2 Injection Sites and NMT Syringe Information

Injection Sites

Changing where you inject FUZEON on your body each time is an important way to lessen how bad your injection site reactions get. For more detailed information about each injection site, see *Your Guide to Taking FUZEON.*

About the NMT Safety Syringe

- There are two different-sized NMT Safety Syringes, a 3-mL (large) syringe and a 1-mL (small) syringe
- NMT Safety Syringes are included with FUZEON because the used needle springs back by itself into the syringe after use, lowering the chance of accidental needlesticks

  Important! When first picking up the NMT Safety Syringe or injecting air or sterile water into vials, **do not** push the plunger past the 0.2-mL/cc mark on the barrel of the 3-mL (large) syringe or past the 0.05-mL/cc mark on the barrel of the 1-mL (small) syringe. This could make the needle spring back into the barrel of the syringe or make it hard to pull the plunger back.

- Your healthcare provider may recommend other types of syringes for use with FUZEON
- Never throw your used syringes into the trash. Put them in the sharps container

3 Getting Started

Gather Supplies

Gather the following supplies for each dose and put them on your FUZEON Preparation Mat or a cleaned surface:

- One vial of FUZEON—at room temperature
- One vial of sterile water
- One 3-mL/cc (large) syringe with a 1-inch needle
- One 1-mL/cc (small) syringe with a 1/2-inch needle
- Alcohol pads
- Sharps container

Mixing Two Doses

- To save time, you can mix both of your daily doses of FUZEON at the same time, but you will need to keep the second vial of mixed FUZEON in the refrigerator. **Do not** store mixed FUZEON in the syringe
- Once sterile water has been added to the FUZEON, the vial can be placed in the refrigerator. The FUZEON will dissolve in time for your next dose
- Before using the dose of refrigerated FUZEON, be sure it is clear and allow it to warm to room temperature
- Mixed FUZEON must be used within 24 hours
- The instructions below are for mixing a single dose. If you want to mix two doses at the same time, be sure to use new alcohol pads, syringes, medicine and sterile water
- Write the date and time on the vial when mixed if you are mixing the dose to be used later

Prepare Supplies

- Open the syringe packages and take the caps off the vials
- Throw the syringe packages and vial caps into the trash

Wash Hands

- Wash your hands well using soap and warm water and dry them with a clean towel
- Once your hands are clean, **do not** touch anything other than the medicine, supplies and the area around the injection site

Clean Vial Tops

- Wipe each vial top with a new alcohol pad and let the tops air-dry
- If you touch the rubber tops after cleaning them, clean them again with a new alcohol pad

4 Mixing FUZEON

Draw Up Sterile Water

- Gently tap the FUZEON vial to loosen the powder
- Using the 3-mL/cc (large) syringe, *slowly* pull the plunger back to get 1.1 mL/cc of air

  Important! To avoid causing the needle to spring back into the barrel of the syringe, **do not** push the plunger past the 0.2-mL/cc mark.

- Before turning the sterile water vial upside down, *slowly* inject the air into the vial—and keep the needle in the vial
- Turn the vial upside down. Make sure the tip of the needle is always below the surface of the water to help keep air bubbles from entering the syringe

  Tip! Gently tap or flick the barrel and push and pull the plunger to remove extra air and bubbles. To be sure you end up with 1.1 mL/cc of sterile water in the syringe, you may need to pull the plunger past the 1.1-mL/cc mark.

- *Slowly* pull the plunger back to get 1.1 mL/cc of sterile water into the syringe
- Carefully remove the needle and syringe from the vial

Inject Sterile Water Into FUZEON

- Insert the syringe with sterile water into the FUZEON vial at an angle
- Inject the sterile water *slowly*, so that it drips down the side of the vial into the FUZEON powder
- Remove the needle from the vial. Push the plunger all the way down with the tip of your thumb until you hear a snap. *This will make the needle spring back into the syringe*
- Put the used syringe in the sharps container

Gently Mix FUZEON

- Gently tap the FUZEON vial with your fingertip for 10 seconds to start dissolving the powder. Then gently roll the FUZEON vial between your hands to reduce the mixing time. Make sure no FUZEON is stuck to the vial wall. After tapping, it could take up to 45 minutes to dissolve

  Important! **Never shake the FUZEON vial.** Shaking will make the medicine foam and it will take much longer to dissolve.

