

PRODUCT MONOGRAPH

PrFUZEON[®]

enfuvirtide for injection

Single-use vials - 108 mg/vial

Antiviral Agent (HIV-1 Fusion Inhibitor)

Hoffmann-La Roche Limited
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Mississauga, Ontario
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PrFUZEON®

enfuvirtide for injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Subcutaneous injection	Single-use vial / 108 mg/vial	mannitol <i>For a complete listing of non-medicinal ingredients see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

FUZEON (enfuvirtide) 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.

Geriatrics (>65 years of age): Clinical studies of FUZEON did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Pediatrics: The safety and pharmacokinetics of FUZEON have not been established in pediatric patients below 6 years of age. Limited data are available in pediatric patients 6 years and older (see CLINICAL TRIALS: Pediatric Patients).

CONTRAINDICATIONS

- FUZEON (enfuvirtide) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Hypersensitivity reactions have been associated with the use of FUZEON (enfuvirtide) in clinical trials (<1%). See section on hypersensitivity reactions below.

General

FUZEON should always be used in combination with other antiretroviral agents.

FUZEON should not be used in antiretroviral treatment-naïve patients.

Alcohol pads, needed by the patient to ensure safe use of the product, are not included in the FUZEON kit. Instruct your patient to purchase alcohol pads at the time FUZEON is prescribed to them (see DOSAGE AND ADMINISTRATION and PART III: CONSUMER INFORMATION).

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

Carcinogenesis and Mutagenesis

Animal carcinogenicity studies of enfuvirtide are ongoing. Enfuvirtide was neither mutagenic nor clastogenic in a series of *in vivo* and *in vitro* assays (see TOXICOLOGY: Mutagenicity).

Hypersensitivity Reactions

Hypersensitivity reactions have been associated with therapy with FUZEON and may recur on re-challenge. Hypersensitivity reactions have occurred in <1% of patients studied and have included individually and in combination: 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 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 (see ADVERSE REACTIONS).

Immune

Immune Reconstitution Inflammatory Syndrome: Immune Reconstitution Syndrome has been reported in patients treated with combination antiretroviral therapy, including FUZEON. During the initial phase of combination antiretroviral treatment, a patient whose immune system

responds to therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP and TB) which may necessitate further evaluation and treatment.

Autoimmune disorders such as Graves' disease and Guillain-Barré syndrome have also been reported in the setting of immune reconstitution; however, the time to onset is variable, and can occur many months after initiation of treatment.

Respiratory

Pneumonia: An increased rate of bacterial pneumonia was observed in patients treated with FUZEON in the Phase III clinical trials compared to the control arm (see ADVERSE REACTIONS). It is unclear if the increased incidence of pneumonia is related to the use of FUZEON. Patients with HIV infection should be 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 lymphocyte count, high initial viral load, intravenous drug use, smoking and prior history of lung disease.

Skin

Local Injection Site Reactions: Local injection site reactions were the most common adverse events associated with the use of FUZEON (98% of patients in Phase III clinical trials had at least one local injection site reaction). Manifestations may include pain and discomfort, induration, erythema, nodules and cysts, pruritus and ecchymosis. Local site reactions that required analgesics or limited usual activities were seen in 11% of patients (see ADVERSE REACTIONS). Patients must be familiar with the 'FUZEON Injection Instructions' in order to know how to inject FUZEON appropriately and how to monitor carefully for signs or symptoms of cellulitis or local infection.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. Enfuvirtide produced no adverse effects on the developing conceptus in teratology studies conducted at exposures of up to 8.9 times higher in rats and 3.2 times higher in rabbits, than estimated human therapeutic exposures. FUZEON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

Nursing Women: It is not known whether enfuvirtide is secreted in human milk. Studies where radio-labeled ³H-enfuvirtide was administered to lactating rats indicated that a very low level of radioactivity was present in the milk. Because of both the potential for HIV transmission and any possible adverse effects in nursing infants, mothers should be instructed not to breast-feed if they

are receiving FUZEON.

