PRODUCT INFORMATION

RETROVIR®

(zidovudine)

IV Infusion

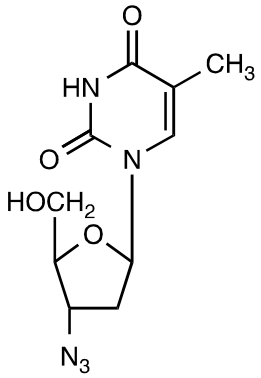
FOR INTRAVENOUS INFUSION ONLY

WARNING: RETROVIR (ZIDOVUDINE) MAY BE ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING NEUTROPENIA AND SEVERE ANEMIA PARTICULARLY IN PATIENTS WITH ADVANCED HIV DISEASE (SEE WARNINGS). PROLONGED USE OF RETROVIR HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY SIMILAR TO THAT PRODUCED BY HUMAN IMMUNODEFICIENCY VIRUS.

RARE OCCURRENCES OF POTENTIALLY FATAL LACTIC ACIDOSIS IN THE ABSENCE OF HYPOXEMIA, AND SEVERE HEPATOMEGALY WITH STEATOSIS HAVE BEEN REPORTED WITH THE USE OF CERTAIN ANTIRETROVIRAL NUCLEOSIDE ANALOGUES (SEE WARNINGS).

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

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 $C_{10}H_{13}N_5O_4$.

MICROBIOLOGY: Mechanism of Action: Zidovudine is a synthetic nucleoside analogue of the naturally occurring nucleoside, thymidine, in which the 3′-hydroxy (-OH) group is replaced by an azido ($-N_3$) group. Within cells, zidovudine is converted to the active metabolite, zidovudine 5′-triphosphate (AztTP), by the sequential action of the cellular enzymes. Zidovudine 5′-triphosphate inhibits the activity of the HIV reverse transcriptase both by competing for utilization with the natural substrate, deoxythymidine 5′-triphosphate (dTTP), and by its incorporation into viral DNA. The lack of a 3′- OH group in the incorporated nucleoside analogue prevents the formation of the 5′ to 3′ phosphodiester linkage essential for DNA chain elongation and, therefore, the viral DNA growth is terminated. The active metabolite AztTP is also a weak inhibitor of the cellular DNA polymerase-alpha and mitochondrial polymerase-gamma and has been reported to be incorporated into the DNA of cells in culture.

In Vitro HIV Susceptibility: The in vitro anti-HIV activity of zidovudine was assessed by infecting cell lines of lymphoblastic and monocytic origin and peripheral blood lymphocytes with laboratory and clinical isolates of HIV. The IC_{50} and IC_{90} values (50% and 90% inhibitory concentrations) were 0.003 to 0.013 and 0.03 to 0.13 mcg/mL, respectively (1 nM = 0.27 ng/mL). The IC_{50} and IC_{90} values of HIV isolates recovered from 18 untreated AIDS/ARC patients were in the range of 0.003 to 0.013 mcg/mL and 0.03 to 0.3 mcg/mL, respectively. Zidovudine showed antiviral activity in all acutely infected cell lines; however, activity was substantially less in chronically infected cell lines. In drug combination studies with zalcitabine, didanosine, lamivudine, saquinavir, indinavir, ritonavir, nevirapine, delavirdine, or interferon-alpha, zidovudine showed additive to synergistic activity in cell culture. The relationship between the in vitro susceptibility of HIV to reverse transcriptase inhibitors and the inhibition of HIV replication in humans has not been established.

Drug Resistance: HIV isolates with reduced sensitivity to zidovudine have been selected in vitro and were also recovered from patients treated with RETROVIR. Genetic analysis of the isolates showed mutations which result in five amino acid substitutions (Met41→Leu, A67→Asn, Lys70→Arg, Thr215→Tyr or Phe, and Lys219→Gln) in the viral reverse transcriptase. In general, higher levels of resistance were associated with greater number of mutations with 215 mutation being the most significant.