- Once the powder starts to dissolve, just set it aside and it will completely dissolve

Inspect FUZEON

- When completely mixed, the liquid FUZEON should be clear

  Important! Completely dissolved FUZEON should be clear and without foam. If the FUZEON is foamy or jelled, allow more time for it to dissolve

- If you see bubbles, gently tap the vial until they disappear

- If you see any particles in the FUZEON once it is completely mixed, **do not** use that vial. Contact the pharmacy that provided it
- Mixed FUZEON must be used right away or stored in the vial in the refrigerator and used within 24 hours. **Do not** store mixed FUZEON in the syringe

5 Giving the Injection

Choose the Injection Site

- Using your FUZEON *Planner* to help you, choose a site **different** from the one you used for your last injection

  Important! With the tips of your fingers, feel for any hard bumps. **Do not** inject in or near bumps or any other types of reactions from past injections. Also, **do not** inject into moles, scars, bruises, your belly button or areas that could be irritated by a belt or waistband.

- Clean the injection site with a new alcohol pad. Start in the center, apply pressure and clean in a circular motion, working outward. Allow the site to air-dry

Draw Up FUZEON

- Clean the FUZEON vial top again, using a new alcohol pad. Allow it to air-dry
- Using the 1-mL/cc (small) syringe, pull back the plunger to get 1 mL/cc of air
- Insert the syringe into the vial of mixed FUZEON
- Before turning the vial upside down, *slowly* inject the air into the FUZEON, and keep the needle in the vial

  Important! To avoid causing the needle to spring back into the barrel of the syringe, **do not** push the plunger past the 0.05-mL/cc mark.

- Gently turn the vial upside down
- Make sure the tip of the needle is always below the surface of the FUZEON to help keep air bubbles from entering the syringe. *Slowly* pull the plunger to get 1 mL/cc of FUZEON

  Tip! Gently tap or flick the barrel and push and pull the plunger to remove extra air and bubbles. To be sure you end up with 1 mL/cc of FUZEON in the syringe, you may need to pull the plunger past the 1-mL/cc mark.

- Carefully remove the needle and syringe from the vial

Inject FUZEON

- Pinch and hold a fold of skin around the injection site
- Pierce the skin at a 45-degree angle. The needle should be inserted 3/4 of the way in

  Tip! Your healthcare provider may teach you to inject in a different way.

- With the tip of your thumb, slowly push the plunger all the way to inject FUZEON. *The needle will pull out of the skin and spring back into the syringe by itself when you are done*

  Tip! **Do not** force the needle deeper into the skin while trying to make the needle spring back into the barrel. If you are having a problem, remove the needle from the skin and right away press the plunger down all the way until the needle springs back into the barrel of the syringe.

- Put the used syringe in the sharps container

- Cover the site with a small bandage if you see any blood or medicine

Safety Information

What is FUZEON?

FUZEON is a medicine called an HIV (human immunodeficiency virus) fusion inhibitor. FUZEON is always used with other anti-HIV medicines to treat adults and children ages 6 years and older with HIV infection.

FUZEON blocks HIV's ability to infect healthy CD4 cells. When used with other anti-HIV medicines, FUZEON can reduce the amount of HIV in the blood and increase the number of CD4 cells. This may keep your immune system healthy, so it can help fight infection.

What are the possible side effects of FUZEON?

