

were attributed to pneumonia; all three had serious concomitant AIDS-related illnesses that contributed to their deaths. Risk factors for pneumonia included low initial CD4 lymphocyte count, high initial viral load, intravenous drug use, smoking, and a prior history of lung disease.

Because it was unclear whether the higher incidence rate of pneumonia was related to FUZEON use, an observational study in 1850 HIV-infected patients (740 FUZEON treated patients and 1110 non-FUZEON treated patients) was conducted to evaluate the risk of pneumonia in patients treated with FUZEON. A total of 123 patients had a confirmed or probable pneumonia event in this study (62 in the FUZEON treatment arm with 1962 patient-years of observation and 61 in the non-FUZEON treatment arm with 3378 patient-years of observation). The incidence of pneumonia was 3.2 events/100 patient-years in the FUZEON treatment arm and 1.8 events/100 patient-years in the non-FUZEON treatment arm. The hazard ratio, adjusting for other baseline risk factors, was 1.34 (95% C.I. = 0.90 – 2.00). Based on this observational study, it is not possible to exclude an increased risk of pneumonia in patients treated with FUZEON compared to non-FUZEON treated patients.

It is unclear if the increased incidence of pneumonia is related to FUZEON use. However, because of these findings, patients with HIV-1 infection should be carefully monitored for signs and symptoms of pneumonia, especially if they have underlying conditions which may predispose them to pneumonia. Risk factors for pneumonia included low initial CD4 cell count, high initial viral load, intravenous drug use, smoking, and a prior history of lung disease.

5.4 Hypersensitivity Reactions

Systemic hypersensitivity reactions have been associated with FUZEON therapy and may recur on re-challenge. Hypersensitivity reactions have occurred in <1% of subjects studied and have included combinations of: rash, fever, nausea and vomiting, chills, rigors, hypotension, and/or elevated serum liver transaminases. Other adverse events that may be immune mediated and have been reported in subjects receiving FUZEON include primary immune complex reaction, respiratory distress, glomerulonephritis, and Guillain-Barre syndrome. Patients developing signs and symptoms suggestive of a systemic hypersensitivity reaction should discontinue FUZEON and should seek medical evaluation immediately. Therapy with FUZEON should not be restarted following systemic signs and symptoms consistent with a hypersensitivity reaction. Risk factors that may predict the occurrence or severity of hypersensitivity to FUZEON have not been identified.

5.5 Non-HIV Infected Individuals

There is a theoretical risk that FUZEON use may lead to the production of anti-enfuvirtide antibodies which cross react with HIV gp41. This could result in a false positive HIV test with an ELISA assay; a confirmatory western blot test would be expected to be negative. FUZEON has not been studied in non-HIV infected individuals.

5.6 Immune Reconstitution Syndrome

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

6 ADVERSE REACTIONS

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

- Administration with Biojector[®] 2000 [see *Warnings and Precautions* (5.2)]
- Pneumonia [see *Warnings and Precautions* (5.3)]
- Hypersensitivity Reactions [see *Warnings and Precautions* (5.4)]

6.1 Clinical Trials Experience

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

The overall safety profile of FUZEON is based on 2131 subjects who received at least 1 dose of FUZEON during various clinical trials. This includes 2051 adults, 658 of whom received the recommended dose for greater than 48 weeks, and 63 pediatric subjects.

Assessment of treatment-emergent adverse events is based on the pooled data from the two randomized, controlled, open-label, multicenter trials in treatment-experienced subjects, T20-301 (TORO 1) and T20-302 (TORO 2).

Local Injection Site Reactions

Local injection site reactions were the most frequent adverse events associated with the use of FUZEON. In T20-301 and T20-302, 98% of subjects had at least one local injection site reaction (ISR). A total of 7% of subjects discontinued treatment with FUZEON because of ISRs (4%) or difficulties with injecting FUZEON (3%) such as injection fatigue and inconvenience. Eighty-five percent of subjects experienced their first ISR during the initial week of treatment; ISRs continued to occur throughout treatment with FUZEON. For most subjects the severity of signs and symptoms associated with ISRs did not change during the 48 weeks of treatment. The majority of ISRs were associated with erythema, induration, the presence of nodules or cysts, and mild to moderate pain at the injection site (Table 2). In addition, the average duration of individual ISRs was between three and seven days in 41% of subjects and more than seven days in 24% of subjects. Also, the numbers of ISRs per subject at any one time was between six to 14 ISRs in 26% of subjects and more than 14 ISRs in 1.3% of subjects. Infection at the injection site (including abscess and cellulitis) was reported in 1.7% of adult subjects.

