

## 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

Dosage and Administration, Pediatric Patients (2.1) September 2008

### 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 (6 weeks to <18 years of age): 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: 50 mg/5 mL (3)

### CONTRAINDICATIONS

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

### WARNINGS AND PRECAUTIONS

- Hematologic toxicity/bone marrow suppression 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)
- 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

- The most commonly reported adverse reactions (incidence  $\geq 15\%$ ) in adult HIV-1 clinical studies were headache, malaise, nausea, anorexia, and vomiting. (6.1)
- The most commonly reported adverse reactions (incidence  $\geq 15\%$ ) in pediatric HIV-1 clinical studies were fever, cough, and digestive disorders. (6.1)
- The 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 GlaxoSmithKline at 1-888-825-5249 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: September 2008  
Version No.

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1

2 **FULL PRESCRIBING INFORMATION**

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

5 **RETROVIR (zidovudine) has been associated with hematologic toxicity including**  
6 **neutropenia and severe anemia, particularly in patients with advanced HIV-1 disease [see**  
7 **Warnings and Precautions (5.1)].**

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

10 **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have**  
11 **been reported with the use of nucleoside analogues alone or in combination, including**  
12 **RETROVIR and other antiretrovirals. Suspend treatment if clinical or laboratory findings**  
13 **suggestive of lactic acidosis or pronounced hepatotoxicity occur [see Warnings and**  
14 **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  
31 prolonged 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 (6 weeks to <18 years of age): 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 6 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 |         |
|------------------|------------------|-------------------------|---------|
|                  |                  | b.i.d.                  | t.i.d.  |
| 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: 2 mg/kg orally every 6 hours starting within 12 hours after birth and  
68 continuing through 6 weeks of age. Neonates unable to receive oral dosing may be administered  
69 RETROVIR intravenously at 1.5 mg/kg, infused over 30 minutes, every 6 hours.

70 **2.3 Patients With Severe Anemia and/or Neutropenia**

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

#### 79 **2.4 Patients With Renal Impairment:**

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

#### 83 **2.5 Patients With Hepatic Impairment:**

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

### 86 **3 DOSAGE FORMS AND STRENGTHS**

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

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

92 **RETROVIR Syrup** (colorless to pale yellow, strawberry-flavored) containing 50 mg  
93 zidovudine in each teaspoonful (5 mL).

### 94 **4 CONTRAINDICATIONS**

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

### 98 **5 WARNINGS AND PRECAUTIONS**

#### 99 **5.1 Hematologic Toxicity/Bone Marrow Suppression**

100 RETROVIR should be used with caution in patients who have bone marrow compromise  
101 evidenced by granulocyte count <1,000 cells/mm<sup>3</sup> or hemoglobin <9.5 g/dL. Hematologic  
102 toxicities appear to be related to pretreatment bone marrow reserve and to dose and duration of  
103 therapy. In patients with advanced symptomatic HIV-1 disease, anemia and neutropenia were the  
104 most significant adverse events observed. In patients who experience hematologic toxicity, a  
105 reduction in hemoglobin may occur as early as 2 to 4 weeks, and neutropenia usually occurs after  
106 6 to 8 weeks. There have been reports of pancytopenia associated with the use of RETROVIR,  
107 which was reversible in most instances after discontinuance of the drug. However, significant  
108 anemia, in many cases requiring dose adjustment, discontinuation of RETROVIR, and/or blood

109 transfusions, has occurred during treatment with RETROVIR alone or in combination with other  
110 antiretrovirals.

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

## 117 **5.2 Myopathy**

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

## 120 **5.3 Lactic Acidosis/Severe Hepatomegaly With Steatosis**

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

## 130 **5.4 Use With Interferon- and Ribavirin-Based Regimens in HIV-1/HCV** 131 **Co-Infected Patients**

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

140 Hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients  
141 receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without  
142 ribavirin. Patients receiving interferon alfa with or without ribavirin and zidovudine should be  
143 closely monitored for treatment-associated toxicities, especially hepatic decompensation,  
144 neutropenia, and anemia.

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

149 **5.5 Use With Other Zidovudine-Containing Products**

150 RETROVIR should not be administered with combination products that contain  
151 zidovudine as one of their components (e.g., COMBIVIR<sup>®</sup> or TRIZIVIR<sup>®</sup>).