Injection site reactions

FUZEON causes injection site reactions. Almost all people get injection site reactions with FUZEON. Reactions are usually mild to moderate, but occasionally may be severe. Reactions on the skin where FUZEON is injected include:

- itching
- swelling
- redness
- pain or tenderness
- hardened skin
- bumps

These reactions generally happen within the first week of FUZEON treatment and usually happen again as you keep using FUZEON. A reaction at one skin injection site usually lasts for less than 7 days.

Injection site reactions may be worse when injections are given again in the same place on the body, or when the injection is given deeper than it should be (for example, into the muscle).

If you are worried about the reaction you are having, call your healthcare provider to help you decide if you need medical care. **If the injection site reaction you are having is severe, call your healthcare provider right away.** If you have an injection site reaction, you can discuss with your healthcare provider ways to help the symptoms.

An injection site can get infected. It is important to follow these FUZEON *Injection Instructions* to lower your chances of getting an injection site infection. **Call your healthcare provider right away if there are signs of infection at the injection site such as oozing, increasing heat, swelling, redness or pain.**

Pneumonia

Patients with HIV get bacterial pneumonia more often than patients without HIV. In clinical trials, patients taking FUZEON with other HIV medicines got bacterial pneumonia more often than patients not receiving

FUZEON. It is unclear if this was related to the use of FUZEON. **You should contact your healthcare provider right away if you have a cough, fever or trouble breathing.** Patients are more likely to get bacterial pneumonia if they had a low number of CD4 cells, increased amount of HIV in the blood, intravenous (injected into the vein) drug use, smoking or had experienced lung disease in the past. It is unclear if pneumonia is related to FUZEON.

Allergic reactions

FUZEON can cause serious allergic reactions. Symptoms of a serious allergic reaction with FUZEON can include:

- trouble breathing
- fever with vomiting and a skin rash
- blood in your urine
- swelling of your feet

Call your healthcare provider right away if you get any of these symptoms.

Other side effects

The following side effects were seen more often in patients using FUZEON with their other anti-HIV medicines than in patients not using FUZEON with their other anti-HIV medicines:

- pain and numbness in feet or legs
- loss of sleep
- depression
- decreased appetite
- sinus problems
- enlarged lymph nodes
- weight decrease
- weakness or loss of strength
- muscle pain
- constipation
- pancreas problems

These are not all the side effects of FUZEON. FUZEON is still being studied in children. The safety of FUZEON in children under 6 years of age is not known. The side effects of FUZEON for HIV-positive children aged 6 through 16 years were the same as seen in adult patients.

If you have questions about side effects, ask your healthcare provider. **Report any new or worsening symptoms to your healthcare provider.** Your healthcare provider will tell you what to do and may be able to help you with these side effects.

For more information on FUZEON, please see the patient package insert, www.FUZEON.com, and 1-877-4 FUZEON (1-877-438-9366).

Roche Pharmaceuticals

TRIMERIS

Trimeris, Inc.
4727 University Drive
Durham, North Carolina 27707
www.trimeris.com

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199
www.rocheusa.com

27898890

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PRESCRIBING INFORMATION

RETROVIR®
(zidovudine)
IV Infusion

FOR INTRAVENOUS INFUSION ONLY

WARNING

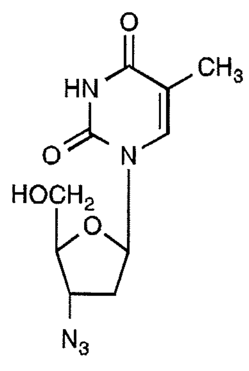
RETROVIR (ZIDOVUDINE) HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY, INCLUDING NEUTROPENIA AND SEVERE ANEMIA, PARTICULARLY IN PATIENTS WITH ADVANCED HIV DISEASE (SEE WARNINGS). PROLONGED USE OF RETROVIR HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY.