Table 2 Summary of Individual Signs/Symptoms Characterizing Local Injection Site Reactions to Enfuvirtide in Studies T20-301 and T20-302 Combined (% of Subjects) Through 48 Weeks

Event Category	N=663		
	Any Severity Grade	% of Subjects with Grade 3 Reactions	% of Subjects with Grade 4 Reactions
Pain/Discomfort ^a	96%	11%	0%
Induration	90%	39% >25 but <50 mm	18% ≥50 mm
Erythema	91%	22% >50 but <85 mm	10% ≥85 mm
Nodules and Cysts	80%	23% >3 cm average diameter	0.2% Draining
Pruritus ^b	65%	3%	NA
Ecchymosis	52%	5% >3 but ≤5 cm	2% >5 cm

^aGrade 3 = severe pain requiring prescription non-topical analgesics or limiting usual activities.

Grade 4 = severe pain requiring hospitalization or prolongation of hospitalization, resulting in death, or persistent or significant disability/incapacity, or life-threatening, or medically significant.

^bGrade 3 = refractory to topical treatment or requiring oral or parenteral treatment.

Grade 4 = not applicable.

Other Adverse Events

In T20-301 and T20-302, after study week 8, subjects on background alone who met protocol defined criteria for virological failure were permitted to revise their background regimens and add FUZEON. Exposure on FUZEON+background was 557 patient-years, and to background alone 162 patient-years. Due to this difference in exposure, safety results are expressed as the number of patients with an adverse event per 100 patient-years of exposure. For FUZEON+background, adverse events are also displayed by percent of subjects.

The events most frequently reported in subjects receiving FUZEON+background regimen, excluding ISRs, were diarrhea (38 per 100 patient-years or 31.7%), nausea (27 per 100 patient-years or 22.8%), and fatigue (24 per 100 patient-years or 20.2%). These events were also commonly observed in subjects that received background regimen alone: diarrhea (73 per 100 patient-years), nausea (50 per 100 patient-years), and fatigue (38 per 100 patient-years).

Treatment-emergent adverse events, regardless of causality and excluding ISRs, from Phase 3 studies are summarized for adult subjects, in Table 3. Any Grade 2 or above events occurring at ≥ 2 percent of subjects and at a higher rate in subjects treated with FUZEON are summarized in Table 3; events that occurred at a higher rate in the control arms are not displayed.

Rates of adverse events for subjects who switched to FUZEON after virological failure were similar.

Table 3 Rates of Treatment-Emergent Adverse Events* (\geq Grade 2) Reported in $\geq 2\%$ of Subjects Treated with FUZEON (Pooled Studies T20-301/T20-302 at 48 Weeks)**

Adverse Event (by System Organ Class)	FUZEON+ Background Regimen (N=663)	FUZEON+ Background Regimen (N=663)	Background Regimen (N=334)
	663 subjects total	557 total patient-years	162 total patient-years
	% frequency	rate/100 patient- years	rate/100 patient-years
Weight Decreased	6.6%	7.9	6.2
Sinusitis	6.0%	7.2	4.9
Abdominal Pain	3.9%	4.7	3.7
Cough	3.9%	4.7	2.5
Herpes Simplex	3.5%	4.1	3.7
Appetite Decreased	3.2%	3.8	2.5
Pancreatitis	3.0%	3.6	2.5
Pain in Limb	2.9%	3.4	3.1
Pneumonia (see text below)	2.7%	3.2	0.6
Myalgia	2.7%	3.2	1.2
Influenza-Like Illness	2.4%	2.9	1.9
Folliculitis	2.4%	2.9	2.5
Anorexia	2.3%	2.7	1.9
Dry Mouth	2.1%	2.5	1.9
Conjunctivitis	2.0%	2.3	1.9

*Excludes Injection Site Reactions

**Events listed occurred more frequently in subjects treated with FUZEON (based on rates/100 patient-years).

Less Common Events

The following adverse events have been reported in 1 or more subjects; however, a causal relationship to FUZEON has not been established.

Immune System Disorders: worsening abacavir hypersensitivity reaction

Renal and Urinary Disorders: glomerulonephritis; tubular necrosis; renal insufficiency; renal failure (including fatal cases)

Blood and Lymphatic Disorders: thrombocytopenia; neutropenia; fever; lymphadenopathy

Endocrine and Metabolic: hyperglycemia

Infections: sepsis; herpes simplex

Nervous System Disorders: taste disturbance; Guillain-Barre syndrome (fatal); sixth nerve palsy; peripheral neuropathy

Cardiac Disorders: unstable angina pectoris

Gastrointestinal Disorders: constipation; abdominal pain upper

General: asthenia

Hepatobiliary Disorders: toxic hepatitis; hepatic steatosis

Investigations: increased amylase; increased lipase; increased AST; increased GGT; increased triglycerides

Psychiatric Disorders: insomnia; depression; anxiety; suicide attempt

Respiratory, Thoracic, and Mediastinal Disorders: pneumopathy; respiratory distress; cough

Skin and Subcutaneous Tissue Disorders: pruritus

Laboratory Abnormalities

Table 4 shows the treatment-emergent laboratory abnormalities that occurred in at least 2 subjects per 100 patient-years and more frequently in those receiving FUZEON+background regimen than background regimen alone from T20-301 and T20-302.