152 **5.6 Immune Reconstitution Syndrome**

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

159 **5.7 Fat Redistribution**

160 Redistribution/accumulation of body fat, including central obesity, dorsocervical fat  
161 enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and  
162 “cushingoid appearance,” have been observed in patients receiving antiretroviral therapy. The  
163 mechanism and long-term consequences of these events are currently unknown. A causal  
164 relationship has not been established.

165 **6 ADVERSE REACTIONS**

166 **6.1 Clinical Trials Experience**

167 The following adverse reactions are discussed in greater detail in other sections of the  
168 labeling:

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

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

179 Adults: The frequency and severity of adverse reactions associated with the use of  
180 RETROVIR are greater in patients with more advanced infection at the time of initiation of  
181 therapy.

182 Table 2 summarizes events reported at a statistically significant greater incidence for  
183 patients receiving RETROVIR in a monotherapy study.

184

185 **Table 2. Percentage (%) of Patients With Adverse Reactions\* in Asymptomatic HIV-1**  
 186 **Infection (ACTG 019)**

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

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

188 <sup>†</sup> Not statistically significant versus placebo.

189

190 In addition to the adverse reactions listed in Table 2, adverse reactions observed at an  
 191 incidence of ≥5% in any treatment arm in clinical studies (NUCA3001, NUCA3002,  
 192 NUCB3001, and NUCB3002) were abdominal cramps, abdominal pain, arthralgia, chills,  
 193 dyspepsia, fatigue, insomnia, musculoskeletal pain, myalgia, and neuropathy. Additionally, in  
 194 these studies hyperbilirubinemia was reported at an incidence of ≤0.8%.

195 Selected laboratory abnormalities observed during a clinical study of monotherapy with  
 196 RETROVIR are shown in Table 3.

197

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

| Test<br>(Abnormal Level)                             | RETROVIR 500 mg/day<br>(n = 453) | Placebo<br>(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%                   |

200 ULN = Upper limit of normal.

201

202 Pediatrics: The clinical adverse reactions reported among adult recipients of  
 203 RETROVIR may also occur in pediatric patients.

204 *Study ACTG300:* Selected clinical adverse reactions and physical findings with a  
 205 ≥5% frequency during therapy with EPIVIR 4 mg/kg twice daily plus RETROVIR 160 mg/m<sup>2</sup>



206 3 times daily compared with didanosine in therapy-naive ( $\leq 56$  days of antiretroviral therapy)  
 207 pediatric patients are listed in Table 4.

208

209 **Table 4. Selected Clinical Adverse Reactions and Physical Findings ( $\geq 5\%$  Frequency) in**  
 210 **Pediatric Patients in Study ACTG300**

| Adverse Reaction                | EPIVIR plus<br>RETROVIR<br>(n = 236) | Didanosine<br>(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*      | 7%                                   | 6%                      |
| Nasal discharge or congestion   | 8%                                   | 11%                     |
| <b>Other</b>                    |                                      |                         |
| Skin rashes                     | 12%                                  | 14%                     |
| Lymphadenopathy                 | 9%                                   | 11%                     |

211 \*Includes pain, discharge, erythema, or swelling of an ear.

212

213 Selected laboratory abnormalities experienced by therapy-naive ( $\leq 56$  days of  
 214 antiretroviral therapy) pediatric patients are listed in Table 5.

215

216 **Table 5. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Pediatric**  
 217 **Patients in Study ACTG300**

| Test<br>(Abnormal Level)                             | EPIVIR plus<br>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%         |

218 ULN = Upper limit of normal.

219 ANC = Absolute neutrophil count.

220  
 221 Macrocytosis was reported in the majority of pediatric patients receiving RETROVIR  
 222 180 mg/m<sup>2</sup> every 6 hours in open-label studies. Additionally, adverse reactions reported at an  
 223 incidence of <6% in these studies were congestive heart failure, decreased reflexes, ECG  
 224 abnormality, edema, hematuria, left ventricular dilation, nervousness/irritability, and weight loss.

