine have been evaluated in  
72 22 adult HIV-infected patients in a Phase 1 dose-escalation study. Following intravenous (IV)  
73 dosing, dose-independent kinetics was observed over the range of 1 to 5 mg/kg. The major  
74 metabolite of zidovudine is 3'-azido-3'-deoxy-5'-O-β-D-glucopyranuronosylthymidine (GZDV).  
75 GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary  
76 recovery of zidovudine and GZDV accounts for 18% and 60%, respectively, following IV  
77 dosing. A second metabolite, 3'-amino-3'-deoxythymidine (AMT), has been identified in the  
78 plasma following single-dose IV administration of zidovudine. The AMT AUC was one-fifth of  
79 the zidovudine AUC.

80 The mean steady-state peak and trough concentrations of zidovudine at 2.5 mg/kg every  
81 4 hours were 1.06 and 0.12 mcg/mL, respectively.

82 The zidovudine cerebrospinal fluid (CSF)/plasma concentration ratio was determined in  
83 39 patients receiving chronic therapy with RETROVIR. The median ratio measured in 50 paired  
84 samples drawn 1 to 8 hours after the last dose of RETROVIR was 0.6.

85  
86 **Table 1. Zidovudine Pharmacokinetic Parameters Following Intravenous Administration**  
87 **in HIV-Infected Patients**

Parameter	Mean ± SD (except where noted)
Apparent volume of distribution (L/kg)	1.6 ± 0.6 (n = 11)
Plasma protein binding (%)	<38
CSF:plasma ratio <sup>a</sup>	0.6 [0.04 to 2.62] (n = 39)
Systemic clearance (L/hr/kg)	1.6 (0.8 to 2.7) (n = 18)
Renal clearance (L/hr/kg)	0.34 ± 0.05 (n = 16)
Elimination half-life (hr) <sup>b</sup>	1.1 (0.5 to 2.9) (n = 19)

88 <sup>a</sup> Median [range].

89 <sup>b</sup> Approximate range.

90  
91 **Adults With Impaired Renal Function:** Zidovudine clearance was decreased resulting in  
92 increased zidovudine and GZDV half-life and AUC in patients with impaired renal function  
93 (n = 14) following a single 200-mg oral dose (Table 2). Plasma concentrations of AMT were not  
94 determined. A dose adjustment should not be necessary for patients with creatinine clearance  
95 (CrCl) ≥15 mL/min.

96

97 **Table 2. Zidovudine Pharmacokinetic Parameters in Patients With Severe Renal**  
 98 **Impairment<sup>a</sup>**

Parameter	Control Subjects (Normal Renal Function) (n = 6)	Patients With Renal Impairment (n = 14)
CrCl (mL/min)	120 ± 8	18 ± 2
Zidovudine AUC (ng•hr/mL)	1,400 ± 200	3,100 ± 300
Zidovudine half-life (hr)	1.0 ± 0.2	1.4 ± 0.1

99 <sup>a</sup> Data are expressed as mean ± standard deviation.

100  
 101 The pharmacokinetics and tolerance of oral zidovudine were evaluated in a multiple-dose  
 102 study in patients undergoing hemodialysis (n = 5) or peritoneal dialysis (n = 6) receiving  
 103 escalating doses up to 200 mg 5 times daily for 8 weeks. Daily doses of 500 mg or less were well  
 104 tolerated despite significantly elevated GZDV plasma concentrations. Apparent zidovudine oral  
 105 clearance was approximately 50% of that reported in patients with normal renal function.  
 106 Hemodialysis and peritoneal dialysis appeared to have a negligible effect on the removal of  
 107 zidovudine, whereas GZDV elimination was enhanced. A dosage adjustment is recommended  
 108 for patients undergoing hemodialysis or peritoneal dialysis (see DOSAGE AND  
 109 ADMINISTRATION: Dose Adjustment).

110 **Adults With Impaired Hepatic Function:** Data describing the effect of hepatic  
 111 impairment on the pharmacokinetics of zidovudine are limited. However, because zidovudine is  
 112 eliminated primarily by hepatic metabolism, it is expected that zidovudine clearance would be  
 113 decreased and plasma concentrations would be increased following administration of the  
 114 recommended adult doses to patients with hepatic impairment (see DOSAGE AND  
 115 ADMINISTRATION: Dose Adjustment).