Pediatrics: The safety and pharmacokinetics of FUZEON have not been fully established in pediatric patients below 6 years of age, as there were too few patients studied in this age group. Limited efficacy data are available in pediatric patients 6 years of age and older (see CLINICAL TRIALS: Pediatric Clinical Trials).

Geriatrics (> 65 years of age): Clinical studies of FUZEON did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In clinical studies the most serious adverse reactions observed with FUZEON (enfuvirtide) were hypersensitivity reactions and pneumonia. Local injection site reactions were the most common adverse events associated with the use of FUZEON.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The overall safety profile of FUZEON (enfuvirtide) is based on 2120 patients who received at least 1 dose of FUZEON during various clinical trials. The safety population consisted of 2051 adults including 658 adults who have been exposed to the recommended dose for greater than 48 weeks and 69 pediatric patients.

Assessment of treatment-emergent adverse events is based on the pooled data from the two Phase III studies TORO-1 and TORO-2. In these studies FUZEON was administered subcutaneously at a dose of 90 mg bid in combination with a background regimen to 663 patients. A total of 334 patients received background antiretroviral agents alone as the control arm.

In the TORO-1 and TORO-2 studies, after study week 8, patients on background alone who met protocol defined criteria for virological failure were permitted to revise their background regimens and add FUZEON. At week 48 of the study the cumulative exposure to 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.

Treatment-emergent adverse events, excluding injection site reactions, from the Phase III studies

(TORO-1 and TORO-2) are summarized for adult patients, regardless of severity and causality in Table 1. Only events occurring at ≥ 2 per 100 patient-years and at a higher rate in patients treated with FUZEON are summarized in the table; events that occurred at a higher rate in the control arms are not displayed.

Table 1: Rates (per 100 patient-years of exposure) of Patients with Selected Treatment-Emergent Adverse Events* Reported in ≥ 2 per 100 Patient-years for Adult Patients and Occurring More Frequently in Patients Treated With FUZEON (Pooled Studies TORO-1/TORO-2 at 48 Weeks)

Adverse Event (by System Organ Class)	FUZEON+ Background Regimen (N=663)	Background Regimen (N=334)
Total Exposure (patient-years)	557	162
Blood and lymphatic system disorders Lymphadenopathy	5.9	1.2
Ear and labyrinth disorders Vertigo	3.6	0.6
Eye disorders Conjunctivitis	4.1	2.5
Gastrointestinal disorders Pancreatitis Gastro-oesophageal reflux disease	3.6 2.7	2.5 2.5
General disorders and administrative site conditions Influenza like illness Weakness	4.5 2.7	3.7 0.6
Infections and Infestations Sinusitis Influenza Skin Papilloma Pneumonia Ear infection	9.5 6.5 6.6 3.6 2.2	6.2 6.2 3.1 0.6 1.2
Immune system disorders Hypersensitivity	2.0	1.9
Investigations Weight decreased Blood triglycerides increased Haematuria present	11.1 2.9 2.2	10.5 1.9 1.9
Metabolism and nutrition disorders Appetite decreased Anorexia Hypertriglyceridaemia	8.6 3.8 2.0	4.9 3.1 1.9

Adverse Event (by System Organ Class)	FUZEON+ Background Regimen (N=663)	Background Regimen (N=334)
Diabetes mellitus	2.0	0.6
Musculoskeletal, connective tissue and bone disorders Myalgia	7.0	5.6
Nervous system disorders Peripheral neuropathy	15.4	13.6
Hypoaesthesia	2.9	1.9
Disturbance in attention	2.3	1.9
Tremor	2.2	1.9
Psychiatric disorders Anxiety	7.5	6.8
Irritability	2.3	1.9
Nightmare	2.3	1.2
Renal and urinary disorders Calculus renal	2.3	1.2
Respiratory, thoracic and mediastinal disorders Nasal congestion	3.1	2.5
Skin and subcutaneous tissue disorders Dry skin	5.0	4.3
Eczema seborrhoeic	2.3	1.9
Erythema	2.2	1.2
Acne	2.0	0.6

*Excludes Injection Site Reactions

Hypersensitivity reactions have been attributed to FUZEON ($\leq 1\%$) and in some cases have recurred upon re-challenge (see WARNINGS AND PRECAUTIONS).