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

## 239 **6.2 Postmarketing Experience**

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

245 Body as a Whole: Back pain, chest pain, flu-like syndrome, generalized pain,  
 246 redistribution/accumulation of body fat [*see Warnings and Precautions (5.6)*].

247            Cardiovascular: Cardiomyopathy, syncope.  
248            Endocrine: Gynecomastia.  
249            Eye: Macular edema.  
250            Gastrointestinal: Dysphagia, flatulence, oral mucosa pigmentation, mouth ulcer.  
251            General: Sensitization reactions including anaphylaxis and angioedema, vasculitis.  
252            Hemic and Lymphatic: Aplastic anemia, hemolytic anemia, leukopenia,  
253 lymphadenopathy, pancytopenia with marrow hypoplasia, pure red cell aplasia.  
254            Hepatobiliary Tract and Pancreas: Hepatitis, hepatomegaly with steatosis, jaundice,  
255 lactic acidosis, pancreatitis.  
256            Musculoskeletal: Increased CPK, increased LDH, muscle spasm, myopathy and  
257 myositis with pathological changes (similar to that produced by HIV-1 disease), rhabdomyolysis,  
258 tremor.  
259            Nervous: Anxiety, confusion, depression, dizziness, loss of mental acuity, mania,  
260 paresthesia, seizures, somnolence, vertigo.  
261            Respiratory: Dyspnea, rhinitis, sinusitis.  
262            Skin: Changes in skin and nail pigmentation, pruritus, Stevens-Johnson syndrome, toxic  
263 epidermal necrolysis, sweat, urticaria.  
264            Special Senses: Amblyopia, hearing loss, photophobia, taste perversion.  
265            Urogenital: Urinary frequency, urinary hesitancy.

## 266    **7    DRUG INTERACTIONS**

### 267    **7.1    Antiretroviral Agents**

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

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

### 273    **7.2    Doxorubicin**

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

### 276    **7.3    Hematologic/Bone Marrow Suppressive/Cytotoxic Agents**

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

## 279    **8    USE IN SPECIFIC POPULATIONS**

### 280    **8.1    Pregnancy**

281            Pregnancy Category C.

282            In humans, treatment with RETROVIR during pregnancy reduced the rate of  
283 maternal-fetal HIV-1 transmission from 24.9% for infants born to placebo-treated mothers to  
284 7.8% for infants born to mothers treated with RETROVIR [*see Clinical Studies (14.3)*]. There  
285 were no differences in pregnancy-related adverse events between the treatment groups. Animal

286 reproduction studies in rats and rabbits showed evidence of embryotoxicity and increased fetal  
287 malformations.

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

295 Increased fetal resorptions occurred in pregnant rats and rabbits treated with doses of  
296 zidovudine that produced drug plasma concentrations 66 to 226 times (rats) and 12 to 87 times  
297 (rabbits) the mean steady-state peak human plasma concentration following a single 100-mg  
298 dose of zidovudine. There were no other reported developmental anomalies. In another  
299 developmental toxicity study, pregnant rats received zidovudine up to near-lethal doses that  
300 produced peak plasma concentrations 350 times peak human plasma concentrations (300 times  
301 the daily AUC in humans given 600 mg/day zidovudine). This dose was associated with marked  
302 maternal toxicity and an increased incidence of fetal malformations. However, there were no  
303 signs of teratogenicity at doses up to one fifth the lethal dose [see *Nonclinical Toxicology*  
304 *(13.2)*].

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

### 308 **8.3 Nursing Mothers**

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

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

### 315 **8.4 Pediatric Use**

316 RETROVIR has been studied in HIV-1-infected pediatric patients  $\geq 6$  weeks of age who  
317 had HIV-1-related symptoms or who were asymptomatic with abnormal laboratory values  
318 indicating significant HIV-1-related immunosuppression. RETROVIR has also been studied in  
319 neonates perinatally exposed to HIV-1 [see *Dosage and Administration (2.1)*, *Adverse Reactions*  
320 *(6.1)*, *Clinical Pharmacology (12.3)*, *Clinical Studies (14.2)*, *(14.3)*].

