



CIGNA PHARMACY COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

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Subject **Enfuvirtide (Fuzeon®)**

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INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Position

CIGNA covers enfuvirtide (Fuzeon®) as medically necessary for EITHER of the following indications:

- treatment of human immunodeficiency virus type 1 (HIV-1) infection in conjunction with other antiretroviral agents
- post-exposure prophylaxis in healthcare workers

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to Enfuvirtide (Fuzeon®).

FDA Approved Indications

Fuzeon in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. This indication is based on results from two controlled studies of 48 weeks duration. Subjects enrolled were treatment-experienced adults; many had advanced disease. There are no studies of Fuzeon in antiretroviral naive subjects.

FDA Recommended Dosing

Adults

The recommended dose of Fuzeon is 90 mg (1 mL) twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen.

Pediatric Patients

Insufficient data are available to establish a dose recommendation of Fuzeon in pediatric patients below the age of 6 years. In pediatric patients 6 years through 16 years of age, the recommended dosage of Fuzeon is 2 mg/kg twice daily up to a maximum dose of 90 mg twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen.

Drug Availability

Fuzeon 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 also 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.

General Background

Pharmacology

Enfuvirtide, a synthetic 36-amino acid peptide antiretroviral agent, is a human immunodeficiency virus (HIV) fusion inhibitor. Enfuvirtide interferes with entry of HIV type 1 (HIV-1) into target cells by inhibiting fusion of the viral and cellular membranes. Enfuvirtide binds to heptad repeat 1 (HR1) in the envelope glycoprotein 41 (gp41) of HIV-1 that is involved in fusion of the virus with the membrane of the host CD4+ T-cell. Binding of enfuvirtide to gp41 blocks conformational changes in the HIV-1 glycoprotein that are required for fusion of the viral and cell membranes. This blockage prevents entry of the viral genome into the healthy CD4+ T-cell.

In vitro studies indicate that enfuvirtide is active against HIV-1, but is inactive against HIV type 2 (HIV-2). HIV-1 strains with reduced susceptibility to enfuvirtide can be produced in vitro, and strains with reduced susceptibility to enfuvirtide have emerged during therapy with the drug. These strains have contained mutations in the HR1 domain of gp41 within the region of amino acids 36–45.

Cross-resistance between enfuvirtide and nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), or HIV protease inhibitors (PIs) is highly unlikely, since the drugs have different mechanisms of action. In vitro studies demonstrate that the antiretroviral effects of enfuvirtide and some NRTIs (lamivudine, zidovudine), NNRTIs (efavirenz), or PIs (indinavir, nelfinavir) can be additive or synergistic against HIV-1.

The pharmacokinetics of enfuvirtide has been evaluated in a limited number of HIV-infected adults and pediatric patients. Enfuvirtide is almost completely absorbed following subcutaneous injection (absolute bioavailability: 84.3%). Systemic absorption is comparable following subcutaneous injection of a 90 mg dose into the abdomen, arm, or thigh. Because enfuvirtide is a peptide, it is expected to undergo catabolism to its constituent amino acids. In vitro studies indicate that enfuvirtide undergoes hydrolysis (not nicotinamide adenine dinucleotide phosphate [NADPH] dependent) to form a deaminated metabolite.

Guidelines

The U.S. Public Health Service guidelines for the management of occupational exposures to HIV recommend the use of enfuvirtide for post-exposure prophylaxis only with expert consultation, ideally persons who have expertise in antiretroviral treatment and HIV transmission. Enfuvirtide should only be used in conjunction with other antiretroviral agents for post-exposure prophylaxis of HIV infection when there is known or suspected risk of HIV resistance.

Fuzeon is recommended as an alternative agent for use in conjunction with other antiretroviral agents for post-exposure prophylaxis of HIV infection in healthcare workers and other individuals exposed occupationally via

percutaneous injury or mucous membrane or non-intact skin contact with blood, tissues, or other body fluids associated with a risk for transmission of the virus. Although Fuzeon is not recommended for routine post-exposure prophylaxis following occupational exposure to HIV because the drug is administered subcutaneously, some experts suggest that Fuzeon can be considered for use in expanded regimens with expert consultation.