The events most frequently reported in patients receiving FUZEON+background regimen, excluding injection site reactions, were diarrhea (38 per 100 patient-years), nausea (27 per 100 patient-years), and fatigue (24 per 100 patient-years). All these events were seen at a lower incidence than in patients that received background regimen alone: diarrhea (73 per 100 patient-years), nausea (50 per 100 patient-years), and fatigue (38 per 100 patient-years). The addition of FUZEON to background antiretroviral therapy generally did not increase the frequency or severity of most adverse events.

Rates of adverse events for patients who switched to FUZEON after virological failure were similar. The only adverse events with a statistically significant risk ratio between the FUZEON regimen and the background regimen alone were pneumonia and lymphadenopathy. Most adverse events were of mild or moderate intensity.

The incidence of pneumonia was 3.6 events/100 patient-years in subjects on the FUZEON+background regimen. On analysis of all diagnoses of pneumonia (pneumonia,

bacterial pneumonia, bronchopneumonia, and related terms) in the Phase 3 clinical trials, an increased rate of bacterial pneumonia was observed in subjects on FUZEON+background compared to background alone (6.6 pneumonia events per 100 patient-years versus 0.6 events per 100 patient-years). Approximately half of the study subjects with pneumonia required hospitalization. Three subject deaths in the FUZEON arm 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. It is unclear if the increased incidence of pneumonia was related to the use of FUZEON. However, because of this finding patients with HIV infection should be carefully monitored for signs and symptoms of pneumonia, especially if they have underlying conditions which may predispose them to pneumonia (see WARNINGS AND PRECAUTIONS). In uncontrolled studies in which only safety events were monitored, a rate of 2.1 pneumonia events per 100 patient-years was reported. The safety population for these studies comprised 1166 patients with exposure to FUZEON of 522 patient-years. Three cases of pneumonia resulted in death; risk factors for pneumonia in two of these cases included low CD4 count at initiation of therapy and one of these cases also had a prior history of recurrent pneumonia.

Local Injection Site Reactions (ISRs)

Local injection site reactions were the most frequent adverse events associated with the use of FUZEON. In the TORO-1 and TORO-2 studies combined, 98% of patients had at least 1 local injection site reaction and 4% of patients discontinued treatment with FUZEON because of injection site reactions (see Table 2). Injection site reactions were generally seen within the first week of initiating therapy with FUZEON, and for the majority were associated with either mild tenderness or moderate pain at the injection site without limitation of usual activities. The percentage of patients that required analgesics or limited usual activities was 11% (Grade 3 reactions). The severity of the pain and discomfort associated with injection site reactions did not increase with treatment duration. The signs/symptoms characterizing the injection site reactions generally lasted ≤ 7 days and the average number of injection site reactions evident at any given study visit was ≤ 5 (in the 72% of patients with injection site reactions evident). In 24% of subjects an individual injection site reaction lasted for longer than 7 days. Individual signs and symptoms characterizing local injection site reactions are summarized in Table 2. Infection at the injection site (including abscess and cellulitis) was reported in 2.4 per 100 patient-years.