### 321 **8.5 Geriatric Use**

322 Clinical studies of RETROVIR did not include sufficient numbers of subjects aged 65  
323 and over to determine whether they respond differently from younger subjects. Other reported  
324 clinical experience has not identified differences in responses between the elderly and younger  
325 patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater

326 frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other  
327 drug therapy.

### 328 **8.6 Renal Impairment**

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

### 331 **8.7 Hepatic Impairment**

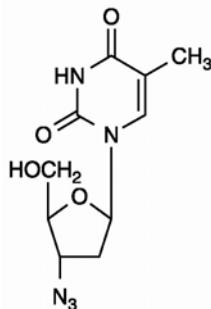
332 Zidovudine is eliminated from the body primarily by renal excretion following  
333 metabolism in the liver (glucuronidation). Although the data are limited, zidovudine  
334 concentrations appear to be increased in patients with severely impaired hepatic function which  
335 may increase the risk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

## 337 **10 OVERDOSAGE**

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

## 345 **11 DESCRIPTION**

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



349 Zidovudine is a white to beige, odorless, crystalline solid with a molecular weight of  
350 267.24 and a solubility of 20.1 mg/mL in water at 25°C. The molecular formula is  $\text{C}_{10}\text{H}_{13}\text{N}_5\text{O}_4$ .

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

354 RETROVIR Capsules are for oral administration. Each capsule contains 100 mg of  
355 zidovudine and the inactive ingredients corn starch, magnesium stearate, microcrystalline  
356 cellulose, and sodium starch glycolate. The 100-mg empty hard gelatin capsule, printed with  
357

358 edible black ink, consists of black iron oxide, dimethylpolysiloxane, gelatin, pharmaceutical  
359 shellac, soya lecithin, and titanium dioxide.

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

## 364 **12 CLINICAL PHARMACOLOGY**

### 365 **12.1 Mechanism of Action**

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

### 367 **12.3 Pharmacokinetics**

368 Absorption and Bioavailability: In adults, following oral administration, zidovudine is  
369 rapidly absorbed and extensively distributed, with peak serum concentrations occurring within  
370 0.5 to 1.5 hours. The extent of absorption (AUC) was equivalent when zidovudine was  
371 administered as RETROVIR Tablets or Syrup compared with RETROVIR Capsules. The  
372 pharmacokinetic properties of zidovudine in fasting adult patients are summarized in Table 6.  
373

374 **Table 6. Zidovudine Pharmacokinetic Parameters in Fasting Adult Patients**

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

375 \*Median [range].

376 <sup>†</sup>Approximate range.

377  
378 Distribution: The apparent volume of distribution of zidovudine, following oral  
379 administration, is 1.6 ± 0.6 L/kg; and binding to plasma protein is low, <38% (Table 6).

380 Metabolism and Elimination: Zidovudine is primarily eliminated by hepatic  
 381 metabolism. The major metabolite of zidovudine is GZDV. GZDV AUC is about 3-fold greater  
 382 than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and  
 383 74%, respectively, of the dose following oral administration. A second metabolite, 3'-amino-3'-  
 384 deoxythymidine (AMT), has been identified in the plasma following single-dose intravenous  
 385 (IV) administration of zidovudine. The AMT AUC was one fifth of the zidovudine AUC.  
 386 Pharmacokinetics of zidovudine were dose independent at oral dosing regimens ranging from  
 387 2 mg/kg every 8 hours to 10 mg/kg every 4 hours.

388 Effect of Food on Absorption: RETROVIR may be administered with or without food.  
 389 The extent of zidovudine absorption (AUC) was similar when a single dose of zidovudine was  
 390 administered with food.

391 Special Populations: Renal Impairment: Zidovudine clearance was decreased  
 392 resulting in increased zidovudine and GZDV half-life and AUC in patients with impaired renal  
 393 function (n = 14) following a single 200-mg oral dose (Table 7). Plasma concentrations of AMT  
 394 were not determined. A dose adjustment should not be necessary for patients with creatinine  
 395 clearance (CrCl)  $\geq 15$  mL/min.

396  
 397 **Table 7. Zidovudine Pharmacokinetic Parameters in Patients With Severe Renal**  
 398 **Impairment\***

| Parameter                 | Control Subjects<br>(Normal Renal Function)<br>(n = 6) | Patients With Renal<br>Impairment<br>(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                                 |

399 \*Data are expressed as mean  $\pm$  standard deviation.