Cross-Resistance: The potential for cross-resistance between HIV reverse transcriptase inhibitors and protease inhibitors is low because of the different enzyme targets involved. Combination therapy with zidovudine plus zalcitabine or didanosine does not appear to prevent the emergence of zidovudine-resistant isolates. Combination therapy with RETROVIR plus EPIVIR® delayed the emergence of mutations conferring resistance to zidovudine. In some patients harboring zidovudine-resistant virus, combination therapy with RETROVIR plus EPIVIR restored phenotypic sensitivity to

zidovudine by 12 weeks of treatment. HIV isolates with multidrug resistance to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine were recovered from a small number of patients treated for ≥1 year with the combination of zidovudine and didanosine or zalcitabine. The pattern of resistant mutations in the combination therapy was different (Ala62→Val, Val75→Ile, Phe77→116Tyr, and Gln→151Met) from monotherapy, with mutation 151 being most significant for multidrug resistance. Site-directed mutagenesis studies showed that these mutations could also result in resistance to zalcitabine, lamivudine, and stavudine.

CLINICAL PHARMACOLOGY:

Pharmacokinetics: ***Adults:*** The pharmacokinetics of zidovudine has been evaluated in 22 adult HIV-infected patients in a Phase 1 dose-escalation study. Following intravenous dosing, dose-independent kinetics was observed over the range of 1 to 5 mg/kg with a mean zidovudine half-life of 1.1 hours (range 0.48 to 2.86 hours). Total body clearance averaged 1900 mL/min per 70 kg, and the apparent volume of distribution was 1.6 L/kg. At a dose of 7.5 mg/kg every 4 hours, total body clearance was calculated to be about 1200 mL/min per 70 kg, with no change in half-life. Renal clearance is estimated to be 400 mL/min per 70 kg, indicating glomerular filtration and active tubular secretion by the kidneys. Zidovudine plasma protein binding is 34% to 38%, indicating that drug interactions involving binding site displacement are not anticipated.

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

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

Zidovudine is rapidly metabolized to GZDV which has an apparent elimination half-life of 1 hour (range 0.61 to 1.73 hours). A second metabolite, 3′-amino-3′-deoxythymidine (AMT), has been identified in the plasma following single-dose intravenous administration of zidovudine. AMT area-under-the-curve (AUC) was one fifth of the AUC of zidovudine and had a half-life of 2.7 ± 0.7 hours. In comparison, GZDV AUC was about threefold greater than the AUC of zidovudine. Following intravenous administration, urinary recoveries of zidovudine and GZDV accounted for 18% and 60% of the dose, respectively, and the total urinary recovery averaged 77% (range 64% to 98%).

Adults with Impaired Renal Function: The pharmacokinetics of zidovudine has been evaluated in patients with impaired renal function following a single 200-mg oral dose. In 14 patients (mean creatinine clearance 18 ± 2 mL/min) the half-life of zidovudine was 1.4 hours compared to 1.0 hour for control subjects with normal renal function; AUC values were approximately twice those of controls. Additionally, GZDV half-life in these patients was 8.0 hours (versus 0.9 hours for control) and AUC was 17 times higher than for control subjects. The pharmacokinetics and tolerance were evaluated in a multiple-dose study in patients undergoing hemodialysis (n = 5) or peritoneal dialysis

(n = 6). Patients received escalating oral doses of zidovudine up to 200 mg five times daily for 8 weeks. Daily oral doses of 500 mg or less were well tolerated despite significantly elevated plasma levels of GZDV. Apparent oral clearance of zidovudine was approximately 50% of that reported in patients with normal renal function. The plasma concentrations of AMT are not known in patients with renal insufficiency. Daily doses of 300 to 400 mg should be appropriate in HIV-infected patients with severe renal dysfunction (see DOSAGE AND ADMINISTRATION: Dose Adjustment). Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, whereas GZDV elimination is enhanced.

Pediatrics: The pharmacokinetics and bioavailability of zidovudine have been evaluated in 21 HIV-infected pediatric patients, aged 6 months through 12 years, following intravenous doses administered over the range of 80 to 160 mg/m^2 every 6 hours, and following oral doses of the intravenous solution administered over the range of 90 to 240 mg/m^2 every 6 hours. After discontinuation of the IV infusion, zidovudine plasma concentrations decayed biexponentially, consistent with two-compartment pharmacokinetics. Proportional increases in AUC and in zidovudine concentrations were observed with increasing dose, consistent with dose-independent kinetics over the dose range studied. The mean terminal half-life and total body clearance across all dose levels administered were 1.5 hours and 30.9 mL/min per kg, respectively. These values compare to mean half-life and total body clearance in adults of 1.1 hours and 27.1 mL/min per kg.