Table 4 Treatment-Emergent Laboratory Abnormalities in $\geq 2\%$ of Subjects Receiving FUZEON* (Pooled Studies T20-301 and T20-302 at 48 Weeks)

Laboratory Parameters	Grading	FUZEON+ Background Regimen (N=663)	FUZEON+ Background Regimen (N=663)	Background Regimen (N=334)
		663 subjects total	557 total patient-years	162 total patient-years
		% frequency	rate/100 patient-years	rate/100 patient-years
Eosinophilia				
1-2 X ULN ($0.7 \times 10^9/L$)	$0.7-1.4 \times 10^9/L$	9.1%	10.8	3.7
>2 X ULN ($0.7 \times 10^9/L$)	$>1.4 \times 10^9/L$	1.8%	2.2	1.8
ALT				
Grade 3	$>5-10 \times ULN$	4.1%	4.8	4.3
Grade 4	$>10 \times ULN$	1.2%	1.4	1.2
Creatine Phosphokinase (U/L)				
Grade 3	$>5-10 \times ULN$	6.9%	8.3	8.0
Grade 4	$>10 \times ULN$	2.6%	3.1	8.6

*Events listed occurred more frequently in subjects treated with FUZEON (based on rates/100 patient-years).

Adverse Events in Pediatric Patients

FUZEON has been studied in 63 pediatric subjects 5 through 16 years of age with duration of FUZEON exposure ranging from 1 dose to 134 weeks. Adverse experiences seen during clinical trials were similar to those observed in adult subjects, although infections at site of injection (cellulitis or abscess) were more frequent in adolescents than in adults, with 4 events occurring in 3 of 28 (11%) subjects.

7 DRUG INTERACTIONS

See also Clinical Pharmacology (12.3)

7.1 Potential for FUZEON to Affect Other Drugs

Based on the results from an *in vitro* human microsomal study, enfuvirtide is not an inhibitor of CYP450 enzymes. In an *in vivo* human metabolism study (N=12), FUZEON at the recommended dose of 90 mg twice daily did not alter the metabolism of CYP3A4, CYP2D6, CYP1A2, CYP2C19 or CYP2E1 substrates.

7.2 Potential for Other Drugs to Affect Enfuvirtide

Based on the available data, co-administration of FUZEON and other drugs which are inducers or inhibitors of CYP450 is not expected to alter the pharmacokinetics of enfuvirtide. No dose adjustments are needed when FUZEON is co-administered with other antiretroviral and non-antiretroviral drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to 27 times and 3.2 times the adult human dose on a m^2 basis and have revealed no evidence of impaired fertility or harm to the fetus due to enfuvirtide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry

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

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommends that HIV-infected mothers not breast-feed their infants to avoid the risk of postnatal transmission of HIV. It is not known whether enfuvirtide is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving FUZEON.

Studies where radio-labeled ^3H -enfuvirtide was administered to lactating rats indicated that radioactivity was present in the milk. It is not known whether the radioactivity in the milk was from radio-labeled enfuvirtide or from radio-labeled metabolites of enfuvirtide (i.e., amino acids and peptide fragments).

8.4 Pediatric Use

The safety and pharmacokinetics of FUZEON have been evaluated in the age groups of 6 to 16 years of age supported by evidence from adequate and well-controlled studies of FUZEON in adults. Limited efficacy data are available in pediatric subjects 6 years of age and older [see *Clinical Pharmacology (12.3)*].

Sixty-three HIV-1 infected pediatric subjects ages 5 through 16 years have received FUZEON in two open-label, single-arm clinical trials. Adverse experiences, including ISRs, were similar to those observed in adult subjects.

T20-204 was an open-label, multicenter trial that evaluated the safety and antiviral activity of FUZEON in treatment-experienced pediatric subjects. Eleven subjects from 6 to 12 years were enrolled (median age of 9 years). Median baseline CD4 cell count was 495 cells/ μL and the median baseline HIV-1 RNA was 4.6 \log_{10} copies/mL.

Ten of the 11 study subjects completed 48 weeks of chronic therapy. At week 48, 6/11 (55%) subjects had ≥ 1 \log_{10} decline in HIV-1 RNA and 4/11 (36%) subjects were below 400 copies/mL of HIV-1 RNA. The median changes from baseline (for the As Treated population) in HIV-1 RNA and CD4 cell count were -1.48 \log_{10} copies/mL and +122 cells/ μL , respectively.

T20-310 was an open-label, multicenter trial that evaluated the pharmacokinetics, safety, and antiviral activity of FUZEON in treatment-experienced pediatric subjects and adolescents. Fifty-two subjects from 5 through 16 years were enrolled (median age of 12 years). Median baseline CD4 cell count was 117 cells/ μL and the median baseline HIV-1 RNA was 5.0 \log_{10} copies/mL.