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 (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 that result in 5 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 have been evaluated in 22 adult HIV-infected patients in a Phase 1 dose-escalation study. Following intravenous (IV) dosing, dose-independent kinetics was observed over the range of 1 to 5 mg/kg. The major metabolite of zidovudine is 3′-azido-3′-deoxy-5′-*O*-β-*D*-glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 18% and 60%, respectively, following IV dosing. A second metabolite, 3′-amino-3′-deoxythymidine (AMT), has been identified in the plasma following single-dose IV administration of zidovudine. The AMT AUC was one fifth of the zidovudine AUC.

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.

Table 1. Zidovudine Pharmacokinetic Parameters Following Intravenous Administration in HIV-Infected Patients

Parameter	Mean ± SD (except where noted)
Apparent volume of distribution (L/kg)	1.6 ± 0.6 (n = 11)
Plasma protein binding (%)	<38
CSF:plasma ratio*	0.6 [0.04 to 2.62] (n = 39)
Systemic clearance (L/hr/kg)	1.6 (0.8 to 2.7) (n =18)
Renal clearance (L/hr/kg)	0.34 ± 0.05 (n = 16)
Elimination half-life (hr)†	1.1 (0.5 to 2.9) (n = 19)

*Median [range].

†Approximate range.

Adults with Impaired Renal Function: 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 2). Plasma concentrations of AMT were not determined. A dose adjustment should not be necessary for patients with creatinine clearance (CrCl) ≥15 mL/min.

Table 2. Zidovudine Pharmacokinetic Parameters in Patients With Severe Renal Impairment*

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

*Data are expressed as mean ± standard deviation.

The pharmacokinetics and tolerance of oral 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: Dose Adjustment).

Adults with Impaired Hepatic Function: 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: Dose Adjustment).

Pediatrics: Zidovudine pharmacokinetics have been evaluated in HIV-infected pediatric patients (Table 3).

Patients from 3 Months to 12 Years of Age: Overall, zidovudine pharmacokinetics in pediatric patients >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: Pediatrics).

Patients Younger Than 3 Months of Age: 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: Neonatal Dosing.

Table 3. Zidovudine Pharmacokinetic Parameters in Pediatric Patients*

Parameter	Birth to 14 Days of Age	14 Days to 3 Months of Age	3 Months to 12 Years of Age
Oral bioavailability (%)	89 ± 19 (n = 15)	61 ± 19 (n = 17)	65 ± 24 (n = 18)
CSF:plasma ratio	no data	no data	0.26 ± 0.17† (n = 28)
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)

*Data presented as mean ± standard deviation except where noted.
†CSF ratio determined at steady-state on constant intravenous infusion.

Pregnancy: Zidovudine pharmacokinetics have been studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. Zidovudine pharmacokinetics were similar to that 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. Although data are limited, methadone maintenance therapy in 5 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 Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.** 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).

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 exposure (AUC) when a single dose of zidovudine was administered as the 300-mg RETROVIR Tablet.

Drug Interactions: See Table 4 and PRECAUTIONS: Drug Interactions.

Zidovudine Plus Lamivudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single oral dose of zidovudine (200 mg) in combination with multiple oral doses of lamivudine (300 mg every 12 hours).

Table 4. Effect of Coadministered Drugs on Zidovudine AUC*

Note: ROUTINE DOSE MODIFICATION OF ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.

Coadministered Drug and Dose	Zidovudine Oral Dose	n	Zidovudine Concentrations AUC	Zidovudine Concentrations Variability	Concentration of Coadministered Drug
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	↑AUC 31%	Range 23% to 78%†	↔
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑AUC 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑AUC 43%	Range 16% to 64%†	↔
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%†	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%†	Not Assessed

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

*This table is not all inclusive.

†Estimated range of percent difference.

INDICATIONS AND USAGE

RETROVIR IV Infusion in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

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: Therapy with 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.