116 **Pediatrics:** Zidovudine pharmacokinetics have been evaluated in HIV-infected pediatric  
 117 patients (Table 3).

118 **Patients Aged 3 Months to 12 Years:** Overall, zidovudine pharmacokinetics in  
 119 pediatric patients >3 months of age are similar to those in adult patients. Proportional increases  
 120 in plasma zidovudine concentrations were observed following administration of oral solution  
 121 from 90 to 240 mg/m<sup>2</sup> every 6 hours. Oral bioavailability, terminal half-life, and oral clearance  
 122 were comparable to adult values. As in adult patients, the major route of elimination was by  
 123 metabolism to GZDV. After intravenous dosing, about 29% of the dose was excreted in the urine  
 124 unchanged and about 45% of the dose was excreted as GZDV (see DOSAGE AND  
 125 ADMINISTRATION: Pediatrics).

126 **Patients Aged Less Than 3 Months:** Zidovudine pharmacokinetics have been  
 127 evaluated in pediatric patients from birth to 3 months of life. Zidovudine elimination was  
 128 determined immediately following birth in 8 neonates who were exposed to zidovudine in utero.  
 129 The half-life was 13.0 ± 5.8 hours. In neonates ≤14 days old, bioavailability was greater, total  
 130 body clearance was slower, and half-life was longer than in pediatric patients >14 days old. For

131 dose recommendations for neonates, see DOSAGE AND ADMINISTRATION: Neonatal  
132 Dosing.

133

134 **Table 3. Zidovudine Pharmacokinetic Parameters in Pediatric Patients<sup>a</sup>**

Parameter	Birth to 14 Days	Aged 14 Days to 3 Months	Aged 3 Months to 12 Years
Oral bioavailability (%)	89 ± 19 (n = 15)	61 ± 19 (n = 17)	65 ± 24 (n = 18)
CSF:plasma ratio	no data	no data	0.26 ± 0.17 <sup>b</sup> (n = 28)
CL (L/hr/kg)	0.65 ± 0.29 (n = 18)	1.14 ± 0.24 (n = 16)	1.85 ± 0.47 (n = 20)
Elimination half-life (hr)	3.1 ± 1.2 (n = 21)	1.9 ± 0.7 (n = 18)	1.5 ± 0.7 (n = 21)

135 <sup>a</sup> Data presented as mean ± standard deviation except where noted.

136 <sup>b</sup> CSF ratio determined at steady-state on constant intravenous infusion.

137

138 **Pregnancy:** Zidovudine pharmacokinetics have been studied in a Phase 1 study of 8 women  
139 during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug  
140 accumulation. Zidovudine pharmacokinetics were similar to those of nonpregnant adults.  
141 Consistent with passive transmission of the drug across the placenta, zidovudine concentrations  
142 in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery.  
143 Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear  
144 to alter zidovudine pharmacokinetics. However, in another patient population, a potential for  
145 interaction has been identified (see PRECAUTIONS).

146 **Nursing Mothers:** The Centers for Disease Control and Prevention recommend that  
147 **HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission**  
148 **of HIV.** After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women,  
149 the mean concentration of zidovudine was similar in human milk and serum (see  
150 PRECAUTIONS: Nursing Mothers).

151 **Geriatric Patients:** Zidovudine pharmacokinetics have not been studied in patients over  
152 65 years of age.

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

156 **Drug Interactions:** See Table 4 and PRECAUTIONS: Drug Interactions.

157 **Zidovudine Plus Lamivudine:** No clinically significant alterations in lamivudine or  
158 zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients

159 given a single oral dose of zidovudine (200 mg) in combination with multiple oral doses of  
 160 lamivudine (300 mg every 12 hours).

