

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RETROVIR safely and effectively. See full prescribing information for RETROVIR.

RETROVIR (zidovudine) Tablets, Capsules, and Syrup  
Initial U.S. Approval: 1987

### WARNING: RISK OF HEMATOLOGICAL TOXICITY, MYOPATHY, LACTIC ACIDOSIS

See full prescribing information for complete boxed warning.

- Hematologic toxicity including neutropenia and severe anemia have been associated with the use of zidovudine. (5.1)
- Symptomatic myopathy associated with prolonged use of zidovudine. (5.2)
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues including RETROVIR. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.3)

### RECENT MAJOR CHANGES

Warnings and Precautions, Immune Reconstitution Syndrome (5.6) ----- November 2011

Dosage and Administration, Prevention of Maternal-Fetal HIV-1 Transmission ----- May 2012

### INDICATIONS AND USAGE

RETROVIR is a nucleoside analogue reverse transcriptase inhibitor indicated for:

- Treatment of Human Immunodeficiency Virus (HIV-1) infection in combination with other antiretroviral agents. (1.1)
- Prevention of maternal-fetal HIV-1 transmission. (1.2)

### DOSAGE AND ADMINISTRATION

- Treatment of HIV-1 infection:  
Adults: 600 mg/day in divided doses with other antiretroviral agents. Pediatric patients (aged 4 weeks to <18 years): Dosage should be calculated based on body weight not to exceed adult dose. (2.1)
- Prevention of maternal-fetal HIV-1 transmission:  
Specific dosage instructions for mother and infant. (2.2)
- Patients with severe anemia and/or neutropenia:  
Dosage interruption may be necessary. (2.3)
- Renal impairment: Recommended dosage in hemodialysis or peritoneal dialysis patients is 100 mg every 6 to 8 hours. (2.4)

### DOSAGE FORMS AND STRENGTHS

Tablets: 300 mg (3)  
Capsules: 100 mg (3)  
Syrup: 10 mg/mL (3)

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: RISK OF HEMATOLOGICAL TOXICITY, MYOPATHY, LACTIC ACIDOSIS

#### 1 INDICATIONS AND USAGE

- 1.1 Treatment of HIV-1
- 1.2 Prevention of Maternal-Fetal HIV-1 Transmission

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 Treatment of HIV-1 Infection
- 2.2 Prevention of Maternal-Fetal HIV-1 Transmission
- 2.3 Patients With Severe Anemia and/or Neutropenia
- 2.4 Patients With Renal Impairment
- 2.5 Patients With Hepatic Impairment

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 Hematologic Toxicity/Bone Marrow Suppression
- 5.2 Myopathy
- 5.3 Lactic Acidosis/Severe Hepatomegaly With Steatosis
- 5.4 Use With Interferon- and Ribavirin-Based Regimens in HIV-1/HCV Co-Infected Patients
- 5.5 Use With Other Zidovudine-Containing Products
- 5.6 Immune Reconstitution Syndrome
- 5.7 Fat Redistribution

#### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

#### 7 DRUG INTERACTIONS

- 7.1 Antiretroviral Agents

### CONTRAINDICATIONS

Hypersensitivity to zidovudine (e.g., anaphylaxis, Stevens-Johnson syndrome). (4)

### WARNINGS AND PRECAUTIONS

- See boxed warning for information about the following: hematologic toxicity, myopathy, and lactic acidosis and severe hepatomegaly (5.1, 5.2, 5.3)
- Exacerbation of anemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine. Coadministration of ribavirin and zidovudine is not advised. (5.4)
- Hepatic decompensation, (some fatal), has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with/without ribavirin. Discontinue zidovudine as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- RETROVIR should not be administered with other zidovudine-containing combination products. (5.5)
- Immune reconstitution syndrome (5.6) and redistribution/accumulation of body fat (5.7) have been reported in patients treated with combination antiretroviral therapy.

### ADVERSE REACTIONS

- Most commonly reported adverse reactions (incidence  $\geq 15\%$ ) in adult HIV-1 clinical studies were headache, malaise, nausea, anorexia, and vomiting. (6.1)
- Most commonly reported adverse reactions (incidence  $\geq 15\%$ ) in pediatric HIV-1 clinical studies were fever, cough, and digestive disorders. (6.1)
- Most commonly reported adverse reactions in neonates (incidence  $\geq 15\%$ ) in the prevention of maternal-fetal transmission of HIV-1 clinical trial were anemia and neutropenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Stavudine: Concomitant use with zidovudine should be avoided. (7.1)
- Doxorubicin: Use with zidovudine should be avoided. (7.2)
- Bone marrow suppressive/cytotoxic agents: May increase the hematologic toxicity of zidovudine. (7.3)

### USE IN SPECIFIC POPULATIONS

Pregnancy: Physicians are encouraged to register patients in the Antiretroviral Pregnancy Registry by calling 1-800-258-4263. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2012

- 7.2 Doxorubicin
- 7.3 Hematologic/Bone Marrow Suppressive/Cytotoxic Agents

#### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

#### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Reproductive and Developmental Toxicology Studies

#### 14 CLINICAL STUDIES

- 14.1 Adults
- 14.2 Pediatric Patients
- 14.3 Prevention of Maternal-Fetal HIV-1 Transmission

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

- 17.1 Information About Therapy With RETROVIR

\*Sections or subsections omitted from the full prescribing information are not listed.

1

2 **FULL PRESCRIBING INFORMATION**

3 **WARNING: RISK OF HEMATOLOGICAL TOXICITY, MYOPATHY, LACTIC**  
4 **ACIDOSIS**

5 **Hematologic Toxicity:** RETROVIR<sup>®</sup> (zidovudine) Tablets, Capsules, and Syrup have  
6 been associated with hematologic toxicity including neutropenia and severe anemia,  
7 particularly in patients with advanced HIV-1 disease [*see Warnings and Precautions (5.1)*].

8 **Myopathy:** Prolonged use of RETROVIR has been associated with symptomatic myopathy  
9 [*see Warnings and Precautions (5.2)*].

10 **Lactic Acidosis and Severe Hepatomegaly:** Lactic acidosis and severe hepatomegaly  
11 with steatosis, including fatal cases, have been reported with the use of nucleoside  
12 analogues alone or in combination, including RETROVIR and other antiretrovirals.

13 **Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or**  
14 **pronounced hepatotoxicity occur [*see Warnings and Precautions (5.3)*].**

15 **1 INDICATIONS AND USAGE**

16 **1.1 Treatment of HIV-1**

17 RETROVIR, a nucleoside reverse transcriptase inhibitor, is indicated in combination with  
18 other antiretroviral agents for the treatment of HIV-1 infection.