The pharmacokinetics of zidovudine has been studied in pediatric patients from birth to 3 months of life. In one study of the pharmacokinetics of zidovudine in women during the last trimester of pregnancy, zidovudine elimination was determined immediately after birth in eight neonates who were exposed to zidovudine in utero. The half-life was 13.0 ± 5.8 hours. In another study, the pharmacokinetics of zidovudine was evaluated in pediatric patients (ranging in age of 1 day to 3 months) of normal birth weight for gestational age and with normal renal and hepatic function. In neonates less than or equal to 14 days old, mean ± SD total body clearance was 10.9 ± 4.8 mL/min per kg (n = 18) and half-life was 3.1 ± 1.2 hours (n = 21). In neonates and infants greater than 14 days old, total body clearance was 19.0 ± 4.0 mL/min per kg (n = 16) and half-life was 1.9 ± 0.7 hours (n = 18).

Concentrations of zidovudine in cerebrospinal fluid were measured after both intermittent oral and IV drug administration in 21 pediatric patients during Phase 1 and Phase 2 studies. The mean zidovudine CSF/plasma concentration ratio measured at an average time of 2.2 hours postdose at oral doses of 120 to 240 mg/m^2 was 0.52 ± 0.44 (n = 28); after an IV infusion of doses of 80 to 160 mg/m^2 over 1 hour, the mean CSF/plasma concentration ratio was 0.87 ± 0.66 (n = 23) at 3.2 hours after the start of the infusion. During continuous IV infusion, mean steady-state CSF/plasma ratio was 0.26 ± 0.17 (n = 28).

As in adult patients, the major route of elimination in pediatric patients was by metabolism to GZDV. After IV dosing, about 29% of the dose was excreted in the urine unchanged and about 45%

of the dose was excreted as GZDV. Overall, the pharmacokinetics of zidovudine in pediatric patients greater than 3 months of age is similar to that of zidovudine in adult patients.

Pregnancy: The pharmacokinetics of zidovudine has been studied in a Phase 1 study of eight women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. The pharmacokinetics of zidovudine was similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in infant plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in five pregnant women did not appear to alter zidovudine pharmacokinetics. However, in another patient population, a potential for interaction has been identified (see PRECAUTIONS).

Nursing Mothers: The US Public Health Service Centers for Disease Control and Prevention advises HIV-infected women not to breastfeed to avoid postnatal transmission of HIV to a child who may not yet be infected. After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum (see PRECAUTIONS: Nursing Mothers).

INDICATIONS AND USAGE: RETROVIR IV Infusion is indicated for the treatment of HIV infection when antiretroviral therapy is warranted (see Description of Clinical Studies).

The duration of clinical benefit from antiretroviral therapy may be limited. Alterations in antiretroviral therapy should be considered if disease progression occurs during treatment.

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

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

Other randomized studies suggest that the duration of the clinical benefit of monotherapy with RETROVIR is time-limited.

Pregnant Women and Their Neonates: The utility of RETROVIR for the prevention of maternal-fetal HIV transmission was demonstrated in a randomized, double-blind, placebo-controlled trial (ACTG 076) conducted in HIV-infected pregnant women with CD4 cell counts of 200 to 1818 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 intravenous administration of RETROVIR during labor and delivery. After birth, neonates received oral RETROVIR Syrup for 6 weeks. The study showed a statistically significant difference in the incidence of HIV 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 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.

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

WARNINGS: The incidence of adverse reactions appears to increase with disease progression, and patients should be monitored carefully, especially as disease progression occurs.

Bone Marrow Suppression: RETROVIR should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1000 cells/mm^3 or hemoglobin <9.5 g/dL. In patients with advanced symptomatic HIV disease, anemia and neutropenia were the most significant adverse events observed (see ADVERSE REACTIONS). 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 in patients with advanced HIV disease who are treated with RETROVIR. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended. If anemia or neutropenia develops, dosage adjustments may be necessary (see DOSAGE AND ADMINISTRATION).