161

162 **Table 4. Effect of Coadministered Drugs on Zidovudine AUC<sup>a</sup>**

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

Coadministered Drug and Dose	Zidovudine Oral Dose	n	Zidovudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	↑AUC 31%	Range 23% to 78% <sup>b</sup>	↔
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑AUC 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑AUC 43%	Range 16% to 64% <sup>b</sup>	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 200 mg	11	↓AUC 35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑AUC 106%	Range 100% to 170% <sup>b</sup>	Not Assessed
Rifampin 600 mg daily x 14 days	200 mg q 8 hr x 14 days	8	↓AUC 47%	90% CI: 41% to 53%	Not Assessed
Ritonavir 300 mg q 6 hr x 4 days	200 mg q 8 hr x 4 days	9	↓AUC 25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑AUC 80%	Range 64% to 130% <sup>b</sup>	Not Assessed

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

167 <sup>a</sup> This table is not all inclusive.

168 <sup>b</sup> Estimated range of percent difference.

169

170 **Ribavirin:** In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine,  
 171 and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular  
 172 triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV/HCV

173 virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18),  
174 stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to  
175 HIV/HCV co-infected patients (see WARNINGS).

## 176 **INDICATIONS AND USAGE**

177 RETROVIR IV Infusion in combination with other antiretroviral agents is indicated for the  
178 treatment of HIV infection.

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

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

190 RETROVIR in combination with other antiretroviral agents has been shown to be superior to  
191 monotherapy in one or more of the following endpoints: delaying death, delaying development  
192 of AIDS, increasing CD4+ cell counts, and decreasing plasma HIV-1 RNA. The complete  
193 prescribing information for each drug should be consulted before combination therapy that  
194 includes RETROVIR is initiated.

195 **Pregnant Women and Their Neonates:** The utility of RETROVIR for the prevention of  
196 maternal-fetal HIV transmission was demonstrated in a randomized, double-blind,  
197 placebo-controlled trial (ACTG 076) conducted in HIV-infected pregnant women with CD4+  
198 cell counts of 200 to 1,818 cells/mm<sup>3</sup> (median in the treated group: 560 cells/mm<sup>3</sup>) who had little  
199 or no previous exposure to RETROVIR. Oral RETROVIR was initiated between 14 and  
200 34 weeks of gestation (median 11 weeks of therapy) followed by intravenous administration of  
201 RETROVIR during labor and delivery. Following birth, neonates received oral RETROVIR  
202 Syrup for 6 weeks. The study showed a statistically significant difference in the incidence of  
203 HIV infection in the neonates (based on viral culture from peripheral blood) between the group  
204 receiving RETROVIR and the group receiving placebo. Of 363 neonates evaluated in the study,  
205 the estimated risk of HIV infection was 7.8% in the group receiving RETROVIR and 24.9% in  
206 the placebo group, a relative reduction in transmission risk of 68.7%. RETROVIR was well  
207 tolerated by mothers and infants. There was no difference in pregnancy-related adverse events  
208 between the treatment groups.

## 209 **CONTRAINDICATIONS**

210 RETROVIR IV Infusion is contraindicated for patients who have potentially life-threatening  
211 allergic reactions to any of the components of the formulation.

212 **WARNINGS**

213 COMBIVIR<sup>®</sup> (lamivudine and zidovudine) Tablets and TRIZIVIR<sup>®</sup> (abacavir sulfate,  
214 lamivudine, and zidovudine) Tablets are combination product tablets that contain zidovudine as  
215 one of their components. RETROVIR should not be administered concomitantly with  
216 COMBIVIR or TRIZIVIR.

217 The incidence of adverse reactions appears to increase with disease progression; patients  
218 should be monitored carefully, especially as disease progression occurs.

219 **Bone Marrow Suppression:** RETROVIR should be used with caution in patients who have  
220 bone marrow compromise evidenced by granulocyte count <1,000 cells/mm<sup>3</sup> or hemoglobin  
221 <9.5 g/dL. In patients with advanced symptomatic HIV disease, anemia and neutropenia were the  
222 most significant adverse events observed. There have been reports of pancytopenia associated  
223 with the use of RETROVIR, which was reversible in most instances, after discontinuance of the  
224 drug. However, significant anemia, in many cases requiring dose adjustment, discontinuation of  
225 RETROVIR, and/or blood transfusions, has occurred during treatment with RETROVIR alone or  
226 in combination with other antiretrovirals.