Table 2: Summary of Individual Signs/Symptoms Characterizing Local Injection Site Reactions to Enfuvirtide in Studies TORO-1 and TORO-2 Combined (% of Subjects) through 48 Weeks

	N=663		
Withdrawal Rate Due to Injection Site Reactions	4%		
Event Category	FUZEON+ Background Regimen^a	% of Events Comprising Grade 3 Reactions	% of Events Comprising Grade 4 Reactions
Pain/Discomfort	96%	11% ^b	0% ^b
Induration	90%	44% ^c	19% ^c

Erythema	91%	24% ^d	11% ^d
Nodules and Cysts	80%	29% ^e	0.2% ^e
Pruritus	65%	4% ^f	NA ^f
Ecchymosis	52%	9% ^g	5% ^g

a Any severity grade

b Grade 3 = severe pain requiring analgesics (or narcotic analgesics for ≤ 72 hours) and/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.

c Grade 3 = ≥ 25 mm but <50 mm average diameter; Grade 4 = ≥ 50 mm average diameter

d Grade 3 = ≥ 50 mm but <85 mm average diameter; Grade 4 = ≥ 85 mm average diameter

e Grade 3 = ≥ 3 cm; Grade 4 = if draining

f Grade 3 = refractory to topical treatment or requiring oral or parenteral treatment; Grade 4 = not defined

g Grade 3 = >3 cm but ≤ 5 cm; Grade 4 = >5 cm

A non-blinded, randomized, 4 cohort, crossover study (N=66) evaluated the effects of gentle manual massage, heated moist cloth, topical hydrocortisone (1% cream) and self vs partner injection on ISRs. The severity of ISR signs and symptoms with each intervention was compared with no intervention (control) based on patient recall and clinical assessments. In general, manual gentle massage, and partner injection appear to be interventions that may offer a slight benefit in some patients for reducing the severity of ISR signs and symptoms.

Adverse Events in Pediatric Patients

FUZEON has been studied in 69 pediatric patients 4 through 16 years of age with duration of exposure to FUZEON ranging from 1 dose to 134 weeks. Adverse reactions seen during clinical trials were similar to those observed in adult patients.

Less Common Clinical Trial Adverse Events

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

Blood and Lymphatic Disorders: thrombocytopenia with neutropenia and fever

Cardiac Disorders: unstable angina pectoris

Endocrine and Metabolic: hyperglycemia

Gastrointestinal Disorders: constipation; abdominal pain upper

General: asthenia

Hepato-Biliary Disorders: toxic hepatitis; hepatic steatosis

Immune System Disorders: worsening abacavir hypersensitivity reaction

Infections: sepsis; herpes simplex

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

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

Psychiatric Disorders: insomnia; depression

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

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

Skin and Subcutaneous Tissue Disorders: pruritus.

Abnormal Hematologic and Clinical Chemistry Findings

Table 3 shows the treatment-emergent laboratory abnormalities that occurred in at least 2 patients per 100 patient-years and more frequently in those receiving FUZEON+background regimen than background regimen alone, from the pooled studies TORO-1 and TORO-2.

Table 3: Percentage of Treatment-Emergent Laboratory Abnormalities That Occurred in ≥ 2 per 100 Patient-years for Adult Patients and More Frequently in Patients Receiving FUZEON (pooled studies TORO-1 and TORO-2, 48 weeks)

Laboratory Parameters	Grading	FUZEON + Background Regimen	Background Regimen
		N=663	N=334
ALT			
Gr. 3	>5-10 x ULN	4.8	4.3
Gr. 4	>10 x ULN	1.4	1.2
Creatine Phosphokinase (U/L)			
Gr. 3	>5-10 x ULN	8.3	8.0
Gr. 4	>10 x ULN	3.1	8.6
Eosinophilia			
1-2 X ULN (0.7×10^9 cells/L)	$0.7-1.4 \times 10^9/L$	10.8	3.7
>2 X ULN (0.7×10^9 cells/L)	$>1.4 \times 10^9/L$	2.2	1.8
Hemoglobin (g/dL)			
Gr. 3	6.5-7.9 g/dL	2.0	1.9
Gr. 4	< 6.5 g/dL	0.7	1.2

Post-Market Adverse Drug Reactions

Skin and Subcutaneous Tissue Disorders: cutaneous amyloidosis at the injection site.

