

# Enfuvirtide

**Brand Name: Fuzeon**

**Drug Class: Entry and Fusion Inhibitors**

## Drug Description

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

## HIV/AIDS-Related Uses

Enfuvirtide was approved by the FDA on March 13, 2003, for the treatment of HIV-1 infection in combination with other antiretroviral agents in previously treated adults and children 6 years of age or older with evidence of HIV-1 replication despite ongoing antiretroviral therapy.[2] [3]

Enfuvirtide continues to be studied to determine if it will decrease the level of HIV in resting CD4 cells in patients already on antiretroviral therapy or starting an antiretroviral drug regimen for the first time.[4] [5]

## Pharmacology

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.[6]

The initial step of HIV-1 entry into the human host cell is the binding of virions with the CD4 molecule and chemokine coreceptor molecules (CXCR4 or CCR5) on the surface of the target cell. Entry of HIV-1 into the target cell is mediated by two viral envelope glycoproteins, gp120 and gp41, which form complexes that facilitate entry of the virion into the host cell. The surface glycoprotein gp120 mediates CD4 and coreceptor binding. The function of the transmembrane glycoprotein gp41 is to anchor the gp120-gp41 glycoprotein complex within the viral envelope and mediate envelope-host cell membrane fusion.[7]

After gp120 interactions with CD4 and the coreceptors, conformational changes occur in gp41

that expose a fusion peptide located near the N-terminus, which is believed to insert into the target cell membrane. It is thought that the bridged target cell and viral membranes are brought together via two heptad repeats (HR1 and HR2) within gp41. Studies have shown that HR1 and HR2 are essential for virus-host cell fusion to occur. Enfuvirtide corresponds to a linear 36-amino acid sequence within HR2 and likely interacts with a target sequence in HR1, inhibiting association with native HR2 and preventing apposition of the viral and cellular membranes.[8]

The mean maximum plasma concentration (C<sub>max</sub>) following a single 90 mg subcutaneous (SQ) injection of enfuvirtide into the abdomen in 12 HIV-1 infected subjects was approximately 4.59 mcg/mL; area under the plasma concentration-time curve (AUC) was approximately 55.8 mcg hr/mL; the median time to maximum plasma concentration (T<sub>max</sub>) was 8 hours (ranging from 3 to 12 h). The absolute bioavailability (using a 90 mg IV dose as a reference) was approximately 84.3%. Following 90 mg twice daily dosing of SQ enfuvirtide in combination with other antiretroviral agents in 11 HIV-1 infected patients, the mean steady-state C<sub>max</sub> was approximately 5.0 mcg/mL and AUC from zero to 12 hours was approximately 48.7 mcg hr/mL. The median T<sub>max</sub> was 4 hours (ranging 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.[9]

The mean steady-state volume of distribution after IV administration of a 90 mg dose of enfuvirtide was approximately 5.5 liters. Enfuvirtide is approximately 92% bound to plasma proteins in HIV infected plasma over a concentration range of 2 to 10 mcg/ml. It is bound predominantly to albumin and to a lower extent to alpha-1 acid glycoprotein.[10]

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 pathways of enfuvirtide have not been performed in humans. In vitro studies with human microsomes and hepatocytes indicate that enfuvirtide undergoes

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## Pharmacology (cont.)

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hydrolysis to form a deamidated metabolite at the C-terminal phenylalanine residue, M3. 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.[11]

After a 90 mg single SQ dose of enfuvirtide in 12 patients, the mean elimination half-life was approximately 3.8 hours and the mean apparent clearance was approximately 24.8 +/- 4.1 mL/h/kg. Following 90 mg twice daily dosing of enfuvirtide SQ in combination with other antiretroviral agents in 11 HIV-1 infected patients, the mean apparent clearance was approximately 30.6 +/- 10.6 mL/h/kg.[12]

Enfuvirtide is in FDA Pregnancy Category B. There are no adequate and well-controlled studies in pregnant women. Enfuvirtide should be used during pregnancy only if clearly needed. To monitor maternal-fetal outcomes of pregnant women exposed to enfuvirtide and other antiretroviral drugs, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by either calling 1-800-258-4263 or accessing the website at <http://www.APRegistry.com>. It is not known whether enfuvirtide is distributed into human milk; however, because of the potential for HIV transmission and serious adverse effects in nursing infants, mothers should be instructed not to breast-feed while they are taking enfuvirtide.[13]