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

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

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

243 **Use With Interferon- and Ribavirin-Based Regimens:** In vitro studies have shown  
244 ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as zidovudine.  
245 Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of  
246 HIV/HCV virologic suppression) was seen when ribavirin was coadministered with zidovudine  
247 in HIV/HCV co-infected patients (see CLINICAL PHARMACOLOGY: Drug Interactions),  
248 **hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients**  
249 **receiving combination antiretroviral therapy for HIV and interferon alfa with or without**  
250 **ribavirin.** Patients receiving interferon alfa with or without ribavirin and RETROVIR should be  
251 closely monitored for treatment-associated toxicities, especially hepatic decompensation,  
252 neutropenia, and anemia. Discontinuation of RETROVIR should be considered as medically  
253 appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be  
254 considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g.,  
255 Childs Pugh >6) (see the complete prescribing information for interferon and ribavirin).

## 256 **PRECAUTIONS**

257 **General:** Zidovudine is eliminated from the body primarily by renal excretion following  
258 metabolism in the liver (glucuronidation). In patients with severely impaired renal function  
259 ( $\text{CrCl} < 15 \text{ mL/min}$ ), dosage reduction is recommended. Although the data are limited, zidovudine  
260 concentrations appear to be increased in patients with severely impaired hepatic function, which  
261 may increase the risk of hematologic toxicity (see CLINICAL PHARMACOLOGY:  
262 Pharmacokinetics and DOSAGE AND ADMINISTRATION).

263 **Immune Reconstitution Syndrome:** Immune reconstitution syndrome has been reported in  
264 patients treated with combination antiretroviral therapy, including RETROVIR. During the initial  
265 phase of combination antiretroviral treatment, patients whose immune system responds may  
266 develop an inflammatory response to indolent or residual opportunistic infections (such as  
267 *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or  
268 tuberculosis), which may necessitate further evaluation and treatment.

269 Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome)  
270 have also been reported to occur in the setting of immune reconstitution, however, the time to  
271 onset is more variable, and can occur many months after initiation of treatment.

272 **Information for Patients:** RETROVIR is not a cure for HIV-1 infection, and patients may  
273 continue to experience illnesses associated with HIV-1 infection, including opportunistic  
274 infections. Patients should remain under the care of a physician when using RETROVIR.

275 Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- 276 • **Do not share needles or other injection equipment.**
- 277 • **Do not share personal items that can have blood or body fluids on them, like**  
278 **toothbrushes and razor blades.**
- 279 • **Do not have any kind of sex without protection.** Always practice safe sex by using a  
280 latex or polyurethane condom or other barrier method to lower the chance of sexual  
281 contact with semen, vaginal secretions, or blood.

282 • **Do not breastfeed.** Zidovudine is excreted in human breast milk. Mothers with HIV-1  
283 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

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

286 Patients should be informed that the major toxicities of RETROVIR are neutropenia and/or  
287 anemia. The frequency and severity of these toxicities are greater in patients with more advanced  
288 disease and in those who initiate therapy later in the course of their infection. They should be  
289 told that if toxicity develops, they may require transfusions or drug discontinuation. They should  
290 be told of the extreme importance of having their blood counts followed closely while on  
291 therapy, especially for patients with advanced symptomatic HIV disease. They should be  
292 cautioned about the use of other medications, including ganciclovir and interferon alfa, which  
293 may exacerbate the toxicity of RETROVIR (see PRECAUTIONS: Drug Interactions). Patients  
294 should be informed that other adverse effects of RETROVIR include nausea and vomiting.  
295 Patients should also be encouraged to contact their physician if they experience muscle  
296 weakness, shortness of breath, symptoms of hepatitis or pancreatitis, or any other unexpected  
297 adverse events while being treated with RETROVIR.

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

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

304 **Drug Interactions:** See CLINICAL PHARMACOLOGY section (Table 4) for information on  
305 zidovudine concentrations when coadministered with other drugs. For patients experiencing  
306 pronounced anemia or other severe zidovudine-associated events while receiving chronic  
307 administration of zidovudine and some of the drugs (e.g., fluconazole, valproic acid) listed in  
308 Table 4, zidovudine dose reduction may be considered.

309 **Antiretroviral Agents:** Concomitant use of zidovudine with stavudine should be avoided  
310 since an antagonistic relationship has been demonstrated in vitro.