Thirty-two of the 52 study subjects completed 48 weeks of chronic therapy. At week 48, 17/52 (33%) of subjects had ≥ 1 \log_{10} decline in HIV-1 RNA, 11/52 (21%) of subjects were below 400 copies/mL of HIV-1 RNA and 5/52 (10%) were below 50 copies/mL. The median changes from baseline (for the As Treated population) in HIV-1 RNA and CD4 cell count were -1.17 \log_{10} copies/mL and +106 cells/ μL , respectively.

8.5 Geriatric Use

Clinical studies of FUZEON did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, appropriate caution should be exercised in the administration and monitoring of FUZEON in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Use in Patients with Hepatic Impairment

No dose adjustments of enfuvirtide are needed in patients with hepatic impairment [see *Clinical Pharmacology (12.3)*].

8.7 Use in Patients with Renal Impairment

No dose adjustments of enfuvirtide are needed in patients with renal impairment [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

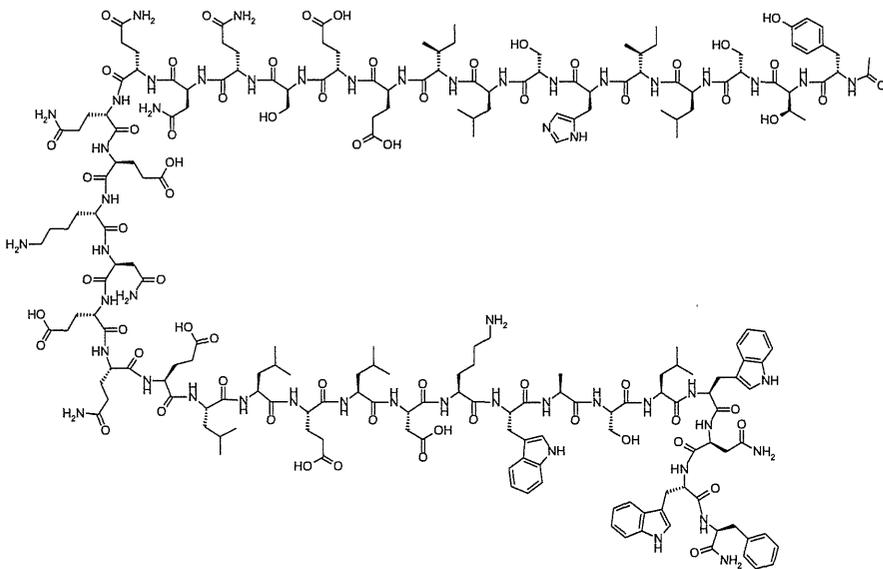
There are no reports of human experience of acute overdose with FUZEON. The highest dose administered to 12 subjects in a clinical trial was 180 mg as a single dose subcutaneously. There is no specific antidote for overdose with FUZEON. Treatment of overdose should consist of general supportive measures.

11 DESCRIPTION

FUZEON (enfuvirtide) is an inhibitor of the fusion of HIV-1 with CD4 cells. Enfuvirtide is a linear 36-amino acid synthetic peptide with the N-terminus acetylated and the C-terminus is a carboxamide. It is composed of naturally occurring L-amino acid residues.

Enfuvirtide is a white to off-white amorphous solid. It has negligible solubility in pure water and the solubility increases in aqueous buffers (pH 7.5) to 85-142 g/100 mL. The empirical formula of enfuvirtide is $C_{204}H_{301}N_{51}O_{64}$, and the molecular weight is 4492. It has the following primary amino acid sequence:

CH₃CO-Tyr-Thr-Ser-Leu-Ile-His-Ser-Leu-Ile-Glu-Glu-Ser-Gln-Asn-Gln-Gln-Glu-Lys-Asn-Glu-Gln-Glu-Leu-Leu-Glu-Leu-Asp-Lys-Trp-Ala-Ser-Leu-Trp-Asn-Trp-Phe-NH₂ and the following structural formula:



The drug product, FUZEON (enfuvirtide) for Injection, is a white to off-white, sterile, lyophilized powder. Each single-use vial contains 108 mg of enfuvirtide for the delivery of 90 mg. Prior to subcutaneous administration, the contents of the vial are reconstituted with 1.1 mL of Sterile Water for Injection giving a volume of approximately 1.2 mL to provide the delivery of 1 mL of the solution. Each 1 mL of the reconstituted solution contains approximately 90 mg of enfuvirtide with approximate amounts of the following excipients: 22.55 mg of mannitol, 2.39 mg of sodium carbonate (anhydrous), and sodium hydroxide and hydrochloric acid for pH adjustment as needed. The reconstituted solution has an approximate pH of 9.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Enfuvirtide is an antiviral drug [see *Clinical Pharmacology (12.4)*].

12.3 Pharmacokinetics

The pharmacokinetic properties of enfuvirtide were evaluated in HIV-1 infected adult and pediatric subjects.