DRUG INTERACTIONS

Overview

CYP450 Metabolized Drugs

Results from *in vitro* and *in vivo* studies suggest that enfuvirtide is unlikely to have significant drug interactions with concomitantly administered drugs metabolized by CYP450 enzymes.

Antiretroviral Agents

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.

Drug-Drug Interactions

Influence of FUZEON (enfuvirtide) on the Metabolism of Concomitant 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 bid did not affect the metabolic activity of CYP3A4, CYP2D6 and N-acetyltransferase, increased the metabolic activity of CYP2C19 by 13% (90% CI: -2% to +28%) and of CYP2E1 by 8% (90% CI: -13% to +29%) and decreased the metabolic activity for CYP1A2 by 6% (90% CI: -29% to +17%).

Influence of Concomitant Drugs on the Metabolism of Enfuvirtide: In separate pharmacokinetic interaction studies, coadministration of ritonavir (N=12), saquinavir/ritonavir (N=12), and rifampin (N=12) did not result in clinically significant pharmacokinetic interactions with FUZEON (see Table 4).

Table 4: 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 ^{†#} (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 sequential crossover design.

† ↑=increase; ↓=decrease; ↔ = No Effect (↑ or ↓ < 10%)

No interactions were clinically significant

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Adults: The recommended dose of FUZEON (enfuvirtide) is 90 mg (1 mL) twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen. The injection should be given at a site different from the preceding injection site and where there is no current injection site reaction from an earlier dose. Also, do not inject into moles, scar tissue, bruises, and navel (see PART III: FUZEON Injection Directions).

Pediatric Patients: There are insufficient data available to establish a dose recommendation of FUZEON in pediatric patients below the age of 6 years. Based on limited data in pediatric patients 6 through 16 years of age, it is expected that a dosage of 2.0 mg/kg twice daily up to a maximum dose of 90 mg bid injected subcutaneously into the upper arm, anterior thigh or abdomen will produce enfuvirtide plasma concentrations similar to those achieved in adult patients receiving 90 mg bid dosage. The injection should be given at a site different from the preceding injection site and where there is no current injection site reaction from an earlier dose. Do not inject into moles, scar tissue, bruises, and navel (see Injection Directions). Table 5 contains dosing guidelines for FUZEON based on body weight. Weight should be monitored periodically and the dose of FUZEON adjusted accordingly.

Table 5: Pediatric Dosing Guidelines

Weight		Dose per bid injection (mg/dose)	Injection volume (90 mg enfuvirtide per mL)
Kilograms (kg)	Pounds (lbs)		
11.0 to 15.5	24.2 to 34.1	27	0.3 mL
15.6 to 20.0	34.2 to 44.0	36	0.4 mL
20.1 to 24.5	44.1 to 53.9	45	0.5 mL
24.6 to 29.0	54.0 to 63.8	54	0.6 mL
29.1 to 33.5	63.9 to 73.7	63	0.7 mL
33.6 to 38.0	73.8 to 83.6	72	0.8 mL
38.1 to 42.5	83.7 to 93.5	81	0.9 mL
≥ 42.6	≥ 93.6	90	1.0 mL

Missed Dose

If a dose of FUZEON is missed, you should take the missed dose as soon as you can and then take the next dose as scheduled. If you have missed a dose of FUZEON and it is close to the time for your next dose, wait and take the next dose as regularly scheduled. Do not take two doses of FUZEON at the same time.

Administration

For more detailed instructions, see PART III: FUZEON Injection Directions.

Before needle insertion, ensure rubbing alcohol, alcohol pads or another antiseptic are used for sterilization of the vials and skin in order to prevent contamination from microorganisms (see PART III: FUZEON Injection Directions). Antiseptics for use in sterilization are not included in the FUZEON convenience kit and must be separately acquired. Instruct your patients to purchase antiseptic pads at the time of dispensing FUZEON to the patient.