311 Some nucleoside analogues affecting DNA replication, such as ribavirin, antagonize the  
312 in vitro antiviral activity of RETROVIR against HIV; concomitant use of such drugs should be  
313 avoided.

314 **Doxorubicin:** Concomitant use of zidovudine with doxorubicin should be avoided since an  
315 antagonistic relationship has been demonstrated in vitro (see CLINICAL PHARMACOLOGY  
316 for additional drug interactions).

317 **Phenytoin:** Phenytoin plasma levels have been reported to be low in some patients receiving  
318 RETROVIR, while in 1 case a high level was documented. However, in a pharmacokinetic  
319 interaction study in which 12 HIV-positive volunteers received a single 300-mg phenytoin dose  
320 alone and during steady-state zidovudine conditions (200 mg every 4 hours), no change in  
321 phenytoin kinetics was observed. Although not designed to optimally assess the effect of

322 phenytoin on zidovudine kinetics, a 30% decrease in oral zidovudine clearance was observed  
323 with phenytoin.

324 **Overlapping Toxicities:** Coadministration of ganciclovir, interferon alfa, and other bone  
325 marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

326 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Zidovudine was administered  
327 orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each  
328 group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and  
329 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after day 90  
330 because of treatment-related anemia, whereas in rats only the high dose was reduced to  
331 450 mg/kg/day on day 91, and then to 300 mg/kg/day on day 279.

332 In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous  
333 cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given  
334 the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a  
335 middle-dose animal. No vaginal tumors were found at the lowest dose.

336 In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell  
337 carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or  
338 middle dose in rats. No other drug-related tumors were observed in either sex of either species.

339 At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by  
340 AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at  
341 the recommended therapeutic dose of 100 mg every 4 hours.

342 Two transplacental carcinogenicity studies were conducted in mice. One study administered  
343 zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10 through parturition  
344 and lactation with dosing continuing in offspring for 24 months postnatally. The doses of  
345 zidovudine employed in this study produced zidovudine exposures approximately 3 times the  
346 estimated human exposure at recommended doses. After 24 months, an increase in incidence of  
347 vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in  
348 either gender. These findings are consistent with results of the standard oral carcinogenicity  
349 study in mice, as described earlier. A second study administered zidovudine at maximum  
350 tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or  
351 ~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation. There  
352 was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the  
353 offspring of mice receiving the higher dose level of zidovudine. It is not known how predictive  
354 the results of rodent carcinogenicity studies may be for humans.

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

359 Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose  
360 based on body surface area considerations, had no effect on fertility judged by conception rates.

361 **Pregnancy:** Pregnancy Category C. Oral teratology studies in the rat and in the rabbit at doses  
362 up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine  
363 treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal  
364 resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used  
365 in the teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the  
366 daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human  
367 plasma concentrations (after one-sixth of the daily dose) achieved with the recommended daily  
368 dose (100 mg every 4 hours). In an in vitro experiment with fertilized mouse oocytes, zidovudine  
369 exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional  
370 teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats  
371 of 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal  
372 malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak  
373 human plasma concentrations. (Estimated area under the curve [AUC] in rats at this dose level  
374 was 300 times the daily AUC in humans given 600 mg per day.) No evidence of teratogenicity  
375 was seen in this experiment at doses of 600 mg/kg/day or less.

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

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

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

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

391 Zidovudine is excreted in human milk (see CLINICAL PHARMACOLOGY:  
392 Pharmacokinetics: Nursing Mothers). Because of both the potential for HIV transmission and the  
393 potential for serious adverse reactions in nursing infants, **mothers should be instructed not to**  
394 **breastfeed if they are receiving RETROVIR** (see Pediatric Use and INDICATIONS AND  
395 USAGE: Maternal-Fetal HIV Transmission).

396 **Pediatric Use:** RETROVIR has been studied in HIV-infected pediatric patients over 3 months  
397 of age who had HIV-related symptoms or who were asymptomatic with abnormal laboratory  
398 values indicating significant HIV-related immunosuppression. RETROVIR has also been studied  
399 in neonates perinatally exposed to HIV (see ADVERSE REACTIONS, DOSAGE AND

400 ADMINISTRATION, INDICATIONS AND USAGE: Description of Clinical Studies, and  
401 CLINICAL PHARMACOLOGY: Pharmacokinetics).