Formal pharmacokinetic studies of enfuvirtide have not been conducted in patients with hepatic insufficiency. Analysis of plasma concentration data from participants in clinical trials indicated the clearance of enfuvirtide is not affected in patients with creatinine clearance greater than 35 mL/min. No dose adjustment is recommended for patients with impaired renal function.[14]

HIV-1 isolates with reduced susceptibility to enfuvirtide have been selected in vitro. Genotypic analysis of the in vitro-selected resistant isolates showed mutations resulting in amino acid substitutions at the enfuvirtide binding HR1 domain (positions 36 to 38) of the HIV-1 envelope gp41. Phenotypic analysis of site-directed mutants

at positions 36 to 38 in an HIV-1 molecular clone showed a 5-fold to 684-fold decrease in susceptibility to enfuvirtide.[15]

Enfuvirtide exhibited additive to synergistic effects in vitro when combined with individual members of various antiretroviral classes, including zidovudine, lamivudine, nelfinavir, indinavir, and efavirenz. In vitro studies of enfuvirtide in combination with an investigational HIV-1 entry inhibitor, PRO542, and with an investigational CXCR4 blocker, AMD-3100, indicated that these compounds show synergistic antiviral activity. It is unknown whether this synergy will translate into clinical benefit.[16] [17]

In clinical trials, HIV-1 isolates with reduced susceptibility to enfuvirtide have been recovered from patients failing an enfuvirtide containing regimen. Post-treatment HIV-1 virus from 227 patients experiencing virologic failure at 48 weeks exhibited decreases in susceptibility to enfuvirtide. The decreased susceptibility ranged from 0.4- to 6318-fold (median 33.4-fold) relative to their respective baseline virus and coincided with 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.[18]

HIV-1 clinical isolates resistant to nucleoside analogue reverse transcriptase inhibitors, non-nucleoside analogue reverse transcriptase inhibitors, and protease inhibitors were susceptible to enfuvirtide in cell culture.[19]

## Adverse Events/Toxicity

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The most common adverse effects associated with enfuvirtide use include local injection site reactions, peripheral neuropathy, sinusitis, conjunctivitis, pancreatitis, skin papilloma, anxiety, decreased appetite, asthenia, cough, depression, herpes simplex, pruritis, insomnia, myalgia, and weight loss.[20]

The majority of local injection site reactions were associated with mild to moderate pain and discomfort, induration, erythema, nodules and cysts, pruritus, and ecchymosis. Infection at the

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## Adverse Events/Toxicity (cont.)

injection site, including abscess and cellulitis, was reported in 1.7% of study patients receiving enfuvirtide. Ninety-eight percent of patients had at least one local injection site reaction, and 7% of patients discontinued enfuvirtide treatment due to these reactions.[21]

Nerve pain (neuralgia and/or paresthesia) lasting up to 6 months associated with administration at anatomical sites where large nerves course through the skin, bruising, and hematomas have occurred with use of the needle-free device provided with the product. Individuals taking anticoagulants or who have hemophilia or other coagulation disorders may have a higher risk of postinjection bleeding after enfuvirtide use.[22]

An increased rate of bacterial pneumonia was observed in trial patients treated with enfuvirtide compared to control patients. It is unclear if the increased incidence of pneumonia is related to enfuvirtide use. Risk factors for pneumonia included low initial CD4 count, high initial viral load, IV drug use, smoking, and a prior history of lung disease.[23]

Hypersensitivity reactions have been associated with enfuvirtide therapy and may recur on rechallenge. Hypersensitivity reactions have included rash, fever, nausea and vomiting, chills, rigors, hypotension, and elevated serum liver transaminases. Other adverse events that may be immune-mediated and have been reported in patients receiving enfuvirtide 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 enfuvirtide and should seek medical evaluation immediately. Therapy with enfuvirtide 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 enfuvirtide have not been identified.[24]

There is a theoretical risk that enfuvirtide use may lead to the production of anti-enfuvirtide antibodies that cross react with HIV gp41. This could result in

a false-positive enzyme-linked immunosorbent assay (ELISA) diagnostic HIV test in HIV uninfected patients. A confirmatory western blot test would be expected to be negative in such cases.[25]

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including enfuvirtide. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis, which may necessitate further evaluation and treatment.[26]