FUZEON must only be reconstituted with 1.1 mL of Sterile Water for Injection. After adding the water, the vial should be gently tapped for 10 seconds and then allowed to stand until the powder goes completely into solution, which could take up to 45 minutes. Before the solution is withdrawn for administration, the vial should be inspected visually to ensure that the contents are fully in solution, and that the solution is clear, colourless and without bubbles or particulate matter. If there is evidence of particulate matter, the vial must not be used and should be discarded or returned to the pharmacy.

FUZEON contains no preservative. Once reconstituted, FUZEON should be injected immediately. If the reconstituted FUZEON cannot be injected immediately, it must be kept refrigerated in the vial until use and used within 24 hours. Refrigerated reconstituted solution should be brought to room temperature before injection and the vial should be inspected visually again to ensure that the contents are fully in solution and that the solution is clear, colourless and without bubbles or particulate matter.

The reconstituted solution should be injected subcutaneously in the upper arm, abdomen or anterior thigh. The injection should be given at a site different from the preceding injection site and where there is no current injection site reaction. Also, do not inject into moles, scar tissue, bruises, and navel. A vial is suitable for single use only; unused portions must be discarded.

Patients should contact their healthcare professional for any questions regarding the administration of FUZEON. Patients should be taught to recognize the signs and symptoms of injection site reactions and instructed when to contact their healthcare professional about these reactions.

Reconstitution:

FUZEON Vial Size	Volume of Diluent to be added to FUZEON Vial	Approximate Available Volume	Nominal Concentration per mL
3 mL	1.1 mL	1.2 mL	90 mg/mL*

* 1 mL of the reconstituted solution contains the label claim of 90 mg enfuvirtide.

FUZEON must only be reconstituted with the diluent supplied, 1.1 mL of sterile water for injection. Once reconstituted, FUZEON solution should be injected immediately. If the reconstituted solution cannot be injected immediately it must be refrigerated until use and used within 24 hours.

OVERDOSAGE

There are no reports of human experience of acute overdose with FUZEON (enfuvirtide). The highest dose administered to 12 patients in a clinical trial was 180 mg as a single dose subcutaneously. These patients did not experience any adverse events that were not seen with the recommended dose. There is no specific antidote for overdose with FUZEON. Treatment of overdose should consist of general supportive measures.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

FUZEON (enfuvirtide) is an inhibitor of HIV-1 gp41 mediated fusion derived from a naturally occurring motif, amino acid residues (643-678) within the gp41 transmembrane glycoprotein of human immunodeficiency virus type 1 strain LAI (HIV-1_{LAI}).

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 Vitro*: The *in vitro* antiviral activity of enfuvirtide was assessed by infecting different CD4+ cell types with laboratory and clinical isolates of HIV-1. The IC₅₀ (50% inhibitory concentration) for enfuvirtide in laboratory and primary isolates representing HIV-1 clades A to G ranged from 4 to 280 nM (18 to 1260 ng/mL). The IC₅₀ for baseline clinical isolates ranged from 0.089 to 107 nM (0.4 to 480 ng/mL) by the cMAGI assay (n=130). (see MICROBIOLOGY: Antiviral activity *in vitro*). The relationship between the *in vitro* susceptibility of HIV-1 to enfuvirtide and inhibition of HIV-1 replication in humans has not been established.

Pharmacokinetics

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

Table 6: Summary of Pharmacokinetic Parameters in HIV-1 Infected Patients

C _{max} (µg/mL)	t _{1/2} (h)	AUC _{0-∞} (µ.h/mL)	Clearance (L/h)	Volume of Distribution (L)*
4.59	3.8	55.8	1.7	5.5

*Intravenous administration of a 90 mg dose of FUZEON.

Absorption: After a 90 mg subcutaneous single dose of FUZEON in the abdomen in 12 HIV-1 infected patients, the mean (±SD) C_{max} was 4.59 ± 1.5 µg/mL, AUC was 55.8 ± 12.1 µg•h/mL and absolute bioavailability (using the 90 mg intravenous dose as a reference) was 84.3% ± 15.5%.