400  
 401 Hemodialysis and Peritoneal Dialysis: The pharmacokinetics and tolerance of  
 402 zidovudine were evaluated in a multiple-dose study in patients undergoing hemodialysis (n = 5)  
 403 or peritoneal dialysis (n = 6) receiving escalating doses up to 200 mg 5 times daily for 8 weeks.  
 404 Daily doses of 500 mg or less were well tolerated despite significantly elevated GZDV plasma  
 405 concentrations. Apparent zidovudine oral clearance was approximately 50% of that reported in  
 406 patients with normal renal function. Hemodialysis and peritoneal dialysis appeared to have a  
 407 negligible effect on the removal of zidovudine, whereas GZDV elimination was enhanced. A  
 408 dosage adjustment is recommended for patients undergoing hemodialysis or peritoneal dialysis  
 409 [see Dosage and Administration (2.4)].

410 Hepatic Impairment: Data describing the effect of hepatic impairment on the  
 411 pharmacokinetics of zidovudine are limited. However, because zidovudine is eliminated  
 412 primarily by hepatic metabolism, it is expected that zidovudine clearance would be decreased

413 and plasma concentrations would be increased following administration of the recommended  
 414 adult doses to patients with hepatic impairment [see *Dosage and Administration (2.5)*].

415 **Pediatric Patients:** Zidovudine pharmacokinetics have been evaluated in  
 416 HIV-1-infected pediatric patients (Table 8).

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

425 **Patients <3 Months of Age:** Zidovudine pharmacokinetics have been evaluated in  
 426 pediatric patients from birth to 3 months of life. Zidovudine elimination was determined  
 427 immediately following birth in 8 neonates who were exposed to zidovudine in utero. The  
 428 half-life was 13.0 ± 5.8 hours. In neonates ≤14 days old, bioavailability was greater, total body  
 429 clearance was slower, and half-life was longer than in pediatric patients >14 days old. For dose  
 430 recommendations for neonates [see *Dosage and Administration (2.2)*].

431

432 **Table 8. Zidovudine Pharmacokinetic Parameters in Pediatric Patients\***

| Parameter                  | Birth to 14 Days of Age | 14 Days to 3 Months of Age | 3 Months to 12 Years of Age                  |
|----------------------------|-------------------------|----------------------------|--|
| Oral bioavailability (%)   | 89 ± 19<br>(n = 15)     | 61 ± 19<br>(n = 17)        | 65 ± 24<br>(n = 18)                          |
| CSF:plasma ratio           | no data                 | no data                    | 0.68 [0.03 to 3.25] <sup>†</sup><br>(n = 38) |
| CL (L/hr/kg)               | 0.65 ± 0.29<br>(n = 18) | 1.14 ± 0.24<br>(n = 16)    | 1.85 ± 0.47<br>(n = 20)                      |
| Elimination half-life (hr) | 3.1 ± 1.2<br>(n = 21)   | 1.9 ± 0.7<br>(n = 18)      | 1.5 ± 0.7<br>(n = 21)                        |

433 \*Data presented as mean ± standard deviation except where noted.

434 <sup>†</sup>Median [range].

435

436 **Pregnancy:** Zidovudine pharmacokinetics have been studied in a Phase I study of  
 437 8 women during the last trimester of pregnancy. Zidovudine pharmacokinetics were similar to  
 438 those of nonpregnant adults. Consistent with passive transmission of the drug across the  
 439 placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in  
 440 maternal plasma at delivery [see *Use in Specific Populations (8.1)*].