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

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Rare occurrences of potentially fatal lactic acidosis in the absence of hypoxemia, and severe hepatomegaly with steatosis have been reported with the use of certain antiretroviral nucleoside analogues. Lactic acidosis should be considered whenever a patient receiving therapy with RETROVIR develops unexplained tachypnea, dyspnea, or fall in serum bicarbonate level. Under these circumstances, therapy with RETROVIR should be suspended until the diagnosis of lactic acidosis has been excluded. Caution should be exercised when administering RETROVIR to any patient, particularly obese women, with hepatomegaly, hepatitis, or other known risk factor for liver disease. These patients should be followed closely while on therapy with RETROVIR. The significance of elevated aminotransferase levels suggesting hepatic

injury in HIV-infected patients prior to starting RETROVIR or while on RETROVIR is unclear. Treatment with RETROVIR should be suspended in the setting of rapidly elevating aminotransferase levels, progressive hepatomegaly, or metabolic/lactic acidosis of unknown etiology.

Other Serious Adverse Reactions: Several serious adverse events have been reported with use of RETROVIR in clinical practice. Reports of pancreatitis, sensitization reactions (including anaphylaxis in one patient), vasculitis, and seizures have been rare. These adverse events, except for sensitization, have also been associated with HIV disease. Changes in skin and nail pigmentation have been associated with the use of RETROVIR.

PRECAUTIONS:

General: Zidovudine is eliminated from the body primarily by renal excretion following metabolism in the liver (glucuronidation). In patients with severely impaired renal function, dosage reduction is recommended (see CLINICAL PHARMACOLOGY: Pharmacokinetics and DOSAGE AND ADMINISTRATION). Although very little data are available, patients with severely impaired hepatic function may be at greater risk of toxicity.

Information for Patients: RETROVIR is not a cure for HIV infection, and patients may continue to acquire illnesses associated with HIV infection, including opportunistic infections. Therefore, patients should be advised to seek medical care for any significant change in their health status.

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

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. They should be told that if toxicity develops, they may require transfusions or dose modifications including possible discontinuation. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced symptomatic HIV disease. They should be cautioned about the use of other medications, including ganciclovir and interferon-alpha, that may exacerbate the toxicity of RETROVIR (see PRECAUTIONS: Drug Interactions). Patients should be informed that other adverse effects of RETROVIR include nausea and vomiting. Patients should also 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.

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

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

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

Drug Interactions: ***Ganciclovir:*** Use of RETROVIR in combination with ganciclovir increases the risk of hematologic toxicities in some patients with advanced HIV disease. Should the use of this combination become necessary in the treatment of patients with HIV disease, dose reduction or interruption of one or both agents may be necessary to minimize hematologic toxicity. Hematologic parameters, including hemoglobin, hematocrit, and white blood cell count with differential, should be monitored frequently in all patients receiving this combination.

Interferon-alpha: Hematologic toxicities have also been seen when RETROVIR is used concomitantly with interferon-alpha. As with the concomitant use of RETROVIR and ganciclovir, dose reduction or interruption of one or both agents may be necessary, and hematologic parameters should be monitored frequently.

Bone Marrow Suppressive Agents/Cytotoxic Agents: Coadministration of RETROVIR with drugs that are cytotoxic or which interfere with RBC/WBC number or function (e.g., dapsone, flucytosine, vincristine, vinblastine, or adriamycin) may increase the risk of hematologic toxicity.

Probenecid: Limited data suggest that probenecid may increase zidovudine levels by inhibiting glucuronidation and/or by reducing renal excretion of zidovudine. Some patients who have used RETROVIR concomitantly with probenecid have developed flu-like symptoms consisting of myalgia, malaise, and/or fever and maculopapular rash.

***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-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.

Methadone: In a pharmacokinetic study of nine HIV-positive patients receiving methadone-maintenance (30 to 90 mg daily) concurrent with 200 mg of RETROVIR every 4 hours, no changes were observed in the pharmacokinetics of methadone upon initiation of therapy with RETROVIR and after 14 days of treatment with RETROVIR. No adjustments in methadone-maintenance requirements were reported. For four patients, the mean zidovudine AUC was elevated twofold, while for five patients, the value was equal to that of control patients. The exact mechanism and clinical significance of these data are unknown.