Absorption

Following a 90-mg single subcutaneous injection of FUZEON into the abdomen in 12 HIV-1 infected subjects, the mean (\pm SD) C_{\max} was 4.59 ± 1.5 $\mu\text{g/mL}$, AUC was 55.8 ± 12.1 $\mu\text{g}\cdot\text{h/mL}$ and the median T_{\max} was 8 hours (ranged from 3 to 12 h). The absolute bioavailability (using a 90-mg intravenous dose as a reference) was $84.3\% \pm 15.5\%$. Following 90-mg twice daily dosing of FUZEON subcutaneously in combination with other antiretroviral agents in 11 HIV-1 infected subjects, the mean (\pm SD) steady-state C_{\max} was 5.0 ± 1.7 $\mu\text{g/mL}$, C_{trough} was 3.3 ± 1.6 $\mu\text{g/mL}$, $\text{AUC}_{0-12\text{h}}$ was 48.7 ± 19.1 $\mu\text{g}\cdot\text{h/mL}$, and the median T_{\max} was 4 hours (ranged from 4 to 8 h).

Absorption of the 90-mg dose was comparable when injected into the subcutaneous tissue of the abdomen, thigh or arm.

Distribution

The mean (\pm SD) steady-state volume of distribution after intravenous administration of a 90-mg dose of FUZEON (N=12) was 5.5 ± 1.1 L.

Enfuvirtide is approximately 92% bound to plasma proteins in HIV-infected plasma over a concentration range of 2 to 10 $\mu\text{g/mL}$. It is bound predominantly to albumin and to a lower extent to α -1 acid glycoprotein.

The CSF levels of enfuvirtide (measured from 2 hours to 18 hours after administration of enfuvirtide) in 4 HIV-infected subjects were below the limit of quantification (0.025 $\mu\text{g/mL}$).

Metabolism/Elimination

As a peptide, enfuvirtide is expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool.

Mass balance studies to determine elimination pathway(s) of enfuvirtide have not been performed in humans.

In vitro studies with human microsomes and hepatocytes indicate that enfuvirtide undergoes hydrolysis to form a deamidated metabolite at the C-terminal phenylalanine residue, M3. The hydrolysis reaction is not NADPH dependent. The M3 metabolite is detected in human plasma following administration of enfuvirtide, with an AUC ranging from 2.4% to 15% of the enfuvirtide AUC.

Following a 90-mg single subcutaneous dose of enfuvirtide (N=12) the mean \pm SD elimination half-life of enfuvirtide is 3.8 ± 0.6 h and the mean \pm SD apparent clearance was 24.8 ± 4.1 mL/h/kg. Following 90-mg twice daily dosing of FUZEON subcutaneously in combination with other antiretroviral agents in 11 HIV-1 infected subjects, the mean \pm SD apparent clearance was 30.6 ± 10.6 mL/h/kg.

Special Populations

Hepatic Impairment

Formal pharmacokinetic studies of enfuvirtide have not been conducted in subjects with hepatic impairment.

Renal Impairment

Analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuvirtide is not affected in patients with creatinine clearance greater than 35 mL/min. The results of a renal impairment

study indicate clearance of enfuvirtide was reduced by 38% in subjects with severe renal impairment (CL = 11 – 35 mL/min; n = 4) and by 14 - 28% in subjects with end-stage renal disease maintained on dialysis (n = 8) compared to subjects with normal renal function (CL >80 mL/min; n = 8). Hemodialysis did not significantly alter enfuvirtide clearance.

No dose adjustment is recommended for patients with impaired renal function.

Gender and Weight

Analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuvirtide is 20% lower in females than males after adjusting for body weight.

Enfuvirtide clearance decreases with decreased body weight irrespective of gender. Relative to the clearance of a 70-kg male, a 40-kg male will have 20% lower clearance and a 110-kg male will have a 26% higher clearance. Relative to a 70-kg male, a 40-kg female will have a 36% lower clearance and a 110-kg female will have the same clearance.

No dose adjustment is recommended for weight or gender.

Race

Analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuvirtide was not different in Blacks compared to Caucasians. Other pharmacokinetic studies suggest no difference between Asians and Caucasians after adjusting for body weight.

Pediatric Patients

The pharmacokinetics of enfuvirtide have been studied in 23 pediatric subjects aged 6 through 16 years at a dose of 2 mg/kg. Enfuvirtide pharmacokinetics were determined in the presence of concomitant medications including antiretroviral agents. A dose of 2 mg/kg twice daily (maximum 90 mg twice daily) provided enfuvirtide plasma concentrations similar to those obtained in adult subjects receiving 90 mg twice daily.

In the 23 pediatric subjects receiving the 2 mg/kg twice daily dose, the mean \pm SD steady-state AUC was 56.3 ± 22.3 $\mu\text{g}\cdot\text{h}/\text{mL}$, C_{max} was 6.3 ± 2.4 $\mu\text{g}/\text{mL}$, C_{trough} was 3.1 ± 1.5 $\mu\text{g}/\text{mL}$, and apparent clearance was 40 ± 17 mL/h/kg [see *Use in Specific Populations (8.4)*].

