

## 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) November 2009

### 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 (4 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: November 2009

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1 **FULL PRESCRIBING INFORMATION**

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

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

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

9 **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have**  
10 **been reported with the use of nucleoside analogues alone or in combination, including**  
11 **RETROVIR and other antiretrovirals. Suspend treatment if clinical or laboratory findings**  
12 **suggestive of lactic acidosis or pronounced hepatotoxicity occur [see Warnings and**  
13 **Precautions (5.3)].**

14 **1 INDICATIONS AND USAGE**

15 **1.1 Treatment of HIV-1**

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

18 **1.2 Prevention of Maternal-Fetal HIV-1 Transmission**

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

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

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

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

36 **2 DOSAGE AND ADMINISTRATION**

37 **2.1 Treatment of HIV-1 Infection**

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

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

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

46 Before prescribing RETROVIR capsules or tablets, children should be assessed for the  
47 ability to swallow capsules or tablets. If a child is unable to reliably swallow a RETROVIR  
48 capsule or tablet, the RETROVIR syrup formulation should be prescribed.

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

52

53 **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  |

54

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

59 **2.2 Prevention of Maternal-Fetal HIV-1 Transmission**

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

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

66 Neonatal Dosing: 2 mg/kg orally every 6 hours starting within 12 hours after birth and  
67 continuing through 6 weeks of age. Neonates unable to receive oral dosing may be administered  
68 RETROVIR intravenously at 1.5 mg/kg, infused over 30 minutes, every 6 hours.

69 **2.3 Patients With Severe Anemia and/or Neutropenia**

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

## 78 **2.4 Patients With Renal Impairment**

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

## 82 **2.5 Patients With Hepatic Impairment**

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

## 85 **3 DOSAGE FORMS AND STRENGTHS**

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

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

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

## 93 **4 CONTRAINDICATIONS**

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

## 97 **5 WARNINGS AND PRECAUTIONS**

### 98 **5.1 Hematologic Toxicity/Bone Marrow Suppression**

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

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

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

## 116 **5.2 Myopathy**

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

## 119 **5.3 Lactic Acidosis/Severe Hepatomegaly With Steatosis**

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

## 129 **5.4 Use With Interferon- and Ribavirin-Based Regimens in HIV-1/HCV** 130 **Co-Infected Patients**

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

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

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

148 **5.5 Use With Other Zidovudine-Containing Products**

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

151 **5.6 Immune Reconstitution Syndrome**

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

158 **5.7 Fat Redistribution**

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

164 **6 ADVERSE REACTIONS**

165 **6.1 Clinical Trials Experience**

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

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

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

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

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

183

184 **Table 2. Percentage (%) of Patients With Adverse Reactions<sup>a</sup> in Asymptomatic HIV-1**  
 185 **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>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%                  |

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

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

188  
 189 In addition to the adverse reactions listed in Table 2, adverse reactions observed at an  
 190 incidence of ≥5% in any treatment arm in clinical studies (NUCA3001, NUCA3002,  
 191 NUCB3001, and NUCB3002) were abdominal cramps, abdominal pain, arthralgia, chills,  
 192 dyspepsia, fatigue, insomnia, musculoskeletal pain, myalgia, and neuropathy. Additionally, in  
 193 these studies hyperbilirubinemia was reported at an incidence of ≤0.8%.

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

196  
 197 **Table 3. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Patients With**  
 198 **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%                   |

199 ULN = Upper limit of normal.

200  
 201 Pediatrics: The clinical adverse reactions reported among adult recipients of  
 202 RETROVIR may also occur in pediatric patients.

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

205 3 times daily compared with didanosine in therapy-naive ( $\leq 56$  days of antiretroviral therapy)  
 206 pediatric patients are listed in Table 4.

207

208 **Table 4. Selected Clinical Adverse Reactions and Physical Findings ( $\geq 5\%$  Frequency) in**  
 209 **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 <sup>a</sup> | 7%                                   | 6%                      |
| Nasal discharge or congestion          | 8%                                   | 11%                     |
| <b>Other</b>                           |                                      |                         |
| Skin rashes                            | 12%                                  | 14%                     |
| Lymphadenopathy                        | 9%                                   | 11%                     |

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

211

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

214

215 **Table 5. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Pediatric**  
 216 **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%         |

217 ULN = Upper limit of normal.

218 ANC = Absolute neutrophil count.

219  
 220 Macrocytosis was reported in the majority of pediatric patients receiving RETROVIR  
 221 180 mg/m<sup>2</sup> every 6 hours in open-label studies. Additionally, adverse reactions reported at an  
 222 incidence of <6% in these studies were congestive heart failure, decreased reflexes, ECG  
 223 abnormality, edema, hematuria, left ventricular dilation, nervousness/irritability, and weight loss.