Fluconazole: The coadministration of fluconazole with RETROVIR has been reported to interfere with the oral clearance and metabolism of RETROVIR. In a pharmacokinetic interaction study in which 12 HIV-positive men received RETROVIR 200 mg every 8 hours alone and in combination with

fluconazole 400 mg daily, fluconazole increased the zidovudine AUC (74%; range 28% to 173%) and the zidovudine half-life (128%; range -4% to 189%) at steady state. The clinical significance of this interaction is unknown.

Atovaquone: Data from 14 HIV-infected volunteers who were given atovaquone tablets 750 mg every 12 hours with zidovudine 200 mg every 8 hours showed a 24% ± 12% decrease in zidovudine oral clearance, leading to a 35% ± 23% increase in plasma zidovudine AUC. The glucuronide metabolite:parent ratio decreased from a mean of 4.5 when zidovudine was administered alone to 3.1 when zidovudine was administered with atovaquone tablets. Zidovudine had no effect on atovaquone pharmacokinetics.

Valproic Acid: The concomitant administration of valproic acid 250 mg (n = 5) or 500 mg (n = 1) every 8 hours and zidovudine 100 mg orally every 8 hours for 4 days to six HIV-infected, asymptomatic male volunteers resulted in a 79% ± 61% (mean ± SD) increase in the plasma zidovudine AUC and a 22% ± 10% decrease in the plasma GZDV AUC as compared to the administration of zidovudine in the absence of valproic acid. The GZDV/zidovudine urinary excretion ratio decreased 58% ± 12%. Because no change in the zidovudine plasma half-life occurred, these results suggest that valproic acid may increase the oral bioavailability of zidovudine through inhibition of first-pass metabolism. Although the clinical significance of this interaction is unknown, patients should be monitored more closely for a possible increase in zidovudine-related adverse effects. The effect of zidovudine on the pharmacokinetics of valproic acid was not evaluated.

Lamivudine: RETROVIR and lamivudine were coadministered to 12 asymptomatic HIV-positive patients in a single-center, open-label, randomized, crossover study. No significant differences were observed in AUC_{∞} or total clearance for lamivudine or zidovudine when the two drugs were administered together. Coadministration of RETROVIR with lamivudine resulted in an increase of 39% ± 62% (mean ± SD) in C_{max} of zidovudine.

Other Agents: Preliminary data from a drug interaction study (n = 10) suggest that coadministration of 200 mg RETROVIR and 600 mg rifampin decreases the area under the plasma concentration curve by an average of 48% ± 34%. However, the effect of once daily dosing of rifampin on multiple daily doses of RETROVIR is unknown. Some nucleoside analogues affecting DNA replication, such as ribavirin, antagonize the in vitro antiviral activity of RETROVIR against HIV; concomitant use of such drugs should be avoided.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Zidovudine was administered orally at three 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 per day in mice and 80, 220, and 600 mg/kg per day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg per day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg per day on day 91, and then to 300 mg/kg per day on day 279.

In mice, seven late-appearing (after 19 months) vaginal neoplasms (five nonmetastasizing squamous cell carcinomas, one squamous cell papilloma, and one 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, two 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 three times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg/kg per day or 40 mg/kg per day from gestation day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine employed in this study produced zidovudine exposures approximately three 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. 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 seven times the usual adult dose based on body surface area considerations, had no effect on fertility judged by conception rates.

Pregnancy: Pregnancy Category C. Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg per 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 per day and rabbits given 500 mg/kg per 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 3000 mg/kg per day (very near the oral median lethal dose in rats of 3683 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 area-under-the-curve [AUC] in rats at this dose level was 300 times the daily AUC in humans given 600 mg per day.) No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg per day or less.

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

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

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.

Nursing Mothers: The US Public Health Service Centers for Disease Control and Prevention advises HIV-infected women not to breastfeed to avoid postnatal transmission of HIV to a child who may not yet be infected.

Zidovudine is excreted in human milk (see Pharmacokinetics).

Pediatric Use: RETROVIR has been studied in HIV-infected pediatric patients over 3 months of age who have HIV-related symptoms or who are asymptomatic with abnormal laboratory values indicating significant HIV-related immunosuppression (see ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, and INDICATIONS AND USAGE: Description of Clinical Studies, and Pharmacokinetics).