Clinical Efficacy

Safety and efficacy of enfuvirtide used in conjunction with other antiretroviral agents have been evaluated in two randomized, open-label, multicenter, international studies in 997 previously treated adults (study T20–301 [T-20 vs. Optimized Regimen Only (TORO) 1] and T20–302 [TORO 2]). Enrolled patients in these studies were adults older than 16 years of age (mean age: 42–43 years; 90% male; 89% white; 7–8% black; median baseline plasma HIV-1 ribonucleic acid [RNA] level: 5.1–5.2 log₁₀ copies/ml; median baseline CD4⁺ T-cell count: 89–97 cells/mm³) who had viremia despite at least 3–6 months of prior therapy with antiretroviral regimens that included an NRTI, an NNRTI, and a PI or who had viremia and documented intolerance or resistance to at least one drug in each class of antiretroviral agents. All patients received an optimized background antiretroviral regimen consisting of 3–5 antiretroviral agents selected on the basis of the individual's prior antiretroviral treatment and results of baseline genotypic and phenotypic viral resistance testing and were randomized to receive enfuvirtide in conjunction with the optimized regimen or the optimized regimen alone. Efficacy data was analyzed based on the intent-to-treat population. Analysis at 48 weeks indicated that enfuvirtide added to an optimized antiretroviral regimen resulted in greater decreases in plasma HIV-1 RNA levels (-1.4 log₁₀ copies/ml) than the optimized background regimen alone (-0.5 log₁₀ copies/ml); a reduction in plasma HIV-1 RNA levels of at least one log₁₀ copies/ml below baseline was achieved in 46% of those receiving enfuvirtide in conjunction with the optimized regimen compared with 18% of those receiving the optimized regimen alone. At 48 weeks, 34 and 23% of adults receiving enfuvirtide in conjunction with an optimized antiretroviral regimen and 13 and 8% of those receiving the optimized regimen alone had plasma HIV-1 RNA levels less than 400 or 50 copies/ml, respectively. At 48 weeks, increases in CD4⁺ T-cell counts were greater in patients receiving enfuvirtide in conjunction with an optimized antiretroviral regimen (increase of 91 cells/mm³) than in those receiving the optimized regimen alone (increase of 45 cells/mm³).

Enfuvirtide used in conjunction with two or more other antiretroviral agents selected on the basis of the individual's prior antiretroviral treatment and results of baseline genotypic and phenotypic viral resistance testing also has been evaluated in an uncontrolled, open-label, phase II study designed to evaluate the long-term safety and antiretroviral activity of an enfuvirtide-containing regimen (study T20–205). At 48 weeks, 32.9% of adults (mean baseline antiretroviral exposure: 9.5 drugs; mean baseline plasma HIV-1 RNA level: greater than 4.81 log₁₀ copies/ml; mean baseline CD4⁺ T-cell count: 134.8 cells/mm³) receiving enfuvirtide (45 mg every 12 hours) in conjunction with other antiretroviral agents achieved a virologic response (i.e., a reduction in plasma HIV-1 RNA levels of at least one log₁₀ copies/ml below baseline or plasma HIV-1 RNA levels below 400 copies/ml) (intent-to-treat analysis). The mean increase in CD4⁺ T-cell count was 84.9 cells/mm³ at 48 weeks.

Fuzeon must be paired with at least one other antiretroviral agent that is active in vitro according to HIV resistance tests and drug history. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in controlled studies of 48 weeks' duration. Subjects enrolled were treatment-experienced adults, many of whom had advanced disease. There are no studies of enfuvirtide in antiretroviral-naïve patients.

Adverse Reactions / Drug Interactions

The most common adverse effects reported with enfuvirtide are injection site reactions. Other adverse effects reported in 2% or more of patients receiving enfuvirtide in conjunction with other antiretrovirals include: abdominal pain, anorexia, anxiety, conjunctivitis, cough, decreased weight, decreased appetite, dry mouth, folliculitis, herpes simplex, influenza-like illness, limb pain, myalgia, pancreatitis, pneumonia, and sinusitis.

Enfuvirtide is not an inhibitor of cytochrome P450 enzymes. At the 90 mg dose administered twice daily, it did not alter the metabolism of CYP3A4, CYP2D6, CYP1A2, CYP2C19, or CYP2E1 substrates. Clinically important drug interactions were not observed when enfuvirtide was administered with ritonavir, saquinavir/ritonavir, or rifampicin. Concomitant administration with ritonavir increased enfuvirtide peak concentration 24%, the AUC 22%, and the trough concentration 14%. Concomitant administration with saquinavir/ritonavir increased the AUC 14% and the trough concentration 26%. Concomitant administration with rifampicin reduced the enfuvirtide trough concentration 15%. None of the interactions were considered clinically significant.

Coding/Billing Information

Note: This section is not in use.

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