Geriatric Patients

The pharmacokinetics of enfuvirtide have not been studied in patients over 65 years of age.

Drug Interactions

See also Drug Interactions (7)

Table 5 shows the results of the drug-drug interaction studies conducted between FUZEON and the following drugs: ritonavir, saquinavir/ritonavir, and rifampin.

Table 5 Effect of Ritonavir, Saquinavir/Ritonavir, and Rifampin on the Steady-State Pharmacokinetics of Enfuvirtide (90 mg bid)*

Coadministered Drug	Dose of Coadministered Drug	N	% Change of Enfuvirtide Pharmacokinetic Parameters ^{†x} (90% CI)		
			C _{max}	AUC	C _{trough}
Ritonavir	200 mg, q12h, 4 days	12	↑24 (↑9 to ↑41)	↑22 (↑8 to ↑37)	↑14 (↑2 to ↑28)
Saquinavir/ Ritonavir	1000/100 mg, q12h, 4 days	12	↔	↑14 (↑5 to ↑24)	↑26 (↑17 to ↑35)
Rifampin	600 mg, qd, 10 days	12	↔	↔	↓15 (↓22 to ↓7)

* All studies were performed in HIV-1+ subjects using a sequential crossover design.

† ↑ = Increase; ↓ = Decrease; ↔ = No Effect (↑ or ↓ <10%)

x No interactions were clinically significant.

12.4 Microbiology

Mechanism of Action

Enfuvirtide interferes with the entry of HIV-1 into cells by inhibiting fusion of viral and cellular membranes. Enfuvirtide binds to the first heptad-repeat (HR1) in the gp41 subunit of the viral envelope glycoprotein and prevents the conformational changes required for the fusion of viral and cellular membranes.

Antiviral Activity in Cell Culture

The antiviral activity of enfuvirtide was assessed by infecting different CD4 cell types with laboratory and clinical isolates of HIV-1. The geometric mean EC₅₀ value for baseline clinical isolates was 3.52 nM (ranged from 0.089 to 107 nM; 0.4 to 480 ng/mL) by the cMAGI assay (n=130) and was 57.9 nM (1.56 to 1680 nM; 7 to 7530 ng/mL) by a recombinant phenotypic entry assay (n=627). Enfuvirtide was similarly active in cell culture against clades A, AE, C, D, E, F, and G (geometric mean EC₅₀ value was 7.7 nM; range 3.9 to 28.6 nM), and R5, X4, and dual tropic viruses. Enfuvirtide has no activity against HIV-2.

Enfuvirtide exhibited additive to synergistic effects in cell culture assays when combined with individual members of various antiretroviral classes, including lamivudine, zidovudine, indinavir, nelfinavir, and efavirenz.

Drug Resistance

HIV-1 isolates with reduced susceptibility to enfuvirtide have been selected in cell culture. Genotypic analysis of these resistant isolates showed mutations that resulted in amino acid substitutions at the enfuvirtide binding HR1 domain positions 36 to 38 of the HIV-1 envelope glycoprotein gp41. Phenotypic analysis of site-directed mutants in positions 36 to 38 in an HIV-1 molecular clone showed a 5-fold to 684-fold decrease in susceptibility to enfuvirtide.

In clinical trials, HIV-1 isolates with reduced susceptibility to enfuvirtide have been recovered from subjects failing a FUZEON containing regimen. Posttreatment HIV-1 virus from 277 subjects experiencing protocol defined virological failure at 48 weeks exhibited a median decrease in susceptibility to enfuvirtide of 33.4-fold (range 0.4-6318-fold) relative to their respective baseline virus. Of these, 249 had decreases in susceptibility to enfuvirtide of greater than 4-fold and all but 3 of those 249 exhibited genotypic changes in the codons encoding gp41 HR1 domain amino acids 36 to 45. Substitutions in this region were observed with decreasing frequency at amino acid positions 38, 43, 36, 40, 42, and 45. Mutations or polymorphisms in other regions of the envelope (e.g., the HR2 region or those yet to be identified) as well as co-receptor usage and density may affect susceptibility to enfuvirtide.

Cross-resistance

HIV-1 clinical isolates resistant to nucleoside analogue reverse transcriptase inhibitors (NRTI), non-nucleoside analogue reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI) were susceptible to enfuvirtide in cell culture.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term animal carcinogenicity studies of enfuvirtide have not been conducted.

Mutagenesis

Enfuvirtide was neither mutagenic nor clastogenic in a series of *in vivo* and *in vitro* assays including the Ames bacterial reverse mutation assay, a mammalian cell forward gene mutation assay in AS52 Chinese Hamster ovary cells or an *in vivo* mouse micronucleus assay.

Impairment of Fertility

Enfuvirtide produced no adverse effects on fertility in male or female rats at doses up to 1.6 times the maximum recommended adult human daily dose on a m² basis.