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.

ADVERSE REACTIONS: The adverse events reported during intravenous administration of RETROVIR IV Infusion are similar to those reported with oral administration; neutropenia and anemia were reported most frequently. Long-term intravenous administration beyond 2 to 4 weeks has not

been studied in adults and may enhance hematologic adverse events. Local reaction, pain, and slight irritation during intravenous administration occur infrequently.

Adults: The frequency and severity of adverse events associated with the use of oral RETROVIR in adults are greater in patients with more advanced infection at the time of initiation of therapy. Table 1 summarizes the relative incidence of hematologic adverse events observed in clinical studies by severity of HIV disease present at the start of treatment with oral RETROVIR:

Table 1

Stage of Disease	RETROVIR Daily Dose* (mg)	Neutropenia (<750 cells/mm^3)	Anemia (Hgb <8.0 g/dL)
Asymptomatic			
ACTG 019	500	1.8%†	1.1%†
Early HIV Disease (CD4 >200 cells/mm^3)			
ACTG 016	1200	4%	4%
Advanced HIV Disease (CD4 >200 cells/mm^3)			
BW 02	1500	10%†	3%†‡
(CD4 ≤200 cells/mm^3)			
ACTG 002	600	37%	29%
BW 02	1500	47%	29%‡

* The currently recommended oral dose is 500 to 600 mg daily.

† Not statistically significant compared to placebo.

‡ Anemia = Hgb <7.5 g/dL.

The anemia reported in patients with advanced HIV disease receiving RETROVIR appeared to be the result of impaired erythrocyte maturation as evidenced by macrocytosis while on drug. Although mean platelet counts in patients receiving RETROVIR were significantly increased compared to mean baseline values, thrombocytopenia did occur in some of these patients with advanced disease. Twelve percent of patients receiving RETROVIR compared to 5% of patients receiving placebo had >50% decreases from baseline platelet count. Mild drug-associated elevations in total bilirubin levels have been reported as an uncommon occurrence in patients treated for asymptomatic HIV infection.

The HIV-infected adults participating in these clinical trials often had baseline symptoms and signs of HIV disease and/or experienced adverse events at some time during study. It was often difficult to

distinguish adverse events possibly associated with administration of RETROVIR from underlying signs of HIV disease or intercurrent illnesses. Table 2 summarizes clinical adverse events or symptoms which occurred in at least 5% of all patients with advanced HIV disease treated with 1500 mg/day of oral RETROVIR in the original placebo-controlled study. Of the items listed in the table, only severe headache, nausea, insomnia, and myalgia were reported at a significantly greater rate in patients receiving RETROVIR.

Table 2: Percentage (%) of Patients with Adverse Events in Advanced HIV Disease (BW 02)

Adverse Event	RETROVIR 1500 mg/day* (n = 144) %	Placebo (n = 137) %
BODY AS A WHOLE		
Asthenia	19	18
Diaphoresis	5	4
Fever	16	12
Headache	42	37
Malaise	8	7
GASTROINTESTINAL		
Anorexia	11	8
Diarrhea	12	18
Dyspepsia	5	4
GI Pain	20	19
Nausea	46	18
Vomiting	6	3
MUSCULOSKELETAL		
Myalgia	8	2
NERVOUS		
Dizziness	6	4
Insomnia	5	1
Paresthesia	6	3
Somnolence	8	9
RESPIRATORY		
Dyspnea	5	3
SKIN		
Rash	17	15
SPECIAL SENSES		
Taste Perversion	5	8

* The currently recommended oral dose is 500 to 600 mg daily.

All events of a severe or life-threatening nature were monitored for adults in the placebo-controlled studies in early HIV disease and asymptomatic HIV infection. Data concerning the occurrence of additional signs or symptoms were also collected. No distinction was made in reporting events between those possibly associated with the administration of the study medication and those due to

the underlying disease. Tables 3 and 4 summarize all those events reported at a statistically significant greater incidence for patients receiving RETROVIR in these studies:

Table 3: Percentage (%) of Patients with Adverse Events in Early HIV Disease (ACTG 016)

Adverse Event	RETROVIR 1200 mg/day* (n = 361) %	Placebo (n = 352) %
BODY AS A WHOLE		
Asthenia	69	62
GASTROINTESTINAL		
Dyspepsia	6	1
Nausea	61	41
Vomiting	25	13

* The currently recommended oral dose is 500 to 600 mg daily.