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



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

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

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

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

454

455 **Table 9. Effect of Coadministered Drugs on Zidovudine AUC\***

| <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<br>750 mg q 12 hr<br>with food   | 200 mg q 8 hr              | 14 | ↑AUC<br>31%               | Range<br>23% to 78% <sup>†</sup>      | ↔                                    |
| Fluconazole<br>400 mg daily   | 200 mg q 8 hr              | 12 | ↑AUC<br>74%               | 95% CI:<br>54% to 98%                 | Not Reported                         |
| Lamivudine<br>300 mg q 12 hr  | single 200 mg              | 12 | ↑AUC<br>13%               | 90% CI:<br>2% to 27%                  | ↔                                    |
| Methadone<br>30 to 90 mg daily  | 200 mg q 4 hr              | 9  | ↑AUC<br>43%               | Range<br>16% to 64% <sup>†</sup>      | ↔                                    |
| Nelfinavir<br>750 mg q 8 hr x<br>7 to 10 days   | single 200 mg              | 11 | ↓AUC<br>35%               | Range<br>28% to 41%                   | ↔                                    |
| Probenecid<br>500 mg q 6 hr x<br>2 days   | 2 mg/kg q 8 hr<br>x 3 days | 3  | ↑AUC<br>106%              | Range<br>100% to<br>170% <sup>†</sup> | Not Assessed                         |
| Rifampin<br>600 mg daily x<br>14 days   | 200 mg q 8 hr<br>x 14 days | 8  | ↓AUC<br>47%               | 90% CI:<br>41% to 53%                 | Not Assessed                         |
| Ritonavir<br>300 mg q 6 hr x<br>4 days  | 200 mg q 8 hr<br>x 4 days  | 9  | ↓AUC<br>25%               | 95% CI:<br>15% to 34%                 | ↔                                    |
| Valproic acid<br>250 mg or 500 mg<br>q 8 hr x 4 days  | 100 mg q 8 hr<br>x 4 days  | 6  | ↑AUC<br>80%               | Range<br>64% to<br>130% <sup>†</sup>  | Not Assessed                         |

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

458 \*This table is not all inclusive.

459 <sup>†</sup>Estimated range of percent difference.

460

461 *Phenytoin:* Phenytoin plasma levels have been reported to be low in some patients  
 462 receiving RETROVIR, while in one case a high level was documented. However, in a  
 463 pharmacokinetic interaction study in which 12 HIV-1-positive volunteers received a single  
 464 300-mg phenytoin dose alone and during steady-state zidovudine conditions (200 mg every

465 4 hours), no change in phenytoin kinetics was observed. Although not designed to optimally  
466 assess the effect of phenytoin on zidovudine kinetics, a 30% decrease in oral zidovudine  
467 clearance was observed with phenytoin.

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

#### 474 **12.4 Microbiology**

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

481 **Antiviral Activity:** The antiviral activity of zidovudine against HIV-1 was assessed in a  
482 number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The  
483 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  
484 9  $\mu$ M, respectively. HIV-1 from therapy-naïve subjects with no mutations associated with  
485 resistance gave median EC<sub>50</sub> values of 0.011  $\mu$ M (range: 0.005 to 0.110  $\mu$ M) from Virco (n = 92  
486 baseline samples from COLA40263) and 0.0017  $\mu$ M (0.006 to 0.0340  $\mu$ M) from Monogram  
487 Biosciences (n = 135 baseline samples from ESS30009). The EC<sub>50</sub> values of zidovudine against  
488 different HIV-1 clades (A-G) ranged from 0.00018 to 0.02  $\mu$ M, and against HIV-2 isolates from  
489 0.00049 to 0.004  $\mu$ M. In cell culture drug combination studies, zidovudine demonstrates  
490 synergistic activity with the nucleoside reverse transcriptase inhibitors abacavir, didanosine, and  
491 lamivudine; the non-nucleoside reverse transcriptase inhibitors delavirdine and nevirapine; and  
492 the protease inhibitors indinavir, nelfinavir, ritonavir, and saquinavir; and additive activity with  
493 interferon alfa. Ribavirin has been found to inhibit the phosphorylation of zidovudine in cell  
494 culture.

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

503 **Cross-Resistance:** In a study of 167 HIV-1-infected patients, isolates (n = 2) with  
504 multi-drug resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were

505 recovered from patients treated for  $\geq 1$  year with zidovudine plus didanosine or zidovudine plus  
506 zalcitabine. The pattern of resistance-associated amino acid substitutions with such combination  
507 therapies was different (A62V, V75I, F77L, F116Y, Q151M) from the pattern with zidovudine  
508 monotherapy, with the Q151M substitution being most commonly associated with multi-drug  
509 resistance. The substitution at codon 151 in combination with substitutions at 62, 75, 77, and 116  
510 results in a virus with reduced susceptibility to didanosine, lamivudine, stavudine, zalcitabine,  
511 and zidovudine. Thymidine analogue mutations (TAMs) are selected by zidovudine and confer  
512 cross-resistance to abacavir, didanosine, stavudine, tenofovir, and zalcitabine.