14 CLINICAL STUDIES

14.1 Description of Clinical Studies

Studies in Antiretroviral Experienced Patients

T20-301 and T20-302 were randomized, controlled, open-label, multicenter trials in HIV-1 infected subjects. Subjects were required to have either (1) viremia despite 3 to 6 months prior therapy with a nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), and protease inhibitor (PI) or (2) viremia and documented resistance or intolerance to at least one member in each of the NRTI, NNRTI, and PI classes.

All subjects received an individualized background regimen consisting of 3 to 5 antiretroviral agents selected on the basis of the subject's prior treatment history and baseline genotypic and phenotypic viral resistance measurements. Subjects were then randomized at a 2:1 ratio to FUZEON 90 mg twice daily with background regimen or background regimen alone.

After week 8, subjects on either treatment arm who met protocol defined criteria for virological failure were permitted to revise their background regimens; those on background regimen alone were also permitted to add FUZEON.

Demographic characteristics for studies T20-301 and T20-302 are shown in Table 6. Subjects had prior exposure to a median of 12 antiretrovirals for a median of 7 years.

Table 6 T20-301 and T20-302 Pooled Subject Demographics

	FUZEON+Background Regimen N=663	Background Regimen N=334
Sex		
Male	90%	90%
Female	10%	10%
Race		
White	89%	89%
Black	8%	7%
Mean Age (yr) (range)	42 (16-67)	43 (24-82)
Median Baseline HIV-1 RNA (log ₁₀ copies/mL) (range)	5.2 (3.5-6.7)	5.1 (3.7-7.1)
Median Baseline CD4 Cell Count (cells/mm ³) (range)	89 (1-994)	97 (1-847)

The disposition and efficacy outcomes of T20-301 and T20-302 are shown in Table 7.

Table 7 Outcomes at Week 48 (Pooled Studies T20-301 and T20-302)

Outcomes	FUZEON+Background Regimen 90 mg bid N=663	Background Regimen N=334	
Virological Responder (at least 1 log ₁₀ below baseline)	304 (46%)	61 (18%)	
Virological Non-responder:		220 (66%)	
• Switch	0	12 (4%)	
• Completed 48 weeks randomized regimen*	191 (29%)		
		Continued Background Regimen (N=112)	Switched to FUZEON (N=220)
Discontinued due to insufficient treatment response [#]	37 (5%)	13 (12%)	22 (10%)
Discontinued due to adverse reactions/intercurrent illness/labs	46 (7%)	9 (8%)	13 (6%)
Deaths	15 (2%)	5 (4%)	2 (1%)
Discontinued due to injection:			
• Injection site	27 (4%)	NA	10 (5%)

reactions			
• Difficulty with injecting FUZEON ^{##}	18 (3%)	NA	2 (1%)
Discontinued due to other reasons [†]	25 (4%)	14 (13%)	6 (3%)

*Includes never responded, rebound, and missing RNA data.

#Includes study discontinuation for virological failure and insufficient response as per the judgment of the investigator.

##Includes difficulties with injection, such as injection fatigue and inconvenience.

†Includes lost to follow-up, treatment refusal, and non-compliance.

At 48 weeks, 154 (23%) of subjects in the FUZEON+background regimen and 27 (8%) in the background regimen alone had HIV-1 RNA levels <50 copies/mL, and 225 (34%) of subjects receiving FUZEON+background regimen had HIV-1 RNA levels <400 copies/mL compared to 44 (13%) in the background regimen alone. Subjects achieving HIV-1 RNA levels <50 copies/mL were included in the <400 copies/mL category and both categories were incorporated in the overall virologic responder category of achieving HIV-1 RNA at least 1 log₁₀ below baseline.

The mean log change in HIV-1 RNA from baseline was -1.4 log₁₀ copies/mL in subjects receiving FUZEON+background and -0.5 in those receiving background alone. The mean change in CD4 cell count from baseline to week 48 was +91 cells/mm³ in the FUZEON+background arm and +45 cells/mm³ in the background alone arm.

Subjects in the FUZEON+background arm achieved a better virologic and immunologic outcome than subjects in the background alone arm across all subgroups based on baseline CD4 cell count, baseline HIV-1 RNA, number of prior ARVs or number of active ARVs in the background regimen.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

FUZEON (enfuvirtide) for Injection is a white to off-white, sterile, lyophilized powder and it is packaged in a single-use clear glass vial containing 108 mg of enfuvirtide for the delivery of approximately 90 mg/1 mL when reconstituted with 1.1 mL of Sterile Water for Injection.

FUZEON is available in a Convenience Kit containing 60 single-use vials of FUZEON (90 mg strength), 60 vials (2 cartons of 30 each) of Sterile Water for Injection (1.1 mL per vial), 60 reconstitution syringes (3 cc), 60 administration syringes (1 cc), alcohol wipes, Package Insert, Patient Package Insert, and Injection Instructions (NDC 0004-0380-39).