19 **1.2 Prevention of Maternal-Fetal HIV-1 Transmission**

20 RETROVIR is indicated for the prevention of maternal-fetal HIV-1 transmission [*see*  
21 *Dosage and Administration (2.2)*]. The indication is based on a dosing regimen that included  
22 3 components:

- 23 1. antepartum therapy of HIV-1 infected mothers
- 24 2. intrapartum therapy of HIV-1 infected mothers
- 25 3. post-partum therapy of HIV-1 exposed neonate.

26 Points to consider prior to initiating RETROVIR in pregnant women for the prevention of  
27 maternal-fetal HIV-1 transmission include:

- 28 • In most cases, RETROVIR for prevention of maternal-fetal HIV-1 transmission should be  
29 given in combination with other antiretroviral drugs.
- 30 • Prevention of HIV-1 transmission in women who have received RETROVIR for a prolonged  
31 period before pregnancy has not been evaluated.
- 32 • Because the fetus is most susceptible to the potential teratogenic effects of drugs during the  
33 first 10 weeks of gestation and the risks of therapy with RETROVIR during that period are  
34 not fully known, women in the first trimester of pregnancy who do not require immediate  
35 initiation of antiretroviral therapy for their own health may consider delaying use; this  
36 indication is based on use after 14 weeks gestation.

37 **2 DOSAGE AND ADMINISTRATION**

38 **2.1 Treatment of HIV-1 Infection**

39 Adults: The recommended oral dose of RETROVIR is 600 mg/day in divided doses in  
40 combination with other antiretroviral agents.

41 Pediatric Patients (Aged 4 Weeks to <18 Years): Healthcare professionals should  
42 pay special attention to accurate calculation of the dose of RETROVIR, transcription of the  
43 medication order, dispensing information, and dosing instructions to minimize risk for  
44 medication dosing errors.

45 Prescribers should calculate the appropriate dose of RETROVIR for each child based on  
46 body weight (kg) and should not exceed the recommended adult dose.

47 Before prescribing RETROVIR Capsules or Tablets, children should be assessed for the  
48 ability to swallow capsules or tablets. If a child is unable to reliably swallow a RETROVIR  
49 Capsule or Tablet, the RETROVIR Syrup formulation should be prescribed.

50 The recommended dosage in pediatric patients 4 weeks of age and older and weighing  
51  $\geq 4$  kg is provided in Table 1. RETROVIR Syrup should be used to provide accurate dosage  
52 when whole tablets or capsules are not appropriate.

53

54 **Table 1. Recommended Pediatric Dosage of RETROVIR**

Body Weight (kg)	Total Daily Dose	Dosage Regimen and Dose	
		Twice Daily	Three Times Daily
4 to <9	24 mg/kg/day	12 mg/kg	8 mg/kg
$\geq 9$ to <30	18 mg/kg/day	9 mg/kg	6 mg/kg
$\geq 30$	600 mg/day	300 mg	200 mg

55

56 Alternatively, dosing for RETROVIR can be based on body surface area (BSA) for each  
57 child. The recommended oral dose of RETROVIR is 480 mg/m<sup>2</sup>/day in divided doses  
58 (240 mg/m<sup>2</sup> twice daily or 160 mg/m<sup>2</sup> three times daily). In some cases the dose calculated by  
59 mg/kg will not be the same as that calculated by BSA.

60 **2.2 Prevention of Maternal-Fetal HIV-1 Transmission**

61 The recommended dosage regimen for administration to pregnant women (>14 weeks of  
62 pregnancy) and their neonates is:

63 Maternal Dosing: 100 mg orally 5 times per day until the start of labor [*see Clinical*  
64 *Studies (14.3)*]. During labor and delivery, intravenous RETROVIR should be administered at  
65 2 mg/kg (total body weight) over 1 hour followed by a continuous intravenous infusion of  
66 1 mg/kg/hour (total body weight) until clamping of the umbilical cord.

67 Neonatal Dosing: Start neonatal dosing within 12 hours after birth and continue through  
68 6 weeks of age. Neonates unable to receive oral dosing may be administered RETROVIR  
69 intravenously. See Table 2.

70 **Table 2. 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

71 **2.3 Patients With Severe Anemia and/or Neutropenia**

72 Significant anemia (hemoglobin <7.5 g/dL or reduction >25% of baseline) and/or  
 73 significant neutropenia (granulocyte count <750 cells/mm<sup>3</sup> or reduction >50% from baseline)  
 74 may require a dose interruption until evidence of marrow recovery is observed [*see Warnings*  
 75 *and Precautions (5.1)*]. In patients who develop significant anemia, dose interruption does not  
 76 necessarily eliminate the need for transfusion. If marrow recovery occurs following dose  
 77 interruption, resumption in dose may be appropriate using adjunctive measures such as epoetin  
 78 alfa at recommended doses, depending on hematologic indices such as serum erythropoetin level  
 79 and patient tolerance.

80 **2.4 Patients With Renal Impairment**

81 End-Stage Renal Disease: In patients maintained on hemodialysis or peritoneal  
 82 dialysis, the recommended dosage is 100 mg every 6 to 8 hours [*see Clinical Pharmacology*  
 83 *(12.3)*].

84 **2.5 Patients With Hepatic Impairment**

85 There are insufficient data to recommend dose adjustment of RETROVIR in patients with  
 86 mild to moderate impaired hepatic function or liver cirrhosis.

87 **3 DOSAGE FORMS AND STRENGTHS**

88 **RETROVIR Tablets** 300 mg (biconvex, white, round, film-coated) containing 300 mg  
 89 zidovudine, one side engraved “GX CW3” and “300” on the other side.

90 **RETROVIR Capsules** 100 mg (white, opaque cap and body) containing 100 mg  
 91 zidovudine and printed with “Wellcome” and unicorn logo on cap and “Y9C” and “100” on  
 92 body.

93 **RETROVIR Syrup** (colorless to pale yellow, strawberry-flavored) containing 10 mg  
 94 zidovudine in each mL.

95 **4 CONTRAINDICATIONS**

96 RETROVIR Tablets, Capsules, and Syrup are contraindicated in patients who have had  
 97 potentially life-threatening allergic reactions (e.g., anaphylaxis, Stevens-Johnson syndrome) to  
 98 any of the components of the formulations.