RETROVIR in combination with other antiretroviral agents has been shown to be superior to monotherapy in one or more of the following endpoints: delaying death, delaying development of AIDS, increasing CD4 cell counts, and decreasing plasma HIV-1 RNA. The complete prescribing information for each drug should be consulted before combination therapy that includes RETROVIR is initiated.

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 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 intravenous 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 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

COMBIVIR® and TRIZIVIR® are combination product tablets that contain zidovudine as one of their components. RETROVIR should not be administered concomitantly with COMBIVIR or TRIZIVIR.

The incidence of adverse reactions appears to increase with disease progression; 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 <1,000 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. 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: 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).

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 (CrCl<15 mL/min), dosage reduction is recommended. 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 CLINICAL PHARMACOLOGY: Pharmacokinetics and DOSAGE AND ADMINISTRATION).

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 drug 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, which 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: See CLINICAL PHARMACOLOGY section (Table 4) for information on zidovudine concentrations when coadministered with other drugs. For patients experiencing pronounced anemia or other severe zidovudine-associated events while receiving chronic administration of zidovudine and some of the drugs (e.g., fluconazole, valproic acid) listed in Table 4, zidovudine dose reduction may be considered.

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

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.

Doxorubicin: Concomitant use of zidovudine with doxorubicin should be avoided since an antagonistic relationship has been demonstrated in vitro (see CLINICAL PHARMACOLOGY for additional drug interactions).

Phenytoin: Phenytoin plasma levels have been reported to be low in some patients receiving RETROVIR, while in 1 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.

Overlapping Toxicities: Coadministration of ganciclovir, interferon-alpha, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

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.

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 employed 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. 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 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/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 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/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 Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.

Zidovudine is excreted in human milk (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Nursing Mothers). Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving RETROVIR** (see Pediatric Use and INDICATIONS AND USAGE: Maternal-Fetal HIV Transmission).

Pediatric Use: RETROVIR has been studied in HIV-infected pediatric patients over 3 months of age who had HIV-related symptoms or who were asymptomatic with abnormal laboratory values indicating significant HIV-related immunosuppression. RETROVIR has also been studied in neonates perinatally exposed to HIV (see ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, INDICATIONS AND USAGE: Description of Clinical Studies, and CLINICAL PHARMACOLOGY: 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 RETROVIR are greater in patients with more advanced infection at the time of initiation of therapy.

Table 5 summarizes events reported at a statistically significantly greater incidence for patients receiving RETROVIR orally in a monotherapy study:

Table 5. 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%

*Reported in ≥5% of study population.

†Not statistically significant versus placebo.

In addition to the adverse events listed in Table 5, other adverse events observed in clinical studies were abdominal cramps, abdominal pain, arthralgia, chills, dyspepsia, fatigue, hyperbilirubinemia, insomnia, musculoskeletal pain, myalgia, and neuropathy.

Selected laboratory abnormalities observed during a clinical study of monotherapy with oral RETROVIR are shown in Table 6.

Table 6. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Patients with Asymptomatic HIV Infection (ACTG 019)

Adverse Event	RETROVIR 500 mg/day (n = 453)	Placebo (n = 428)
Anemia (Hgb<8 g/dL)	1.1%	0.2%
Granulocytopenia (<750 cells/mm^3)	1.8%	1.6%
Thrombocytopenia (platelets<50,000/mm^3)	0%	0.5%
ALT (>5 x ULN)	3.1%	2.6%
AST (>5 x ULN)	0.9%	1.6%
Alkaline phosphatase (>5 x ULN)	0%	0%

ULN = Upper limit of normal.

Pediatrics: ***Study ACTG300:*** Selected clinical adverse events and physical findings with a ≥5% frequency during therapy with EPIVIR 4 mg/kg twice daily plus RETROVIR 160 mg/m^2 orally 3 times daily compared with didanosine in therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 7.

Table 7. Selected Clinical Adverse Events and Physical Findings (≥5% Frequency) in Pediatric Patients in Study ACTG300

Adverse Event	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*	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

*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 8.