16.2 Storage Conditions

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Reconstituted solution should be stored in the original vial under refrigeration at 2° to 8°C (36° to 46°F) and used within 24 hours.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information)

To assure safe and effective use of FUZEON, the following information and instructions should be given to patients:

- Patients should be informed that injection site reactions occur in almost all patients taking FUZEON. Patients must be familiar with the FUZEON *Injection Instructions* for instructions on how to appropriately

inject FUZEON and how to carefully monitor for signs or symptoms of cellulitis or local infection. Patients should be instructed when to contact their healthcare provider about these reactions.

- Patients should be made aware that an increased rate of bacterial pneumonia was observed in subjects treated with FUZEON in clinical trials. Patients should be advised to seek medical evaluation immediately if they develop signs or symptoms suggestive of pneumonia (cough with fever, rapid breathing, shortness of breath) [see *Warnings and Precautions (5.3)*].
- Patients should be advised of the possibility of a systemic hypersensitivity reaction to FUZEON. Patients should be advised to discontinue therapy and immediately seek medical evaluation if they develop signs/symptoms of systemic hypersensitivity such as combinations of rash, fever, nausea and vomiting, chills, rigors, and/or hypotension [see *Warnings and Precautions (5.4)*].
- FUZEON is not a cure for HIV-1 infection and patients may continue to contract illnesses associated with HIV-1 infection. The long-term effects of FUZEON are unknown at this time. FUZEON therapy has not been shown to reduce the risk of transmitting HIV-1 to others through sexual contact or blood contamination.
- FUZEON must be taken as part of a combination antiretroviral regimen. Use of FUZEON alone may lead to rapid development of virus resistant to FUZEON and possibly other agents of the same class.
- Patients and caregivers must be instructed in the use of aseptic technique when administering FUZEON in order to avoid injection site infections. Appropriate training for FUZEON reconstitution and self-injection must be given by a healthcare provider, including a careful review of the FUZEON Patient Package Insert and FUZEON *Injection Instructions*. The first injection should be performed under the supervision of an appropriately qualified healthcare provider. It is recommended that the patient and/or caregiver's understanding and use of aseptic injection techniques and procedures be periodically re-evaluated.
- Patients and caregivers should be instructed on the preferred anatomical sites for administration (upper arm, abdomen, anterior thigh). FUZEON should not be injected near any anatomical areas where large nerves course close to the skin, such as near the elbow, knee, groin or the inferior or medial sections of the buttocks, skin abnormalities, including directly over a blood vessel, into moles, scar tissue, bruises, or near the navel, surgical scars, tattoos or burn sites.
- Patients and caregivers should be instructed in the proper techniques for preparation, injection and disposal of needles and syringes (including not recapping needles) in order to avoid needle stick injuries. Patients should be told not to reuse needles or syringes, and be instructed in safe disposal procedures including the use of a puncture-resistant container for disposal of used needles and syringes. Patients must be instructed on the safe disposal of full containers as per local requirements. Caregivers who experience an accidental needle stick after patient injection should contact a healthcare provider immediately.
- Patients should contact their healthcare provider for any questions regarding the administration of FUZEON.
- Patients should inform their healthcare provider if they are pregnant, plan to become pregnant or become pregnant while taking this medication.
- Patients should inform their healthcare provider if they are breast-feeding.
- Patients should not change the dose or dosing schedule of FUZEON or any antiretroviral medication without consulting their healthcare provider.
- Patients should contact their healthcare provider immediately if they stop taking FUZEON or any other drug in their antiretroviral regimen.

- Patients should be told that they can obtain more information on the self-administration of FUZEON at www.FUZEON.com or by calling 1-877-4-FUZEON (1-877-438-9366).

Patients should be advised that no studies have been conducted on the ability to drive or operate machinery while taking FUZEON. If patients experience dizziness while taking FUZEON, they should be advised to talk to their healthcare provider before driving or operating machinery.

FUZEON is a trademark of Hoffmann-La Roche Inc.

FUZEON has been jointly developed by Trimeris, Inc. and Hoffmann-La Roche Inc. FUZEON is manufactured by Hoffmann-La Roche Inc.

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PRESCRIBING INFORMATION

RETROVIR[®]

(zidovudine)

IV Infusion

FOR INTRAVENOUS INFUSION ONLY

WARNING

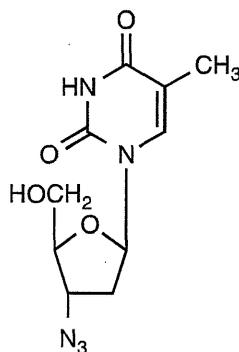
RETROVIR (ZIDOVUDINE) HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY, INCLUDING NEUTROPENIA AND SEVERE ANEMIA, PARTICULARLY IN PATIENTS WITH ADVANCED HIV DISEASE (SEE WARNINGS). PROLONGED USE OF RETROVIR HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY.

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 C₁₀H₁₃N₅O₄.

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 (-

N₃) 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 IC₅₀ and IC₉₀ 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 IC₅₀ and IC₉₀ 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/m² 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).