99 **5 WARNINGS AND PRECAUTIONS**

100 **5.1 Hematologic Toxicity/Bone Marrow Suppression**

101 RETROVIR should be used with caution in patients who have bone marrow compromise  
 102 evidenced by granulocyte count <1,000 cells/mm<sup>3</sup> or hemoglobin <9.5 g/dL. Hematologic  
 103 toxicities appear to be related to pretreatment bone marrow reserve and to dose and duration of  
 104 therapy. In patients with advanced symptomatic HIV-1 disease, anemia and neutropenia were the

105 most significant adverse events observed. In patients who experience hematologic toxicity, a  
106 reduction in hemoglobin may occur as early as 2 to 4 weeks, and neutropenia usually occurs after  
107 6 to 8 weeks. There have been reports of pancytopenia associated with the use of RETROVIR,  
108 which was reversible in most instances after discontinuance of the drug. However, significant  
109 anemia, in many cases requiring dose adjustment, discontinuation of RETROVIR, and/or blood  
110 transfusions, has occurred during treatment with RETROVIR alone or in combination with other  
111 antiretrovirals.

112 Frequent blood counts are strongly recommended to detect severe anemia or neutropenia  
113 in patients with poor bone marrow reserve, particularly in patients with advanced HIV-1 disease  
114 who are treated with RETROVIR. For HIV-1-infected individuals and patients with  
115 asymptomatic or early HIV-1 disease, periodic blood counts are recommended. If anemia or  
116 neutropenia develops, dosage interruption may be needed [*see Dosage and Administration*  
117 (2.3)].

## 118 **5.2 Myopathy**

119 Myopathy and myositis with pathological changes, similar to that produced by HIV-1  
120 disease, have been associated with prolonged use of RETROVIR.

## 121 **5.3 Lactic Acidosis/Severe Hepatomegaly With Steatosis**

122 Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been  
123 reported with the use of nucleoside analogues alone or in combination, including zidovudine and  
124 other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged  
125 exposure to antiretroviral nucleoside analogues may be risk factors. Particular caution should be  
126 exercised when administering RETROVIR to any patient with known risk factors for liver  
127 disease; however, cases have also been reported in patients with no known risk factors.  
128 Treatment with RETROVIR should be suspended in any patient who develops clinical or  
129 laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may  
130 include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

## 131 **5.4 Use With Interferon- and Ribavirin-Based Regimens in HIV-1/HCV** 132 **Co-Infected Patients**

133 In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine  
134 nucleoside analogues such as zidovudine. Although no evidence of a pharmacokinetic or  
135 pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when  
136 ribavirin was coadministered with zidovudine in HIV-1/HCV co-infected patients [*see Clinical*  
137 *Pharmacology (12.3)*], exacerbation of anemia due to ribavirin has been reported when  
138 zidovudine is part of the HIV regimen. Coadministration of ribavirin and zidovudine is not  
139 advised. Consideration should be given to replacing zidovudine in established combination  
140 HIV-1/HCV therapy, especially in patients with a known history of zidovudine-induced anemia.

141 Hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients  
142 receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without  
143 ribavirin. Patients receiving interferon alfa with or without ribavirin and zidovudine should be

144 closely monitored for treatment-associated toxicities, especially hepatic decompensation,  
145 neutropenia, and anemia.

146 Discontinuation of zidovudine should be considered as medically appropriate. Dose  
147 reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if  
148 worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh  
149 >6) (see the complete prescribing information for interferon and ribavirin).

## 150 **5.5 Use With Other Zidovudine-Containing Products**

151 RETROVIR should not be administered with combination products that contain  
152 zidovudine as one of their components (e.g., COMBIVIR<sup>®</sup> [lamivudine and zidovudine] Tablets  
153 or TRIZIVIR<sup>®</sup> [abacavir sulfate, lamivudine, and zidovudine] Tablets).

## 154 **5.6 Immune Reconstitution Syndrome**

155 Immune reconstitution syndrome has been reported in patients treated with combination  
156 antiretroviral therapy, including RETROVIR. During the initial phase of combination  
157 antiretroviral treatment, patients whose immune systems respond may develop an inflammatory  
158 response to indolent or residual opportunistic infections (such as *Mycobacterium avium*  
159 infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which  
160 may necessitate further evaluation and treatment.

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

## 164 **5.7 Fat Redistribution**

165 Redistribution/accumulation of body fat, including central obesity, dorsocervical fat  
166 enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and  
167 "cushingoid appearance," have been observed in patients receiving antiretroviral therapy. The  
168 mechanism and long-term consequences of these events are currently unknown. A causal  
169 relationship has not been established.

# 170 **6 ADVERSE REACTIONS**

171 The following adverse reactions are discussed in greater detail in other sections of the  
172 labeling:

- 173 • Hematologic toxicity, including neutropenia and anemia [*see Boxed Warning, Warnings and*  
174 *Precautions (5.1)*].
- 175 • Symptomatic myopathy [*see Boxed Warning, Warnings and Precautions (5.2)*].
- 176 • Lactic acidosis and severe hepatomegaly with steatosis [*see Boxed Warning, Warnings and*  
177 *Precautions (5.3)*].
- 178 • Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C [*see Warnings*  
179 *and Precautions (5.4)*].

## 180 **6.1 Clinical Trials Experience**

181 Because clinical trials are conducted under widely varying conditions, adverse reaction  
 182 rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical  
 183 trials of another drug and may not reflect the rates observed in practice.

184 **Adults:** The frequency and severity of adverse reactions associated with the use of  
 185 RETROVIR are greater in patients with more advanced infection at the time of initiation of  
 186 therapy.

187 Table 3 summarizes events reported at a statistically significant greater incidence for  
 188 patients receiving RETROVIR in a monotherapy study.

189  
 190 **Table 3. Percentage (%) of Patients With Adverse Reactions<sup>a</sup> in Asymptomatic HIV-1**  
 191 **Infection (ACTG 019)**

Adverse Reaction	RETROVIR 500 mg/day (n = 453)	Placebo (n = 428)
<b>Body as a whole</b>		
Asthenia	9% <sup>b</sup>	6%
Headache	63%	53%
Malaise	53%	45%
<b>Gastrointestinal</b>		
Anorexia	20%	11%
Constipation	6% <sup>b</sup>	4%
Nausea	51%	30%
Vomiting	17%	10%

192 <sup>a</sup> Reported in ≥5% of study population.

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

194  
 195 In addition to the adverse reactions listed in Table 3, adverse reactions observed at an  
 196 incidence of ≥5% in any treatment arm in clinical studies (NUCA3001, NUCA3002,  
 197 NUCB3001, and NUCB3002) were abdominal cramps, abdominal pain, arthralgia, chills,  
 198 dyspepsia, fatigue, insomnia, musculoskeletal pain, myalgia, and neuropathy. Additionally, in  
 199 these studies hyperbilirubinemia was reported at an incidence of ≤0.8%.

200 Selected laboratory abnormalities observed during a clinical study of monotherapy with  
 201 RETROVIR are shown in Table 4.