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

## 408 ADVERSE REACTIONS

409 The adverse events reported during intravenous administration of RETROVIR IV Infusion are  
410 similar to those reported with oral administration; neutropenia and anemia were reported most  
411 frequently. Long-term intravenous administration beyond 2 to 4 weeks has not been studied in  
412 adults and may enhance hematologic adverse events. Local reaction, pain, and slight irritation  
413 during intravenous administration occur infrequently.

414 **Adults:** The frequency and severity of adverse events associated with the use of RETROVIR are  
415 greater in patients with more advanced infection at the time of initiation of therapy.

416 Table 5 summarizes events reported at a statistically significantly greater incidence for  
417 patients receiving RETROVIR orally in a monotherapy study:

418  
419 **Table 5. Percentage (%) of Patients with Adverse Events<sup>a</sup> in Asymptomatic HIV Infection**  
420 **(ACTG 019)**

Adverse Event	RETROVIR 500 mg/day (n = 453)	Placebo (n = 428)
<b>Body as a whole</b>		
Asthenia	8.6% <sup>b</sup>	5.8%
Headache	62.5%	52.6%
Malaise	53.2%	44.9%
<b>Gastrointestinal</b>		
Anorexia	20.1%	10.5%
Constipation	6.4% <sup>b</sup>	3.5%
Nausea	51.4%	29.9%
Vomiting	17.2%	9.8%

421 <sup>a</sup> Reported in  $\geq 5\%$  of study population.

422 <sup>b</sup> Not statistically significant versus placebo.

423  
424 In addition to the adverse events listed in Table 5, other adverse events observed in clinical  
425 studies were abdominal cramps, abdominal pain, arthralgia, chills, dyspepsia, fatigue,  
426 hyperbilirubinemia, insomnia, musculoskeletal pain, myalgia, and neuropathy.

427 Selected laboratory abnormalities observed during a clinical study of monotherapy with oral  
428 RETROVIR are shown in Table 6.

429

430 **Table 6. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Patients with**  
431 **Asymptomatic HIV Infection (ACTG 019)**

Adverse Event	RETROVIR 500 mg/day (n = 453)	Placebo (n = 428)
Anemia (Hgb<8 g/dL)	1.1%	0.2%
Granulocytopenia (<750 cells/mm <sup>3</sup> )	1.8%	1.6%
Thrombocytopenia (platelets<50,000/mm <sup>3</sup> )	0%	0.5%
ALT (>5 x ULN)	3.1%	2.6%
AST (>5 x ULN)	0.9%	1.6%
Alkaline phosphatase (>5 x ULN)	0%	0%

432 ULN = Upper limit of normal.

433

434 **Pediatrics: Study ACTG300:** Selected clinical adverse events and physical findings with a  
435  $\geq 5\%$  frequency during therapy with EPIVIR<sup>®</sup> (lamivudine) 4 mg/kg twice daily plus  
436 RETROVIR 160 mg/m<sup>2</sup> orally 3 times daily compared with didanosine in therapy-naive  
437 ( $\leq 56$  days of antiretroviral therapy) pediatric patients are listed in Table 7.

438

439 **Table 7. Selected Clinical Adverse Events and Physical Findings (≥5% Frequency)**  
 440 **in Pediatric Patients in Study ACTG300**

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

441 <sup>a</sup> Includes pain, discharge, erythema, or swelling of an ear.

442  
 443 Selected laboratory abnormalities experienced by therapy-naive (≤56 days of antiretroviral  
 444 therapy) pediatric patients are listed in Table 8.

445  
 446 **Table 8. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Pediatric**  
 447 **Patients in Study ACTG300**

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

448 ULN = Upper limit of normal.

449 ANC = Absolute neutrophil count.

450

451 Additional adverse events reported in open-label studies in pediatric patients receiving  
452 RETROVIR 180 mg/m<sup>2</sup> every 6 hours were congestive heart failure, decreased reflexes, ECG  
453 abnormality, edema, hematuria, left ventricular dilation, macrocytosis, nervousness/irritability,  
454 and weight loss.

