HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

WARNING: RISK OF HEMATOLOGICAL TOXICITY, MYOPATHY, LACTIC ACIDOSIS

See full prescribing information for complete boxed warning.

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

RECENT MAJOR CHANGES

Warnings and Precautions, Immune Reconstitution Syndrome (5.6) ----- November 2011
Dosage and Administration, Prevention of Maternal-Fetal HIV-1 Transmission ----- May 2012

INDICATIONS AND USAGE

RETROVIR is a nucleoside analogue reverse transcriptase inhibitor indicated for:

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

DOSAGE AND ADMINISTRATION

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: RISK OF HEMATOLOGICAL TOXICITY, MYOPATHY, LACTIC ACIDOSIS

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

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

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

1 INDICATIONS AND USAGE

1.1 Treatment of HIV-1

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

1.2 Prevention of Maternal-Fetal HIV-1 Transmission

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

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

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

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

2 DOSAGE AND ADMINISTRATION

2.1 Treatment of HIV-1 Infection

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

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

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

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

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

Table 1. Recommended Pediatric Dosage of RETROVIR

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

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

2.2 Prevention of Maternal-Fetal HIV-1 Transmission

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

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

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

Table 2. Recommended Neonatal Dosages of RETROVIR

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

2.3 Patients With Severe Anemia and/or Neutropenia

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

2.4 Patients With Renal Impairment

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

2.5 Patients With Hepatic Impairment

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

3 DOSAGE FORMS AND STRENGTHS

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

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

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hematologic Toxicity/Bone Marrow Suppression

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

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

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

5.2 Myopathy

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

5.3 Lactic Acidosis/Severe Hepatomegaly With Steatosis

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

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

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

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

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

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

5.5 Use With Other Zidovudine-Containing Products

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

5.6 Immune Reconstitution Syndrome

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

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

5.7 Fat Redistribution

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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

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

Table 3. Percentage (%) of Patients With Adverse Reactions[a] in Asymptomatic HIV-1 Infection (ACTG 019)

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

[a] Reported in ≥5% of study population.
[b] Not statistically significant versus placebo.

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

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

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

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

ULN = Upper limit of normal.

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

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

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

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

[a] Includes pain, discharge, erythema, or swelling of an ear.

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

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

Test (Abnormal Level)	EPIVIR plus RETROVIR	Didanosine
Neutropenia (ANC<400 cells/mm^3)	8%	3%
Anemia (Hgb<7.0 g/dL)	4%	2%
Thrombocytopenia (platelets<50,000/mm^3)	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%

ULN = Upper limit of normal.
ANC = Absolute neutrophil count.

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

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

6.2 Postmarketing Experience

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

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

Cardiovascular: Cardiomyopathy, syncope.

Endocrine: Gynecomastia.

Eye: Macular edema.

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

General: Sensitization reactions including anaphylaxis and angioedema, vasculitis.

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

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

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

Nervous: Anxiety, confusion, depression, dizziness, loss of mental acuity, mania, paresthesia, seizures, somnolence, vertigo.

Respiratory: Dyspnea, rhinitis, sinusitis.

Skin: Changes in skin and nail pigmentation, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, sweat, urticaria.

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

Urogenital: Urinary frequency, urinary hesitancy.

7 DRUG INTERACTIONS

7.1 Antiretroviral Agents

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

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

7.2 Doxorubicin

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

7.3 Hematologic/Bone Marrow Suppressive/Cytotoxic Agents

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

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

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

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

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

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

8.3 Nursing Mothers

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

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

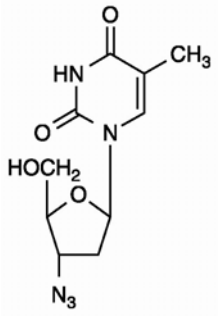
Zidovudine is eliminated from the body primarily by renal excretion following metabolism in the liver (glucuronidation). Although the data are limited, zidovudine concentrations appear to be increased in patients with severely impaired hepatic function, which may increase the risk of hematologic toxicity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

10 OVERDOSAGE

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

11 DESCRIPTION

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



Zidovudine is a white to beige, odorless, crystalline solid with a molecular weight of 267.24 and a solubility of 20.1 mg/mL in water at 25°C. The molecular formula is $C_{10}H_{13}N_5O_4$.

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

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

Table 7. Zidovudine Pharmacokinetic Parameters in Fasting Adult Patients

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

[a] Median [range].
[b] Approximate range.

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

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

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

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

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

Table 8. Zidovudine Pharmacokinetic Parameters in Patients With Severe Renal Impairment[a]

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

[a] Data are expressed as mean ± standard deviation.

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

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

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

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

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

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

Table 9. Zidovudine Pharmacokinetic Parameters in Pediatric Patients[a]

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

[a] Data presented as mean ± standard deviation except where noted.
[b] Median [range].

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

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

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

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

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

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

Table 10. Effect of Coadministered Drugs on Zidovudine AUC[a]

Note: ROUTINE DOSE MODIFICATION OF ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.					
Coadministered Drug and Dose	Zidovudine Dose	n	Zidovudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	↑AUC 31%	Range 23% to 78%[b]	↔
Clarithromycin 500 mg twice daily	100 mg q 4 hr x 7 days	4	↓AUC 12%	Range ↓34% to ↑14%	Not Reported
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑AUC 74%	95% CI: 54% to 98%	Not Reported
Lamivudine 300 mg q 12 hr	single 200 mg	12	↑AUC 13%	90% CI: 2% to 27%	↔
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑AUC 43%	Range 16% to 64%[b]	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 200 mg	11	↓AUC 35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑AUC 106%	Range 100% to 170%[b]	Not Assessed
Rifampin 600 mg daily x 14 days	200 mg q 8 hr x 14 days	8	↓AUC 47%	90% CI: 41% to 53%	Not Assessed
Ritonavir 300 mg q 6 hr x 4 days	200 mg q 8 hr x 4 days	9	↓AUC 25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑AUC 80%	Range 64% to 130%[b]	Not Assessed

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

[a] This table is not all inclusive.

[b] Estimated range of percent difference.

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

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

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

12.4 Microbiology

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

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

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

Zidovudine was mutagenic in a 5178Y/TK$^{+/-}$ mouse lymphoma assay, positive in an in vitro cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.

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

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

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

13.2 Reproductive and Developmental Toxicology Studies

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

14 CLINICAL STUDIES

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

14.1 Adults

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

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

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

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

14.2 Pediatric Patients

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

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

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

14.3 Prevention of Maternal-Fetal HIV-1 Transmission

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

Store at 15° to 25°C (59° to 77°F).

RETROVIR Capsules 100 mg (white, opaque cap and body) containing 100 mg zidovudine and printed with "Wellcome" and unicorn logo on cap and "Y9C" and "100" on body.

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

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

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

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

Store at 15° to 25°C (59° to 77°F).

17 PATIENT COUNSELING INFORMATION

17.1 Advice for the Patient

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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