202

203 **Table 4. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Patients With**  
 204 **Asymptomatic HIV-1 Infection (ACTG 019)**

Test (Abnormal Level)	RETROVIR 500 mg/day (n = 453)	Placebo (n = 428)
Anemia (Hgb<8 g/dL)	1%	<1%
Granulocytopenia (<750 cells/mm <sup>3</sup> )	2%	2%
Thrombocytopenia (platelets<50,000/mm <sup>3</sup> )	0%	<1%
ALT (>5 x ULN)	3%	3%
AST (>5 x ULN)	1%	2%

205 ULN = Upper limit of normal.

206

207 **Pediatrics:** The clinical adverse reactions reported among adult recipients of  
 208 RETROVIR may also occur in pediatric patients.

209 *Study ACTG 300:* Selected clinical adverse reactions and physical findings with a  
 210 ≥5% frequency during therapy with EPIVIR® (lamivudine) Oral Suspension 4 mg/kg twice daily  
 211 plus RETROVIR 160 mg/m<sup>2</sup> 3 times daily compared with didanosine in therapy-naive (≤56 days  
 212 of antiretroviral therapy) pediatric patients are listed in Table 5.

213



214 **Table 5. Selected Clinical Adverse Reactions and Physical Findings (≥5% Frequency) in**  
 215 **Pediatric Patients in Study ACTG 300**

Adverse Reaction	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%

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

217

218 Selected laboratory abnormalities experienced by therapy-naive (≤56 days of  
 219 antiretroviral therapy) pediatric patients are listed in Table 6.

220

221 **Table 6. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Pediatric**  
 222 **Patients in Study ACTG 300**

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%

223 ULN = Upper limit of normal.

224 ANC = Absolute neutrophil count.

225  
226 Macrocytosis was reported in the majority of pediatric patients receiving RETROVIR  
227 180 mg/m<sup>2</sup> every 6 hours in open-label studies. Additionally, adverse reactions reported at an  
228 incidence of <6% in these studies were congestive heart failure, decreased reflexes, ECG  
229 abnormality, edema, hematuria, left ventricular dilation, nervousness/irritability, and weight loss.

230 Use for the Prevention of Maternal-Fetal Transmission of HIV-1: In a randomized,  
231 double-blind, placebo-controlled trial in HIV-1-infected women and their neonates conducted to  
232 determine the utility of RETROVIR for the prevention of maternal-fetal HIV-1 transmission,  
233 RETROVIR Syrup at 2 mg/kg was administered every 6 hours for 6 weeks to neonates  
234 beginning within 12 hours following birth. The most commonly reported adverse reactions were  
235 anemia (hemoglobin <9.0 g/dL) and neutropenia (<1,000 cells/mm<sup>3</sup>). Anemia occurred in 22%  
236 of the neonates who received RETROVIR and in 12% of the neonates who received placebo.  
237 The mean difference in hemoglobin values was less than 1.0 g/dL for neonates receiving  
238 RETROVIR compared with neonates receiving placebo. No neonates with anemia required  
239 transfusion and all hemoglobin values spontaneously returned to normal within 6 weeks after  
240 completion of therapy with RETROVIR. Neutropenia in neonates was reported with similar  
241 frequency in the group that received RETROVIR (21%) and in the group that received placebo  
242 (27%). The long-term consequences of in utero and infant exposure to RETROVIR are  
243 unknown.

## 244 **6.2 Postmarketing Experience**

245 In addition to adverse reactions reported from clinical trials, the following reactions have  
246 been identified during postmarketing use of RETROVIR. Because they are reported voluntarily  
247 from a population of unknown size, estimates of frequency cannot be made. These reactions have  
248 been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or  
249 potential causal connection to RETROVIR.

250 Body as a Whole: Back pain, chest pain, flu-like syndrome, generalized pain,  
251 redistribution/accumulation of body fat [*see Warnings and Precautions (5.7)*].

252 Cardiovascular: Cardiomyopathy, syncope.

253 Endocrine: Gynecomastia.

254 Eye: Macular edema.

255 Gastrointestinal: Dysphagia, flatulence, oral mucosa pigmentation, mouth ulcer.

256 General: Sensitization reactions including anaphylaxis and angioedema, vasculitis.

257 Hemic and Lymphatic: Aplastic anemia, hemolytic anemia, leukopenia,  
258 lymphadenopathy, pancytopenia with marrow hypoplasia, pure red cell aplasia.

259 Hepatobiliary Tract and Pancreas: Hepatitis, hepatomegaly with steatosis, jaundice,  
260 lactic acidosis, pancreatitis.

261 Musculoskeletal: Increased CPK, increased LDH, muscle spasm, myopathy and  
262 myositis with pathological changes (similar to that produced by HIV-1 disease), rhabdomyolysis,  
263 tremor.

264            Nervous: Anxiety, confusion, depression, dizziness, loss of mental acuity, mania,  
265            paresthesia, seizures, somnolence, vertigo.  
266            Respiratory: Dyspnea, rhinitis, sinusitis.  
267            Skin: Changes in skin and nail pigmentation, pruritus, Stevens-Johnson syndrome, toxic  
268            epidermal necrolysis, sweat, urticaria.  
269            Special Senses: Amblyopia, hearing loss, photophobia, taste perversion.  
270            Urogenital: Urinary frequency, urinary hesitancy.

## 271    **7    DRUG INTERACTIONS**

### 272    **7.1    Antiretroviral Agents**

273            Stavudine: Concomitant use of zidovudine with stavudine should be avoided since an  
274            antagonistic relationship has been demonstrated in vitro.

275            Nucleoside Analogues Affecting DNA Replication: Some nucleoside analogues  
276            affecting DNA replication, such as ribavirin, antagonize the in vitro antiviral activity of  
277            RETROVIR against HIV-1; concomitant use of such drugs should be avoided.

### 278    **7.2    Doxorubicin**

279            Concomitant use of zidovudine with doxorubicin should be avoided since an antagonistic  
280            relationship has been demonstrated in vitro.

### 281    **7.3    Hematologic/Bone Marrow Suppressive/Cytotoxic Agents**

282            Coadministration of ganciclovir, interferon alfa, ribavirin, and other bone marrow  
283            suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

## 284    **8    USE IN SPECIFIC POPULATIONS**

### 285    **8.1    Pregnancy**

286            Pregnancy Category C.

287            In humans, treatment with RETROVIR during pregnancy reduced the rate of  
288            maternal-fetal HIV-1 transmission from 24.9% for infants born to placebo-treated mothers to  
289            7.8% for infants born to mothers treated with RETROVIR [*see Clinical Studies (14.3)*]. There  
290            were no differences in pregnancy-related adverse events between the treatment groups. Animal  
291            reproduction studies in rats and rabbits showed evidence of embryotoxicity and increased fetal  
292            malformations.