Table 4: Percentage (%) of Patients with Adverse Events* in Asymptomatic HIV Infection (ACTG 019)

Adverse Event	RETROVIR 500 mg/day (n = 453) %	Placebo (n = 428) %
BODY AS A WHOLE		
Asthenia	8.6†	5.8
Headache	62.5	52.6
Malaise	53.2	44.9
GASTROINTESTINAL		
Anorexia	20.1	10.5
Constipation	6.4†	3.5
Nausea	51.4	29.9
Vomiting	17.2	9.8
NERVOUS		
Dizziness	17.9†	15.2

* Reported in ≥5% of study population.

† Not statistically significant versus placebo.

Several serious adverse events have been reported with the use of RETROVIR in clinical practice. Myopathy and myositis with pathological changes, similar to that produced by HIV disease, have been associated with prolonged use of RETROVIR. Reports of hepatomegaly with steatosis, hepatitis, pancreatitis, lactic acidosis, sensitization reactions (including anaphylaxis in one patient), hyperbilirubinemia, vasculitis, and seizures have been rare. These adverse events, except for sensitization, have also been associated with HIV disease. A single case of macular edema has been reported with the use of RETROVIR.

Additional adverse events reported in clinical trials at a rate not significantly different from placebo are listed below. Selected events from post-marketing clinical experience with RETROVIR are also included. Many of these events may also occur as part of HIV disease. The clinical significance of the association between treatment with RETROVIR and these events is unknown.

Body as a Whole: Abdominal pain, back pain, body odor, chest pain, chills, edema of the lip, fever, flu syndrome, hyperalgesia.

Cardiovascular: Syncope, vasodilation.

Gastrointestinal: Bleeding gums, constipation, diarrhea, dysphagia, edema of the tongue, eructation, flatulence, mouth ulcer, rectal hemorrhage.

Hemic and Lymphatic: Lymphadenopathy.

Musculoskeletal: Arthralgia, muscle spasm, tremor, twitch.

Nervous: Anxiety, confusion, depression, dizziness, emotional lability, loss of mental acuity, nervousness, paresthesia, somnolence, vertigo.

Respiratory: Cough, dyspnea, epistaxis, hoarseness, pharyngitis, rhinitis, sinusitis.

Skin: Acne, changes in skin and nail pigmentation, pruritus, rash, sweat, urticaria.

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

Urogenital**:** Dysuria, polyuria, urinary frequency, urinary hesitancy.

Pediatrics: Anemia and neutropenia among pediatric patients with advanced HIV disease receiving RETROVIR occurred with similar incidence to that reported for adults with AIDS or advanced ARC (see above). Management of neutropenia and anemia included, in some cases, dose modification and/or blood product transfusions. In the open-label studies, 17% had their dose modified (generally a reduction in dose by 30%) due to anemia and 25% had their dose modified (temporary discontinuation or dose reduction by 30%) for neutropenia. Four pediatric patients had RETROVIR permanently discontinued for neutropenia. Table 5 summarizes the occurrence of anemia (Hgb <7.5 g/dL) and neutropenia (<750 cells/mm^3) among 124 pediatric patients receiving oral RETROVIR for a mean of 267 days (range 3 to 855 days):

Table 5

Advanced Pediatric HIV Disease (n = 124)	Neutropenia (<750 cells/mm^3)		Anemia (Hgb <7.5 g/dL)	
	n	%	n	%
	48	39	28*	23

* Twenty-two pediatric patients received one or more transfusions due to a decline in hemoglobin to <7.5 g/dL; an additional 15 pediatric patients were transfused for hemoglobin levels >7.5 g/dL. Fifty-nine percent of the patients transfused had a prestudy history of anemia or transfusion requirement.

Macrocytosis was observed among the majority of pediatric patients enrolled in the studies.

