

Enfuvirtide

Brand Name: Fuzeon

Drug Description

Enfuvirtide 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 is being studied to determine if it will decrease the level of HIV in resting CD4 cells in patients starting an antiretroviral drug regimen for the first time.[4]

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.[5]

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.

Following 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.[6]

The mean maximum plasma concentration (C_{max}) following a single 90 mg subcutaneous (SQ) injection of enfuvirtide into the abdomen in 12 HIV-1 infected adult and pediatric patients was approximately 4.59 mcg/ml; area under the plasma concentration-time curve (AUC) was approximately 55.8 mcg/h/ml, and the median time to maximum plasma concentration (T_{max}) was 8 hours (ranging from 3 to 12 h). The absolute bioavailability (using a 90 mg intravenous 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_{max} was approximately 5.0 mcg/ml and AUC from zero to 12 hours was approximately 48.7 mcg/h/ml. The median T_{max} was 4 hours (with a range 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. The mean steady-state volume of distribution after IV administration of a 90 mg dose of enfuvirtide was approximately 5.5 liters.[7]

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 M3 metabolite is detected in human plasma following administration of enfuvirtide, with an AUC ranging from 2.4% to 15% of the enfuvirtide AUC.[8]

Following a 90 mg single SQ dose of enfuvirtide

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Pharmacology (cont.)

(N=12), the mean elimination half-life is 3.8 to 6 h and the mean apparent clearance is approximately 24.8 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 ml/h/kg.

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.[9]

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 calling 1-800-258-4263 or at www.APRegistry.com.

It is not known whether enfuvirtide is distributed into human milk; however, it is distributed into milk in laboratory animals. Because of the potential for HIV transmission and adverse effects in breast-fed infants, mothers should be instructed not to breast-feed while they are taking enfuvirtide.[10]

Formal pharmacokinetic studies of enfuvirtide have not been conducted in patients with renal insufficiency. There are indications that the clearance of enfuvirtide is not affected in patients with creatinine clearance greater than 35 ml/min. Formal pharmacokinetic studies of enfuvirtide have not been conducted in patients with hepatic impairment.

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

HIV-1 isolates with reduced susceptibility to enfuvirtide have been selected in vitro. Genotypic

analysis of the in vitro-selected resistant isolates showed mutations in the gp41 HRI domain (amino acids 36 to 38). Phenotypic analysis of site-directed mutants at positions 36 to 38 in an HIV-1 molecular clone showed a fivefold to 684-fold decrease in susceptibility to enfuvirtide.

In clinical trials, HIV-1 isolates with reduced susceptibility to enfuvirtide have been recovered from patients treated with enfuvirtide in combination with other antiretroviral agents. Post-treatment HIV-1 virus from 185 patients exhibited decreases in susceptibility to enfuvirtide. The decreased susceptibility ranged from 4-fold to 422-fold relative to their respective baseline virus and coincided with genotypic changes in gp41 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.

HIV-1 clinical isolates resistant to nucleoside analogue reverse transcriptase inhibitors (NRTIs), nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) were susceptible to enfuvirtide in vitro.[11]

Adverse Events/Toxicity

The most common adverse events associated with enfuvirtide use were local injection site reactions. The majority of reactions were associated with mild to moderate pain and discomfort, induration, erythema, nodules and cysts, pruritus, and ecchymosis. Infection at the injection site, including abscess and cellulitis, was reported in 1% of study patients receiving enfuvirtide. Nine percent of patients had local reactions, often at more than one injection site, that required analgesics or limited usual activities; 98% of patients had at least one local injection site reaction and 3% of patients discontinued enfuvirtide treatment due to injection site reactions.[12]

An increased rate of bacterial pneumonia was observed in trial patients treated with enfuvirtide compared to control patients not treated with enfuvirtide. It is unclear if the increased incidence of pneumonia is related to enfuvirtide use. Risk factors for pneumonia included low initial CD4 cell count, high initial viral load, IV drug use, smoking, and a prior history of lung disease.

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Adverse Events/Toxicity (cont.)

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.[13]

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.

The events most frequently reported in patients receiving enfuvirtide in combination with an antiretroviral background regimen, excluding injection site reactions, were diarrhea (26.8%), nausea (20.1%), and fatigue (16.1%). These events were also commonly observed in patients who received a background regimen alone: diarrhea (33.5%), nausea (23.7%), and fatigue (17.4%).

Other adverse events reported in greater than 2% of patients in clinical trials include anorexia; anxiety; asthenia; conjunctivitis; constipation; cough; decreased weight; depression; herpes simplex infection; influenza-like illness; insomnia; lymphadenopathy; myalgia; pancreatitis; peripheral neuropathy; pruritus; taste disturbance; sinusitis; skin papilloma; and upper abdominal pain.[14]

Drug and Food Interactions

Based on the results from an in vitro study,

enfuvirtide is not an inhibitor of CYP450 enzymes. A human metabolism study reported that enfuvirtide did not alter the metabolism of CYP3A4, CYP2D6, CYP1A2, CYP2C19, or CYP2E1 substrates.

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.[15]

In vitro studies of enfuvirtide in combination with an investigational HIV-1 entry inhibitor, PRO542,[16] and with an investigational CXCR4 blocker, AMD-3100,[17] indicated that these compounds show synergistic antiviral activity. It is unknown whether this synergy will translate into clinical benefit.[18] [19]

Contraindications

Enfuvirtide is contraindicated in patients with known hypersensitivity to the drug or any of its components.[20]

Clinical Trials

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

Mode of Delivery: Subcutaneous (SQ) injection.[21]

Dosage Form: Single-use glass vials containing 108 mg of enfuvirtide 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.

The recommended dose of enfuvirtide is 90 mg (1 ml) twice daily. For children age 6 to 16 years, the recommended dose is 2 mg/kg twice daily (maximum dose 90 mg twice daily). The

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Dosing Information (cont.)

manufacturer's prescribing information provides pediatric dosing guidelines by weight.[22]

Storage: Store at 25 C (77 F); excursions permitted to 15 to 30 C (59 to 86 F).[23]

Chemistry

CAS Number: 159519-65-0[24]

Molecular formula: C₂₀₄H₃₀₁N₅₁O₆₄[25]

C54.55%, H6.75%, N15.90%, O22.80%[26]

Molecular weight: 4492[27]

Physical Description: Enfuvirtide is a white to off-white sterile amorphous solid.[28]

Stability: Reconstituted solution should be stored under refrigeration at 2 C to 8 C (36 F to 46 F) and used within 24 hours.[29]

Solubility: Enfuvirtide has negligible solubility in pure water; the solubility increases in aqueous buffers (pH 7.5) to 85 to 142 g/100 ml.[30]

Other Names

DP 178[31]

DP178[32]

T-20[33]

T 20[34]

T20[35]

Pentafuside[36]

Further Reading

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Manufacturer Information

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

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For More Information (cont.)

- 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 Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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