293            A randomized, double-blind, placebo-controlled trial was conducted in HIV-1-infected  
294            pregnant women to determine the utility of RETROVIR for the prevention of maternal-fetal  
295            HIV-1-transmission [*see Clinical Studies (14.3)*]. Congenital abnormalities occurred  
296            with similar frequency between neonates born to mothers who received RETROVIR and  
297            neonates born to mothers who received placebo. The observed abnormalities included problems  
298            in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately  
299            after initiation of study drug.

300            Increased fetal resorptions occurred in pregnant rats and rabbits treated with doses of  
301            zidovudine that produced drug plasma concentrations 66 to 226 times (rats) and 12 to 87 times  
302            (rabbits) the mean steady-state peak human plasma concentration following a single 100-mg

303 dose of zidovudine. There were no other reported developmental anomalies. In another  
304 developmental toxicity study, pregnant rats received zidovudine up to near-lethal doses that  
305 produced peak plasma concentrations 350 times peak human plasma concentrations (300 times  
306 the daily exposure [AUC] in humans given 600 mg/day zidovudine). This dose was associated  
307 with marked maternal toxicity and an increased incidence of fetal malformations. However, there  
308 were no signs of teratogenicity at doses up to one-fifth the lethal dose [*see Nonclinical*  
309 *Toxicology (13.2)*].

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

### 313 **8.3 Nursing Mothers**

314 Zidovudine is excreted in human milk [*see Clinical Pharmacology (12.3)*].

315 The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers  
316 in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1  
317 infection. Because of both the potential for HIV-1 transmission and the potential for serious  
318 adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are  
319 receiving RETROVIR.

### 320 **8.4 Pediatric Use**

321 RETROVIR has been studied in HIV-1-infected pediatric patients  $\geq 6$  weeks of age who  
322 had HIV-1-related symptoms or who were asymptomatic with abnormal laboratory values  
323 indicating significant HIV-1-related immunosuppression. RETROVIR has also been studied in  
324 neonates perinatally exposed to HIV-1 [*see Dosage and Administration (2.1), Adverse*  
325 *Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.2),*  
326 *(14.3)*].

### 327 **8.5 Geriatric Use**

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

### 334 **8.6 Renal Impairment**

335 In patients with severely impaired renal function ( $\text{CrCl} < 15 \text{ mL/min}$ ), dosage reduction is  
336 recommended [*see Dosage and Administration (2.4), Clinical Pharmacology (12.3)*].

### 337 **8.7 Hepatic Impairment**

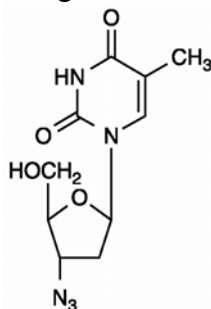
338 Zidovudine is eliminated from the body primarily by renal excretion following  
339 metabolism in the liver (glucuronidation). Although the data are limited, zidovudine  
340 concentrations appear to be increased in patients with severely impaired hepatic function, which  
341 may increase the risk of hematologic toxicity [*see Dosage and Administration (2.5), Clinical*  
342 *Pharmacology (12.3)*].

343 **10 OVERDOSAGE**

344 Acute overdoses of zidovudine have been reported in pediatric patients and adults. These  
345 involved exposures up to 50 grams. No specific symptoms or signs have been identified  
346 following acute overdose with zidovudine apart from those listed as adverse events such as  
347 fatigue, headache, vomiting, and occasional reports of hematological disturbances. All patients  
348 recovered without permanent sequelae. Hemodialysis and peritoneal dialysis appear to have a  
349 negligible effect on the removal of zidovudine while elimination of its primary metabolite, 3'-  
350 azido-3'-deoxy-5'-O-β-D-glucopyranuronosylthymidine (GZDV), is enhanced.

351 **11 DESCRIPTION**

352 RETROVIR is the brand name for zidovudine (formerly called azidothymidine [AZT]), a  
353 pyrimidine nucleoside analogue active against HIV-1. The chemical name of zidovudine is 3'-  
354 azido-3'-deoxythymidine; it has the following structural formula:



355  
356 Zidovudine is a white to beige, odorless, crystalline solid with a molecular weight of  
357 267.24 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>.

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

361 RETROVIR Capsules are for oral administration. Each capsule contains 100 mg of  
362 zidovudine and the inactive ingredients corn starch, magnesium stearate, microcrystalline  
363 cellulose, and sodium starch glycolate. The 100-mg empty hard gelatin capsule, printed with  
364 edible black ink, consists of black iron oxide, dimethylpolysiloxane, gelatin, pharmaceutical  
365 shellac, soya lecithin, and titanium dioxide.

366 RETROVIR Syrup is for oral administration. Each mL of RETROVIR Syrup contains  
367 10 mg of zidovudine and the inactive ingredients sodium benzoate 0.2% (added as a  
368 preservative), citric acid, flavors, glycerin, and liquid sucrose. Sodium hydroxide may be added  
369 to adjust pH.

370 **12 CLINICAL PHARMACOLOGY**

371 **12.1 Mechanism of Action**

372 Zidovudine is an antiviral agent [see *Clinical Pharmacology (12.4)*].

373 **12.3 Pharmacokinetics**

374 **Absorption and Bioavailability:** In adults, following oral administration, zidovudine is  
 375 rapidly absorbed and extensively distributed, with peak serum concentrations occurring within  
 376 0.5 to 1.5 hours. The AUC was equivalent when zidovudine was administered as RETROVIR  
 377 Tablets or Syrup compared with RETROVIR Capsules. The pharmacokinetic properties of  
 378 zidovudine in fasting adult patients are summarized in Table 7.

379  
 380 **Table 7. Zidovudine Pharmacokinetic Parameters in Fasting Adult Patients**

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

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

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

383  
 384 **Distribution:** The apparent volume of distribution of zidovudine, following oral  
 385 administration, is 1.6 ± 0.6 L/kg; and binding to plasma protein is low, <38% (Table 7).

386 **Metabolism and Elimination:** Zidovudine is primarily eliminated by hepatic  
 387 metabolism. The major metabolite of zidovudine is GZDV. GZDV AUC is about 3-fold greater  
 388 than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and  
 389 74%, respectively, of the dose following oral administration. A second metabolite, 3'-amino-3'-  
 390 deoxythymidine (AMT), has been identified in the plasma following single-dose intravenous  
 391 (IV) administration of zidovudine. The AMT AUC was one-fifth of the zidovudine AUC.  
 392 Pharmacokinetics of zidovudine were dose independent at oral dosing regimens ranging from  
 393 2 mg/kg every 8 hours to 10 mg/kg every 4 hours.