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

457 **Use for the Prevention of Maternal-Fetal Transmission of HIV:** In a randomized,  
458 double-blind, placebo-controlled trial in HIV-infected women and their neonates conducted to  
459 determine the utility of RETROVIR for the prevention of maternal-fetal HIV transmission,  
460 RETROVIR Syrup at 2 mg/kg was administered every 6 hours for 6 weeks to neonates  
461 beginning within 12 hours following birth. The most commonly reported adverse experiences  
462 were anemia (hemoglobin <9.0 g/dL) and neutropenia (<1,000 cells/mm<sup>3</sup>). Anemia occurred in  
463 22% of the neonates who received RETROVIR and in 12% of the neonates who received  
464 placebo. The mean difference in hemoglobin values was less than 1.0 g/dL for neonates  
465 receiving RETROVIR compared to neonates receiving placebo. No neonates with anemia  
466 required transfusion and all hemoglobin values spontaneously returned to normal within 6 weeks  
467 after completion of therapy with RETROVIR. Neutropenia was reported with similar frequency  
468 in the group that received RETROVIR (21%) and in the group that received placebo (27%). The  
469 long-term consequences of in utero and infant exposure to RETROVIR are unknown.

470 **Observed During Clinical Practice:** In addition to adverse events reported from clinical  
471 trials, the following events have been identified during use of RETROVIR in clinical practice.  
472 Because they are reported voluntarily from a population of unknown size, estimates of frequency  
473 cannot be made. These events have been chosen for inclusion due to either their seriousness,  
474 frequency of reporting, potential causal connection to RETROVIR, or a combination of these  
475 factors.

476 **Body as a Whole:** Back pain, chest pain, flu-like syndrome, generalized pain.

477 **Cardiovascular:** Cardiomyopathy, syncope.

478 **Endocrine:** Gynecomastia.

479 **Eye:** Macular edema.

480 **Gastrointestinal:** Constipation, dysphagia, flatulence, oral mucosal pigmentation, mouth  
481 ulcer.

482 **General:** Sensitization reactions including anaphylaxis and angioedema, vasculitis.

483 **Hemic and Lymphatic:** Aplastic anemia, hemolytic anemia, leukopenia, lymphadenopathy,  
484 pancytopenia with marrow hypoplasia, pure red cell aplasia.

485 **Hepatobiliary Tract and Pancreas:** Hepatitis, hepatomegaly with steatosis, jaundice,  
486 lactic acidosis, pancreatitis.

487 **Musculoskeletal:** Increased CPK, increased LDH, muscle spasm, myopathy and myositis  
488 with pathological changes (similar to that produced by HIV disease), rhabdomyolysis, tremor.

489       **Nervous:** Anxiety, confusion, depression, dizziness, loss of mental acuity, mania,  
490       paresthesia, seizures, somnolence, vertigo.  
491       **Respiratory:** Cough, dyspnea, rhinitis, sinusitis.  
492       **Skin:** Changes in skin and nail pigmentation, pruritus, rash, Stevens-Johnson syndrome, toxic  
493       epidermal necrolysis, sweat, urticaria.  
494       **Special Senses:** Amblyopia, hearing loss, photophobia, taste perversion.  
495       **Urogenital:** Urinary frequency, urinary hesitancy.

## 496       **OVERDOSAGE**

497       Acute overdoses of zidovudine have been reported in pediatric patients and adults. These  
498       involved exposures up to 50 grams. No specific symptoms or signs have been identified  
499       following acute overdosage with zidovudine apart from those listed as adverse events such as  
500       fatigue, headache, vomiting, and occasional reports of hematological disturbances. All patients  
501       recovered without permanent sequelae. Hemodialysis and peritoneal dialysis appear to have a  
502       negligible effect on the removal of zidovudine, while elimination of its primary metabolite,  
503       GZDV, is enhanced.

## 504       **DOSAGE AND ADMINISTRATION**

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

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

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

515       **Maternal Dosing:** 100 mg orally 5 times per day until the start of labor. During labor and  
516       delivery, intravenous RETROVIR should be administered at 2 mg/kg (total body weight) over  
517       1 hour followed by a continuous intravenous infusion of 1 mg/kg/hour (total body weight)  
518       until clamping of the umbilical cord.