## 513 **13 NONCLINICAL TOXICOLOGY**

### 514 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

515 Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats  
516 (60 females and 60 males in each group). Initial single daily doses were 30, 60, and  
517 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced  
518 to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats  
519 only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on  
520 day 279.

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

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

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

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

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

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

539 Two transplacental carcinogenicity studies were conducted in mice. One study  
540 administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10  
541 through parturition and lactation with dosing continuing in offspring for 24 months postnatally.  
542 The doses of zidovudine administered in this study produced zidovudine exposures  
543 approximately 3 times the estimated human exposure at recommended doses. After 24 months,

544 an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or  
545 lung or any other organ in either gender. These findings are consistent with results of the  
546 standard oral carcinogenicity study in mice, as described earlier. A second study administered  
547 zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg  
548 nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12  
549 through 18 of gestation. There was an increase in the number of tumors in the lung, liver, and  
550 female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.

### 551 **13.2 Reproductive and Developmental Toxicology Studies**

552 Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed  
553 no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal  
554 toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or  
555 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies  
556 resulted in peak zidovudine plasma concentrations (after one half of the daily dose) in rats 66 to  
557 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations  
558 (after one sixth of the daily dose) achieved with the recommended daily dose (100 mg every  
559 4 hours). In an in vitro experiment with fertilized mouse oocytes, zidovudine exposure resulted  
560 in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a  
561 dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/kg) caused  
562 marked maternal toxicity and an increase in the incidence of fetal malformations. This dose  
563 resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations.  
564 (Estimated area under the curve [AUC] in rats at this dose level was 300 times the daily AUC in  
565 humans given 600 mg/day.) No evidence of teratogenicity was seen in this experiment at doses  
566 of 600 mg/kg/day or less.

## 567 **14 CLINICAL STUDIES**

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

### 571 **14.1 Adults**

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

576 The clinical efficacy of a combination regimen that includes RETROVIR was  
577 demonstrated in study ACTG320. This study was a multi-center, randomized, double-blind,  
578 placebo-controlled trial that compared RETROVIR 600 mg/day plus EPIVIR<sup>®</sup> 300 mg/day to  
579 RETROVIR plus EPIVIR plus indinavir 800 mg t.i.d. The incidence of AIDS-defining events or  
580 death was lower in the triple-drug-containing arm compared with the 2-drug-containing arm  
581 (6.1% versus 10.9%, respectively).

582 **Monotherapy:** In controlled studies of treatment-naive patients conducted between 1986  
 583 and 1989, monotherapy with RETROVIR, as compared with placebo, reduced the risk of HIV-1  
 584 disease progression, as assessed using endpoints that included the occurrence of HIV-1-related  
 585 illnesses, AIDS-defining events, or death. These studies enrolled patients with advanced disease  
 586 (BW002), and asymptomatic or mildly symptomatic disease in patients with CD4+ cell counts  
 587 between 200 and 500 cells/mm<sup>3</sup> (ACTG016 and ACTG019). A survival benefit for monotherapy  
 588 with RETROVIR was not demonstrated in the latter 2 studies. Subsequent studies showed that  
 589 the clinical benefit of monotherapy with RETROVIR was time limited.

590 **14.2 Pediatric Patients**

591 ACTG300 was a multi-center, randomized, double-blind study that provided for  
 592 comparison of EPIVIR plus RETROVIR to didanosine monotherapy. A total of  
 593 471 symptomatic, HIV-1-infected therapy-naive pediatric patients were enrolled in these  
 594 2 treatment arms. The median age was 2.7 years (range 6 weeks to 14 years), the mean baseline  
 595 CD4+ cell count was 868 cells/mm<sup>3</sup>, and the mean baseline plasma HIV-1 RNA was  
 596 5.0 log<sub>10</sub> copies/mL. The median duration that patients remained on study was approximately  
 597 10 months. Results are summarized in Table 10.