394 **Effect of Food on Absorption:** RETROVIR may be administered with or without food.  
 395 The zidovudine AUC was similar when a single dose of zidovudine was administered with food.

396 **Special Populations: Renal Impairment:** Zidovudine clearance was decreased  
 397 resulting in increased zidovudine and GZDV half-life and AUC in patients with impaired renal

398 function (n = 14) following a single 200-mg oral dose (Table 8). Plasma concentrations of AMT  
399 were not determined. A dose adjustment should not be necessary for patients with creatinine  
400 clearance (CrCl)  $\geq 15$  mL/min.

401

402 **Table 8. Zidovudine Pharmacokinetic Parameters in Patients With Severe Renal**  
403 **Impairment<sup>a</sup>**

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

404 <sup>a</sup> Data are expressed as mean  $\pm$  standard deviation.

405

406 **Hemodialysis and Peritoneal Dialysis:** The pharmacokinetics and tolerance of  
407 zidovudine were evaluated in a multiple-dose study in patients undergoing hemodialysis (n = 5)  
408 or peritoneal dialysis (n = 6) receiving escalating doses up to 200 mg 5 times daily for 8 weeks.  
409 Daily doses of 500 mg or less were well tolerated despite significantly elevated GZDV plasma  
410 concentrations. Apparent zidovudine oral clearance was approximately 50% of that reported in  
411 patients with normal renal function. Hemodialysis and peritoneal dialysis appeared to have a  
412 negligible effect on the removal of zidovudine, whereas GZDV elimination was enhanced. A  
413 dosage adjustment is recommended for patients undergoing hemodialysis or peritoneal dialysis  
414 [see *Dosage and Administration* (2.4)].

415 **Hepatic Impairment:** Data describing the effect of hepatic impairment on the  
416 pharmacokinetics of zidovudine are limited. However, because zidovudine is eliminated  
417 primarily by hepatic metabolism, it is expected that zidovudine clearance would be decreased  
418 and plasma concentrations would be increased following administration of the recommended  
419 adult doses to patients with hepatic impairment [see *Dosage and Administration* (2.5)].

420 **Pediatric Patients:** Zidovudine pharmacokinetics have been evaluated in  
421 HIV-1-infected pediatric patients (Table 9).

422 **Patients Aged 3 Months to 12 Years:** Overall, zidovudine pharmacokinetics in  
423 pediatric patients greater than 3 months of age are similar to those in adult patients. Proportional  
424 increases in plasma zidovudine concentrations were observed following administration of oral  
425 solution from 90 to 240 mg/m<sup>2</sup> every 6 hours. Oral bioavailability, terminal half-life, and oral  
426 clearance were comparable to adult values. As in adult patients, the major route of elimination  
427 was by metabolism to GZDV. After intravenous dosing, about 29% of the dose was excreted in  
428 the urine unchanged, and about 45% of the dose was excreted as GZDV [see *Dosage and*  
429 *Administration* (2.1)].

430 **Patients Aged Less Than 3 Months:** Zidovudine pharmacokinetics have been  
431 evaluated in pediatric patients from birth to 3 months of life. Zidovudine elimination was

432 determined immediately following birth in 8 neonates who were exposed to zidovudine in utero.  
 433 The half-life was  $13.0 \pm 5.8$  hours. In neonates  $\leq 14$  days old, bioavailability was greater, total  
 434 body clearance was slower, and half-life was longer than in pediatric patients  $>14$  days old. For  
 435 dose recommendations for neonates [see *Dosage and Administration (2.2)*].

436

437 **Table 9. 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 (%)	$89 \pm 19$ (n = 15)	$61 \pm 19$ (n = 17)	$65 \pm 24$ (n = 18)
CSF:plasma ratio	no data	no data	0.68 [0.03 to 3.25] <sup>b</sup> (n = 38)
CL (L/hr/kg)	$0.65 \pm 0.29$ (n = 18)	$1.14 \pm 0.24$ (n = 16)	$1.85 \pm 0.47$ (n = 20)
Elimination half-life (hr)	$3.1 \pm 1.2$ (n = 21)	$1.9 \pm 0.7$ (n = 18)	$1.5 \pm 0.7$ (n = 21)

438 <sup>a</sup> Data presented as mean  $\pm$  standard deviation except where noted.

439 <sup>b</sup> Median [range].

440

441 **Pregnancy:** Zidovudine pharmacokinetics have been studied in a Phase I study of  
 442 8 women during the last trimester of pregnancy. Zidovudine pharmacokinetics were similar to  
 443 those of nonpregnant adults. Consistent with passive transmission of the drug across the  
 444 placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in  
 445 maternal plasma at delivery [see *Use in Specific Populations (8.1)*].

446 Although data are limited, methadone maintenance therapy in 5 pregnant women did not  
 447 appear to alter zidovudine pharmacokinetics.

448 **Nursing Mothers:** The Centers for Disease Control and Prevention recommend that  
 449 HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of  
 450 HIV-1. After administration of a single dose of 200 mg zidovudine to 13 HIV-1-infected women,  
 451 the mean concentration of zidovudine was similar in human milk and serum [see *Use in Specific*  
 452 *Populations (8.3)*].

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

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

458 **Drug Interactions:** [See *Drug Interactions (7)*].

459



460 **Table 10. Effect of Coadministered Drugs on Zidovudine AUC<sup>a</sup>**

<b>Note: ROUTINE DOSE MODIFICATION OF ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.</b>					
Coadministered Drug and Dose	Zidovudine 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>	↔
Clarithromycin 500 mg twice daily	100 mg q 4 hr x 7 days	4	↓AUC 12%	Range ↓34% to ↑14%	Not Reported
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑AUC 74%	95% CI: 54% to 98%	Not Reported
Lamivudine 300 mg q 12 hr	single 200 mg	12	↑AUC 13%	90% CI: 2% to 27%	↔
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

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

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

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

465  
 466 *Phenytoin:* Phenytoin plasma levels have been reported to be low in some patients  
 467 receiving RETROVIR, while in one case a high level was documented. However, in a  
 468 pharmacokinetic interaction study in which 12 HIV-1-positive volunteers received a single

469 300-mg phenytoin dose alone and during steady-state zidovudine conditions (200 mg every  
470 4 hours), no change in phenytoin kinetics was observed. Although not designed to optimally  
471 assess the effect of phenytoin on zidovudine kinetics, a 30% decrease in oral zidovudine  
472 clearance was observed with phenytoin.

473 *Ribavirin:* In vitro data indicate ribavirin reduces phosphorylation of lamivudine,  
474 stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or  
475 intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss  
476 of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine  
477 (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug  
478 regimen to HIV-1/HCV co-infected patients [see *Warnings and Precautions (5.4)*].