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

## 238 **6.2 Postmarketing Experience**

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

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

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

## 265 **7 DRUG INTERACTIONS**

### 266 **7.1 Antiretroviral Agents**

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

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

### 272 **7.2 Doxorubicin**

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

### 275 **7.3 Hematologic/Bone Marrow Suppressive/Cytotoxic Agents**

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

## 278 **8 USE IN SPECIFIC POPULATIONS**

### 279 **8.1 Pregnancy**

280 Pregnancy Category C.

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

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

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

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

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

### 307 **8.3 Nursing Mothers**

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

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

### 314 **8.4 Pediatric Use**

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

### 320 **8.5 Geriatric Use**

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

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

### 327 **8.6 Renal Impairment**

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

### 330 **8.7 Hepatic Impairment**

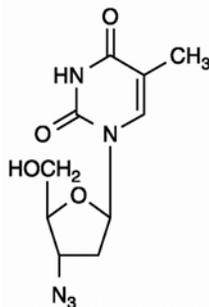
331 Zidovudine is eliminated from the body primarily by renal excretion following  
332 metabolism in the liver (glucuronidation). Although the data are limited, zidovudine  
333 concentrations appear to be increased in patients with severely impaired hepatic function which  
334 may increase the risk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

## 336 **10 OVERDOSAGE**

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

## 344 **11 DESCRIPTION**

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



348 Zidovudine is a white to beige, odorless, crystalline solid with a molecular weight of  
349 267.24 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 edible black ink, consists of black iron oxide, dimethylpolysiloxane, gelatin, pharmaceutical  
358 shellac, soya lecithin, and titanium dioxide.

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

## 363 **12 CLINICAL PHARMACOLOGY**

### 364 **12.1 Mechanism of Action**

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

### 366 **12.3 Pharmacokinetics**

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

373 **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 <sup>a</sup>           | 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>b</sup> | 0.5 to 3<br>(n = 19)              |

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

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

376

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

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

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

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

395  
 396 **Table 7. Zidovudine Pharmacokinetic Parameters in Patients With Severe Renal**  
 397 **Impairment<sup>a</sup>**

| 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                                 |

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

399  
 400 **Hemodialysis and Peritoneal Dialysis:** The pharmacokinetics and tolerance of  
 401 zidovudine were evaluated in a multiple-dose study in patients undergoing hemodialysis (n = 5)  
 402 or peritoneal dialysis (n = 6) receiving escalating doses up to 200 mg 5 times daily for 8 weeks.  
 403 Daily doses of 500 mg or less were well tolerated despite significantly elevated GZDV plasma  
 404 concentrations. Apparent zidovudine oral clearance was approximately 50% of that reported in  
 405 patients with normal renal function. Hemodialysis and peritoneal dialysis appeared to have a  
 406 negligible effect on the removal of zidovudine, whereas GZDV elimination was enhanced. A  
 407 dosage adjustment is recommended for patients undergoing hemodialysis or peritoneal dialysis  
 408 [see Dosage and Administration (2.4)].

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

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

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

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

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

430

431 **Table 8. Zidovudine Pharmacokinetic Parameters in Pediatric Patients<sup>a</sup>**

| 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>b</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)                        |

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

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

434

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

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

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

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

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

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

453

**Table 9. 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<br>750 mg q 12 hr<br>with food                                                                           | 200 mg q 8 hr              | 14 | ↑AUC<br>31%               | Range<br>23% to 78% <sup>b</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>b</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>b</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>b</sup>  | Not Assessed                         |

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

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

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

459

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

464 4 hours), no change in phenytoin kinetics was observed. Although not designed to optimally  
465 assess the effect of phenytoin on zidovudine kinetics, a 30% decrease in oral zidovudine  
466 clearance was observed with phenytoin.

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

## 473 **12.4 Microbiology**

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

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

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

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

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

## 512 **13 NONCLINICAL TOXICOLOGY**

### 513 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

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

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

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

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

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

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

### 550 **13.2 Reproductive and Developmental Toxicology Studies**

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

## 566 **14 CLINICAL STUDIES**

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

### 570 **14.1 Adults**

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

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

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

589 **14.2 Pediatric Patients**

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

597  
 598 **Table 10. Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease**  
 599 **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%)               |

600  
 601 **14.3 Prevention of Maternal-Fetal HIV-1 Transmission**

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

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

## 615 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

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

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

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

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

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

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

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

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

## 630 **17 PATIENT COUNSELING INFORMATION**

### 631 **17.1 Information About Therapy With RETROVIR**

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

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

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

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

649 Redistribution/Accumulation of Body Fat: Patients should be informed that  
650 redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy

651 and that the cause and long-term health effects of these conditions are not known at this time  
652 *[see Warnings and Precautions (5.6)]*.

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

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

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

668 HIV-1-infected pregnant women should be informed not to breastfeed to avoid postnatal  
669 transmission of HIV to a child who may not yet be infected *[see Use in Specific Populations*  
670 *(8.3)]*.

671 **Information About Therapy With RETROVIR:** RETROVIR is not a cure for HIV-1  
672 infection, and patients may continue to acquire illnesses associated with HIV-1 infection,  
673 including opportunistic infections. Therefore, patients should be informed to seek medical care  
674 for any significant change in their health status.

675 Patients should be informed of the importance of taking RETROVIR exactly as  
676 prescribed. They should be informed not to share medication and not to exceed the  
677 recommended dose. Patients should be informed that the long-term effects of RETROVIR are  
678 unknown at this time.

679 Patients should be informed that therapy with RETROVIR has not been shown to reduce  
680 the risk of transmission of HIV-1 to others through sexual contact or blood contamination.

681  
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