598  
 599 **Table 10. Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease**  
 600 **Progression or Death)**

| Endpoint                                 | EPIVIR plus<br>RETROVIR<br>(n = 236) | Didanosine<br>(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%)               |

601  
 602 **14.3 Prevention of Maternal-Fetal HIV-1 Transmission**

603 The utility of RETROVIR for the prevention of maternal-fetal HIV-1 transmission was  
 604 demonstrated in a randomized, double-blind, placebo-controlled trial (ACTG076) conducted in  
 605 HIV-1-infected pregnant women with CD4+ cell counts of 200 to 1,818 cells/mm<sup>3</sup> (median in  
 606 the treated group: 560 cells/mm<sup>3</sup>) who had little or no previous exposure to RETROVIR. Oral  
 607 RETROVIR was initiated between 14 and 34 weeks of gestation (median 11 weeks of therapy)  
 608 followed by IV administration of RETROVIR during labor and delivery. Following birth,  
 609 neonates received oral RETROVIR Syrup for 6 weeks. The study showed a statistically  
 610 significant difference in the incidence of HIV-1 infection in the neonates (based on viral culture  
 611 from peripheral blood) between the group receiving RETROVIR and the group receiving  
 612 placebo. Of 363 neonates evaluated in the study, the estimated risk of HIV-1 infection was 7.8%  
 613 in the group receiving RETROVIR and 24.9% in the placebo group, a relative reduction in

614 transmission risk of 68.7%. RETROVIR was well tolerated by mothers and infants. There was  
615 no difference in pregnancy-related adverse events between the treatment groups.

## 616 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

619 Bottle of 60 (NDC 0173-0501-00).

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

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

624 Bottles of 100 (NDC 0173-0108-55).

625 Unit Dose Pack of 100 (NDC 0173-0108-56).

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

627 RETROVIR Syrup (colorless to pale yellow, strawberry-flavored) containing 50 mg  
628 zidovudine in each teaspoonful (5 mL).

629 Bottle of 240 mL (NDC 0173-0113-18) with child-resistant cap.

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

## 631 **17 PATIENT COUNSELING INFORMATION**

### 632 **17.1 Information About Therapy With RETROVIR**

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

640 Common Adverse Reactions: Other adverse effects of RETROVIR include nausea and  
641 vomiting. Patients should also be encouraged to contact their physician if they experience muscle  
642 weakness, shortness of breath, symptoms of hepatitis or pancreatitis, or any other unexpected  
643 adverse events while being treated with RETROVIR [*see Adverse Reactions (6)*].

644 Drug Interactions: Patients should be cautioned about the use of other medications,  
645 including ganciclovir, interferon alfa, and ribavirin, which may exacerbate the toxicity of  
646 RETROVIR.

647 Redistribution/Accumulation of Body Fat: Redistribution or accumulation of body fat  
648 may occur in patients receiving antiretroviral therapy and that the cause and long-term health  
649 effects of these conditions are not known at this time [*see Warnings and Precautions (5.6)*].

650 Pregnancy: Pregnant women considering the use of RETROVIR during pregnancy for  
651 prevention of HIV-1 transmission to their infants should be advised that transmission may still

652 occur in some cases despite therapy. The long-term consequences of in utero and infant exposure  
653 to RETROVIR are unknown, including the possible risk of cancer.

654 HIV-1-infected pregnant women should be advised not to breastfeed to avoid postnatal  
655 transmission of HIV to a child who may not yet be infected.

656 Information About Therapy With RETROVIR: RETROVIR is not a cure for HIV-1  
657 infection, and patients may continue to acquire illnesses associated with HIV-1 infection,  
658 including opportunistic infections. Therefore, patients should be advised to seek medical care for  
659 any significant change in their health status.

660 Patients should be told of the importance of taking RETROVIR exactly as prescribed.  
661 They should be told not to share medication and not to exceed the recommended dose. Patients  
662 should be told that the long-term effects of RETROVIR are unknown at this time.

663 Therapy with RETROVIR has not been shown to reduce the risk of transmission of  
664 HIV-1 to others through sexual contact or blood contamination.

665  
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669



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