## 479 **12.4 Microbiology**

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

486 Antiviral Activity: The antiviral activity of zidovudine against HIV-1 was assessed in a  
487 number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The  
488 EC<sub>50</sub> and EC<sub>90</sub> values for zidovudine were 0.01 to 0.49  $\mu$ M (1  $\mu$ M = 0.27 mcg/mL) and 0.1 to  
489 9  $\mu$ M, respectively. HIV-1 from therapy-naïve subjects with no mutations associated with  
490 resistance gave median EC<sub>50</sub> values of 0.011  $\mu$ M (range: 0.005 to 0.110  $\mu$ M) from Virco  
491 (n = 92 baseline samples from COL40263) and 0.0017  $\mu$ M (0.006 to 0.0340  $\mu$ M) from  
492 Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC<sub>50</sub> values of  
493 zidovudine against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02  $\mu$ M, and against  
494 HIV-2 isolates from 0.00049 to 0.004  $\mu$ M. In cell culture drug combination studies, zidovudine  
495 demonstrates synergistic activity with the nucleoside reverse transcriptase inhibitors abacavir,  
496 didanosine, and lamivudine; the non-nucleoside reverse transcriptase inhibitors delavirdine and  
497 nevirapine; and the protease inhibitors indinavir, nelfinavir, ritonavir, and saquinavir; and  
498 additive activity with interferon alfa. Ribavirin has been found to inhibit the phosphorylation of  
499 zidovudine in cell culture.

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

508 **Cross-Resistance:** In a study of 167 HIV-1-infected patients, isolates (n = 2) with  
509 multi-drug resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were  
510 recovered from patients treated for ≥1 year with zidovudine plus didanosine or zidovudine plus  
511 zalcitabine. The pattern of resistance-associated amino acid substitutions with such combination  
512 therapies was different (A62V, V75I, F77L, F116Y, Q151M) from the pattern with zidovudine  
513 monotherapy, with the Q151M substitution being most commonly associated with multi-drug  
514 resistance. The substitution at codon 151 in combination with substitutions at 62, 75, 77, and 116  
515 results in a virus with reduced susceptibility to didanosine, lamivudine, stavudine, zalcitabine,  
516 and zidovudine. Thymidine analogue mutations (TAMs) are selected by zidovudine and confer  
517 cross-resistance to abacavir, didanosine, stavudine, tenofovir, and zalcitabine.

## 518 **13 NONCLINICAL TOXICOLOGY**

### 519 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

520 Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats  
521 (60 females and 60 males in each group). Initial single daily doses were 30, 60, and  
522 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced  
523 to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats  
524 only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on  
525 day 279.

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

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

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

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

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

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

544 Two transplacental carcinogenicity studies were conducted in mice. One study  
545 administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10  
546 through parturition and lactation with dosing continuing in offspring for 24 months postnatally.

547 The doses of zidovudine administered in this study produced zidovudine exposures  
548 approximately 3 times the estimated human exposure at recommended doses. After 24 months,  
549 an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or  
550 lung or any other organ in either gender. These findings are consistent with results of the  
551 standard oral carcinogenicity study in mice, as described earlier. A second study administered  
552 zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg  
553 nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12  
554 through 18 of gestation. There was an increase in the number of tumors in the lung, liver, and  
555 female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.

### 556 **13.2 Reproductive and Developmental Toxicology Studies**

557 Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed  
558 no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal  
559 toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or  
560 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies  
561 resulted in peak zidovudine plasma concentrations (after one-half of the daily dose) in rats 66 to  
562 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations  
563 (after one-sixth of the daily dose) achieved with the recommended daily dose (100 mg every  
564 4 hours). In an in vitro experiment with fertilized mouse oocytes, zidovudine exposure resulted  
565 in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a  
566 dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/kg) caused  
567 marked maternal toxicity and an increase in the incidence of fetal malformations. This dose  
568 resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations.  
569 (Estimated AUC in rats at this dose level was 300 times the daily AUC in humans given  
570 600 mg/day.) No evidence of teratogenicity was seen in this experiment at doses of  
571 600 mg/kg/day or less.

## 572 **14 CLINICAL STUDIES**

573 Therapy with RETROVIR has been shown to prolong survival and decrease the incidence  
574 of opportunistic infections in patients with advanced HIV-1 disease and to delay disease  
575 progression in asymptomatic HIV-1-infected patients.

### 576 **14.1 Adults**

577 Combination Therapy: RETROVIR in combination with other antiretroviral agents has  
578 been shown to be superior to monotherapy for one or more of the following endpoints: delaying  
579 death, delaying development of AIDS, increasing CD4+ cell counts, and decreasing plasma  
580 HIV-1 RNA.

581 The clinical efficacy of a combination regimen that includes RETROVIR was  
582 demonstrated in study ACTG 320. This study was a multi-center, randomized, double-blind,  
583 placebo-controlled trial that compared RETROVIR 600 mg/day plus EPIVIR 300 mg/day to  
584 RETROVIR plus EPIVIR plus indinavir 800 mg three times daily. The incidence of AIDS-

585 defining events or death was lower in the triple-drug-containing arm compared with the 2-drug-  
586 containing arm (6.1% versus 10.9%, respectively).

587 **Monotherapy:** In controlled studies of treatment-naive patients conducted between 1986  
588 and 1989, monotherapy with RETROVIR, as compared with placebo, reduced the risk of HIV-1  
589 disease progression, as assessed using endpoints that included the occurrence of HIV-1-related  
590 illnesses, AIDS-defining events, or death. These studies enrolled patients with advanced disease  
591 (BW 002), and asymptomatic or mildly symptomatic disease in patients with CD4+ cell counts  
592 between 200 and 500 cells/mm<sup>3</sup> (ACTG 016 and ACTG 019). A survival benefit for  
593 monotherapy with RETROVIR was not demonstrated in the latter 2 studies. Subsequent studies  
594 showed that the clinical benefit of monotherapy with RETROVIR was time limited.

#### 595 **14.2 Pediatric Patients**

596 ACTG 300 was a multi-center, randomized, double-blind study that provided for  
597 comparison of EPIVIR plus RETROVIR to didanosine monotherapy. A total of  
598 471 symptomatic, HIV-1-infected therapy-naive pediatric patients were enrolled in these  
599 2 treatment arms. The median age was 2.7 years (range: 6 weeks to 14 years), the mean baseline  
600 CD4+ cell count was 868 cells/mm<sup>3</sup>, and the mean baseline plasma HIV-1 RNA was  
601 5.0 log<sub>10</sub> copies/mL. The median duration that patients remained on study was approximately  
602 10 months. Results are summarized in Table 11.