519       **Neonatal Dosing:** Start neonatal dosing within 12 hours after birth and continue through  
520       6 weeks of age. Neonates unable to receive oral dosing may be administered RETROVIR  
521       intravenously. See Table 9. (See PRECAUTIONS if hepatic disease or renal insufficiency is  
522       present.)

523 **Table 9. Recommended Neonatal Dosages of RETROVIR**

Route	Total Daily Dose	Dose and Dosage Regimen
Oral	8 mg/kg/day	2 mg/kg every 6 hours
IV	6 mg/kg/day	1.5 mg/kg infused over 30 minutes, every 6 hours

524 **Monitoring of Patients:** Hematologic toxicities appear to be related to pretreatment bone  
 525 marrow reserve and to dose and duration of therapy. In patients with poor bone marrow reserve,  
 526 particularly in patients with advanced symptomatic HIV disease, frequent monitoring of  
 527 hematologic indices is recommended to detect serious anemia or neutropenia (see WARNINGS).  
 528 In patients who experience hematologic toxicity, reduction in hemoglobin may occur as early as  
 529 2 to 4 weeks, and neutropenia usually occurs after 6 to 8 weeks.

530 **Dose Adjustment: Anemia:** Significant anemia (hemoglobin of <7.5 g/dL or reduction of  
 531 >25% of baseline) and/or significant neutropenia (granulocyte count of <750 cells/mm<sup>3</sup> or  
 532 reduction of >50% from baseline) may require a dose interruption until evidence of marrow  
 533 recovery is observed (see WARNINGS). In patients who develop significant anemia, dose  
 534 interruption does not necessarily eliminate the need for transfusion. If marrow recovery occurs  
 535 following dose interruption, resumption in dose may be appropriate using adjunctive measures  
 536 such as epoetin alfa at recommended doses, depending on hematologic indices such as serum  
 537 erythropoetin level and patient tolerance.

538 For patients experiencing pronounced anemia while receiving chronic coadministration of  
 539 zidovudine and some of the drugs (e.g., fluconazole, valproic acid) listed in Table 4, zidovudine  
 540 dose reduction may be considered.

541 **End-Stage Renal Disease:** In patients maintained on hemodialysis or peritoneal dialysis  
 542 (CrCl <15 mL/min), recommended dosing is 1 mg/kg every 6 to 8 hours (see CLINICAL  
 543 PHARMACOLOGY: Pharmacokinetics).

544 **Hepatic Impairment:** There are insufficient data to recommend dose adjustment of  
 545 RETROVIR in patients with mild to moderate impaired hepatic function or liver cirrhosis. Since  
 546 RETROVIR is primarily eliminated by hepatic metabolism, a reduction in the daily dose may be  
 547 necessary in these patients. Frequent monitoring of hematologic toxicities is advised (see  
 548 CLINICAL PHARMACOLOGY: Pharmacokinetics and PRECAUTIONS: General).

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

553 After dilution, the solution is physically and chemically stable for 24 hours at room  
 554 temperature and 48 hours if refrigerated at 2° to 8°C (36° to 46°F). Care should be taken during  
 555 admixture to prevent inadvertent contamination. As an additional precaution, the diluted solution  
 556 should be administered within 8 hours if stored at 25°C (77°F) or 24 hours if refrigerated at 2° to  
 557 8°C to minimize potential administration of a microbially contaminated solution.

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

561 **Administration:** RETROVIR IV Infusion is administered intravenously at a constant rate over  
562 1 hour. Rapid infusion or bolus injection should be avoided. RETROVIR IV Infusion should not  
563 be given intramuscularly.

#### 564 **HOW SUPPLIED**

565 RETROVIR IV Infusion, 10 mg zidovudine in each mL.

566 20-mL Single-Use Vial, Tray of 10 (NDC 49702-213-05).

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

568

569 Manufactured for:



570

571 ViiV Healthcare

572 Research Triangle Park, NC 27709

573

574 by:



575

576 GlaxoSmithKline

577 Research Triangle Park, NC 27709

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582 RTV: PI