In the open-label studies involving 124 pediatric patients, 16 clinical adverse events were reported by 24 pediatric patients. No event was reported by more than 5.6% of the study populations. Due to the open-label design of the studies, it was difficult to determine possible events related to the use of RETROVIR versus disease-related events. Therefore, all clinical events reported as associated with therapy with RETROVIR or of unknown relationship to therapy with RETROVIR are presented in Table 6:

Table 6: Percentage (%) of Pediatric Patients with Clinical Events in Open-Label Studies

Adverse Event	n	%
BODY AS A WHOLE		
Fever	4	3.2
Phlebitis*/Bacteremia	2	1.6
Headache	2	1.6
GASTROINTESTINAL		
Nausea	1	0.8
Vomiting	6	4.8
Abdominal Pain	4	3.2
Diarrhea	1	0.8
Weight Loss	1	0.8
NERVOUS		
Insomnia	3	2.4
Nervousness/Irritability	2	1.6
Decreased Reflexes	7	5.6
Seizure	1	0.8
CARDIOVASCULAR		
Left Ventricular Dilation	1	0.8
Cardiomyopathy	1	0.8
S_3 Gallop	1	0.8
Congestive Heart Failure	1	0.8
Generalized Edema	1	0.8
ECG Abnormality	3	2.4
UROGENITAL		
Hematuria/Viral Cystitis	1	0.8

* Peripheral vein IV catheter site.

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

Use for the Prevention of Maternal-Fetal Transmission of HIV: In a randomized, double-blind, placebo-controlled trial in HIV-infected women and their neonates conducted to determine the utility of RETROVIR for the prevention of maternal-fetal HIV transmission, RETROVIR Syrup at 2 mg/kg was administered every 6 hours for 6 weeks to neonates beginning within 12 hours after birth. The most commonly reported adverse experiences were anemia (hemoglobin <9.0 g/dL) and neutropenia (<1000 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 to 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 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 neonatal exposure to RETROVIR are unknown.

OVERDOSAGE: Cases of acute overdoses in both pediatric patients and adults have been reported with doses up to 50 grams. None were fatal. The only consistent finding in these cases of overdose was spontaneous or induced nausea and vomiting. Hematologic changes were transient and not severe. Some patients experienced nonspecific CNS symptoms such as headache, dizziness, drowsiness, lethargy, and confusion. One report of a grand mal seizure possibly attributable to RETROVIR occurred in a 35-year-old male 3 hours after ingesting 36 grams of RETROVIR. No other cause could be identified. All patients recovered without permanent sequelae. Hemodialysis appears to have a negligible effect on the removal of zidovudine while elimination of its primary metabolite, GZDV, is enhanced.

DOSAGE AND ADMINISTRATION:

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

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

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

Maternal Dosing: 100 mg orally five times per day until the start of labor. 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 per hour (total body weight) until clamping of the umbilical cord.

Neonatal Dosing: 2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing through 6 weeks of age. Neonates unable to receive oral dosing may be administered RETROVIR intravenously at 1.5 mg/kg, infused over 30 minutes, every 6 hours. (See PRECAUTIONS if hepatic disease or renal insufficiency is present.)

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

Dose Adjustment: Significant anemia (hemoglobin of <7.5 g/dL or reduction of >25% of baseline) and/or significant neutropenia (granulocyte count of <750 cells/mm^3 or reduction of >50% from baseline) may require a dose interruption until some evidence of marrow recovery is observed. For less severe anemia or neutropenia, a reduction in daily dose may be adequate. In patients who develop significant anemia, dose modification does not necessarily eliminate the need for transfusion. If marrow recovery occurs following dose modification, gradual increases in dose may be appropriate depending on hematologic indices and patient tolerance.

In end-stage renal disease patients maintained on hemodialysis or peritoneal dialysis, recommended dosing is 1 mg/kg every 6 to 8 hours (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

There are insufficient data to recommend dose adjustment of zidovudine in patients with impaired hepatic function.

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

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

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

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

HOW SUPPLIED: RETROVIR IV Infusion, 10 mg zidovudine in each mL. 20-mL Single-Use Vial, Tray of 10 (NDC 0173-0107-93).

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

US Patent Nos. 4,818,538 (Product Patent)
4,724,232; 4,833,130; and 4,837,208 (Use Patents)

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Jeffrey Murray

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