603

604 **Table 11. Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease**  
605 **Progression or Death)**

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

606

#### 607 **14.3 Prevention of Maternal-Fetal HIV-1 Transmission**

608 The utility of RETROVIR for the prevention of maternal-fetal HIV-1 transmission was  
609 demonstrated in a randomized, double-blind, placebo-controlled trial (ACTG 076) conducted in  
610 HIV-1-infected pregnant women with CD4+ cell counts of 200 to 1,818 cells/mm<sup>3</sup> (median in  
611 the treated group: 560 cells/mm<sup>3</sup>) who had little or no previous exposure to RETROVIR. Oral  
612 RETROVIR was initiated between 14 and 34 weeks of gestation (median 11 weeks of therapy)  
613 followed by IV administration of RETROVIR during labor and delivery. Following birth,  
614 neonates received oral RETROVIR Syrup for 6 weeks. The study showed a statistically  
615 significant difference in the incidence of HIV-1 infection in the neonates (based on viral culture  
616 from peripheral blood) between the group receiving RETROVIR and the group receiving  
617 placebo. Of 363 neonates evaluated in the study, the estimated risk of HIV-1 infection was 7.8%

618 in the group receiving RETROVIR and 24.9% in the placebo group, a relative reduction in  
619 transmission risk of 68.7%. RETROVIR was well tolerated by mothers and infants. There was  
620 no difference in pregnancy-related adverse events between the treatment groups.

## 621 **16 HOW SUPPLIED/STORAGE AND HANDLING**

622 RETROVIR Tablets 300 mg (biconvex, white, round, film-coated) containing 300 mg  
623 zidovudine, one side engraved “GX CW3” and “300” on the other side.

624 Bottle of 60 (NDC 49702-214-18).

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

626 RETROVIR Capsules 100 mg (white, opaque cap and body) containing 100 mg  
627 zidovudine and printed with “Wellcome” and unicorn logo on cap and “Y9C” and “100” on  
628 body.

629 Bottles of 100 (NDC 49702-211-20).

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

631 RETROVIR Syrup (colorless to pale yellow, strawberry-flavored) containing 10 mg  
632 zidovudine in each mL.

633 Bottle of 240 mL (NDC 49702-212-48) with child-resistant cap.

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

## 635 **17 PATIENT COUNSELING INFORMATION**

### 636 **17.1 Advice for the Patient**

637 Neutropenia and Anemia: Patients should be informed that the major toxicities of  
638 RETROVIR are neutropenia and/or anemia. The frequency and severity of these toxicities are  
639 greater in patients with more advanced disease and in those who initiate therapy later in the  
640 course of their infection. Patients should be informed that if toxicity develops, they may require  
641 transfusions or drug discontinuation. Patients should be informed of the extreme importance of  
642 having their blood counts followed closely while on therapy, especially for patients with  
643 advanced symptomatic HIV-1 disease [see *Boxed Warning, Warnings and Precautions (5.1)*].

644 Myopathy: Patients should be informed that myopathy and myositis with pathological  
645 changes, similar to that produced by HIV-1 disease, have been associated with prolonged use of  
646 RETROVIR [see *Boxed Warning, Warnings and Precautions (5.2)*].

647 Lactic Acidosis/Hepatomegaly: Patients should be informed that some HIV medicines,  
648 including RETROVIR, can cause a rare, but serious condition called lactic acidosis with liver  
649 enlargement (hepatomegaly) [see *Boxed Warning, Warnings and Precautions (5.3)*].

650 HIV-1/HCV Co-Infection: Patients with HIV-1/HCV co-infection should be informed  
651 that hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients  
652 receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without  
653 ribavirin [see *Warnings and Precautions (5.4)*].

654 Use With Other Zidovudine-Containing Products: RETROVIR should not be  
655 administered with combination products that contain zidovudine as one of their components

656 (e.g., COMBIVIR [lamivudine and zidovudine] Tablets or TRIZIVIR [abacavir sulfate,  
657 lamivudine, and zidovudine] Tablets) [see Warnings and Precautions (5.5)].

658 **Redistribution/Accumulation of Body Fat:** Patients should be informed that  
659 redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy  
660 and that the cause and long-term health effects of these conditions are not known at this time  
661 [see Warnings and Precautions (5.7)].

662 **Common Adverse Reactions:** Patients should be informed that the most commonly  
663 reported adverse reactions in adult patients being treated with RETROVIR were headache,  
664 malaise, nausea, anorexia, and vomiting. The most commonly reported adverse reactions in  
665 pediatric patients receiving RETROVIR were fever, cough, and digestive disorders. Patients also  
666 should be encouraged to contact their physician if they experience muscle weakness, shortness of  
667 breath, symptoms of hepatitis or pancreatitis, or any other unexpected adverse events while being  
668 treated with RETROVIR [see Adverse Reactions (6)].

669 **Drug Interactions:** Patients should be cautioned about the use of other medications,  
670 including ganciclovir, interferon alfa, and ribavirin, which may exacerbate the toxicity of  
671 RETROVIR [see Drug Interactions (7)].

672 **Pregnancy:** Pregnant women considering the use of RETROVIR during pregnancy for  
673 prevention of HIV-1 transmission to their infants should be informed that transmission may still  
674 occur in some cases despite therapy. The long-term consequences of in utero and infant exposure  
675 to RETROVIR are unknown, including the possible risk of cancer [see Use in Specific  
676 Populations (8.1)].

677 HIV-1-infected pregnant women should be informed not to breastfeed to avoid postnatal  
678 transmission of HIV to a child who may not yet be infected [see Use in Specific Populations  
679 (8.3)].

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

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

- 686 • **Do not share needles or other injection equipment.**
- 687 • **Do not share personal items that can have blood or body fluids on them, like**  
688 **toothbrushes and razor blades.**
- 689 • **Do not have any kind of sex without protection.** Always practice safe sex by using a  
690 latex or polyurethane condom or other barrier method to lower the chance of sexual  
691 contact with semen, vaginal secretions, or blood.
- 692 • **Do not breastfeed.** Zidovudine is excreted in human breast milk. Mothers with HIV-1  
693 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

694 Patients should be informed to take all HIV medications exactly as prescribed.

695 RETROVIR, COMBIVIR, EPIVIR, and TRIZIVIR are registered trademarks of ViiV  
696 Healthcare.

697

698

699 Manufactured for:



700

701 ViiV Healthcare

702 Research Triangle Park, NC 27709

703

704 by:



705

706 GlaxoSmithKline

707 Research Triangle Park, NC 27709

708

709 ©2012, ViiV Healthcare. All rights reserved.

710

711 May 2012

712 RTT: PI