## Drug and Food Interactions

Based on the results from an in vitro study, enfuvirtide is not an inhibitor of CYP450 enzymes. In a human metabolism study, enfuvirtide, at the recommended dose of 90 mg twice daily, did not alter the metabolism of CYP3A4, CYP2D6, CYP1A2, CYP2C19, or CYP2E1 substrates.[27]

Coadministration of ritonavir, saquinavir/ritonavir, and rifampin did not result in clinically significant pharmacokinetic interactions with enfuvirtide. No drug interactions with other antiretroviral medications have been identified that would warrant alteration of either the enfuvirtide dose or the dose of the other antiretroviral medication.[28]

Enfuvirtide exhibited additive to synergistic effects in vitro when combined with individual members of various antiretroviral classes, including zidovudine, lamivudine, nelfinavir, indinavir, and efavirenz. In vitro studies of enfuvirtide in combination with an investigational HIV-1 entry inhibitor, PRO542[29], and with an investigational CXCR4 blocker, AMD-3100[30]

## Contraindications

Enfuvirtide is contraindicated in patients with known hypersensitivity to the drug or any of its components.[31]

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## Clinical Trials

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For information on clinical trials that involve Enfuvirtide, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Enfuvirtide AND HIV Infections.

## Dosing Information

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Mode of Delivery: Subcutaneous injection.[32]

Dosage Form: Single-use glass vials containing enfuvirtide 108 mg for the delivery of approximately 90 mg/mL when reconstituted with 1.1 ml of Sterile Water for Injection. Enfuvirtide is available in a convenience kit containing 60 single-use vials with appropriate ancillary supplies.[33]

The recommended dose of enfuvirtide for adults is 90 mg (1 mL) twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen.[34] For children age 6 to 16 years, the recommended dose is 2 mg/kg twice daily (maximum dose 90 mg twice daily). The manufacturer's prescribing information provides pediatric dosing guidelines by weight. Insufficient data are available to establish a recommended dose for children younger than 6 years of age.[35]

Each injection should be given at a different site from the preceding injection site and only where there is no ongoing injection site reaction from a previous dose. Enfuvirtide should not be injected near any areas of the body 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, or bruises; or near the navel, surgical scars, tattoos, or burn sites.[36]

Storage: Store vials at 25 C (77 F); excursions permitted from 15 C to 30 C (59 F to 86 F).[37]

Store reconstituted solution under refrigeration at 2 C to 8 C (36 F to 46 F) and use within 24 hours.[38]

## Chemistry

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CAS Name:

L-Phenylalaninamide,N-acetyl-L-tyrosyl-L-threonyl-L-seryl-L-leucyl-L-isoleucyl-L-histadyl-L-seryl-L-leucyl-L-isoleucyl-L-alpha-glutamyl-L-a-glutamyl- L-seryl-L-glutaminyll-asparaginyll-glutaminyll-glutaminyll-alpha- glutamyl-L-lysyl-L-asparaginyll-alpha- glutamyl-L-glutaminyll-alpha-glutamyl-L-leucyl-L-leucyl-L-alpha-glutamyl- L-leucyl-L-alpha-aspartyl-L-lysyl- L-tryptophyl-L-alan[39]

CAS Number: 159519-65-0[40]

262434-79-7[41]

Molecular formula: C204-H301-N51-O64[42]

C54.55%, H6.75%, N15.90%, O22.80%[43]

Molecular weight: 4491.88[44]

Physical Description: White to off-white sterile lyophilized powder.[45]

Stability: Reconstituted solution should be stored under refrigeration at 2 C to 8 C (36 F to 46 F) and used within 24 hours.[46]

Solubility: Negligible solubility in pure water; 85 to 142 g/100 mL in aqueous buffers (pH 7.5).[47]

## Other Names

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DP 178[48]

DP178[49]

T-20[50]

T 20[51]

T20[52]

Pentafuside[53]

## Further Reading

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## **Further Reading (cont.)**

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## **Manufacturer Information**

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Enfuvirtide  
Roche Laboratories  
340 Kingsland Street  
Nutley, NJ 07110  
(973) 235-5000

Enfuvirtide  
Trimeris Inc  
4727 Univ Dr  
Durham, NC 27707  
(919) 419-6050

Fuzeon  
Roche Laboratories  
340 Kingsland Street  
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## **For More Information**

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Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: [http://aidsinfo.nih.gov/live\\_help](http://aidsinfo.nih.gov/live_help) Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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