The subcutaneous absorption of enfuvirtide is basically proportional to the administered dose over the 45 mg to 180 mg dose range. Subcutaneous absorption at the 90 mg dose is comparable when injected into the abdomen, thigh or arm. In 4 separate studies (N=9 to 12) the mean steady-state trough plasma concentration ranged from 2.6 to 3.4 µg/mL.

Distribution: The mean (±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 92% bound to plasma proteins in HIV infected plasma over a concentration range of 2 to 10 µg/mL. It is bound predominantly to albumin and to a lower extent to α-1 acid glycoprotein. Enfuvirtide was not displaced from its binding sites by saquinavir, nelfinavir, lopinavir, efavirenz, nevirapine, amprenavir, itraconazole, midazolam or warfarin. Enfuvirtide did not displace warfarin, midazolam, amprenavir or efavirenz from their binding sites.

Enfuvirtide levels in the cerebrospinal fluid measured in a small number of HIV infected patients were reported to be negligible. The molecule may be too large to pass the blood brain barrier.

Metabolism: 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.

In *in vitro* human microsomal and hepatocyte studies, hydrolysis of the amide group of the C-terminus amino acid, phenylalanine, results in a deamidated metabolite. This reaction is not NADPH dependent. This metabolite is detected in human plasma following administration of enfuvirtide, with an AUC ranging from 2.4% to 15% of the enfuvirtide AUC.

Excretion: Mass balance studies to determine elimination pathway(s) of enfuvirtide have not been performed in humans. However, such studies in rodents using ³H-enfuvirtide indicated incomplete recovery of the administered radioactivity in the excreta 7 days after the dose. Following a 90 mg subcutaneous dose of enfuvirtide (N=12) the mean ± SD elimination half-life of enfuvirtide is 3.8 ± 0.6 h and the mean ±SD clearance is 1.7 ± 0.4 L/h.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of enfuvirtide have been studied in 25 pediatric patients aged 5 through 16 years (one 5 year old was studied) at a dose of 2 mg/kg. Data from one patient was excluded due to a very low AUC_{12h} value. In the remaining 24 pediatric patients receiving the 2 mg/kg bid dose, the mean \pm SD steady-state AUC_{12} was $56.3 \pm 21.8 \mu\text{g}\cdot\text{h/mL}$, C_{max} was $6.3 \pm 2.3 \mu\text{g/mL}$, C_{trough} was $3.0 \pm 1.5 \mu\text{g/mL}$, and the apparent clearance was $40 \pm 16 \text{ mL/h/kg}$.

A dose of 2 mg/kg bid (maximum 90 mg bid) is expected to provide enfuvirtide plasma concentrations similar to those obtained in adult patients receiving 90 mg bid dosage.

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

Gender and Weight: Analysis of plasma concentration data from patients in clinical trials indicated that the clearance of enfuvirtide is 20% lower in females than males and is increased with increased body weight irrespective of gender (20% higher in a 100 kg and 20% lower in a 40 kg body weight patient relative to a 70 kg reference patient). However, these changes are not clinically significant and no dose adjustment is required.

Race: Analysis of plasma concentration data from patients 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.

Hepatic Insufficiency: The pharmacokinetics of enfuvirtide have not been studied in patients with hepatic impairment.

Renal Insufficiency: Analysis of plasma concentration data from patients in clinical trials indicated that the clearance of enfuvirtide is not affected to any clinically relevant extent in patients with creatinine clearance above 35 mL/min. The results of a renal impairment study indicate clearance of enfuvirtide was reduced by 38% in patients with severe renal impairment (n=4) and by 14-28% in patients with end stage renal disease maintained on dialysis (n=8) compared to patients with normal renal function (n=8). The results were within the range seen in patients in the pivotal studies with normal renal function. Hemodialysis did not significantly alter enfuvirtide clearance. Thus, no dose adjustment is recommended for patients with impaired renal function including those receiving hemodialysis.

STORAGE AND STABILITY

Powder for solution: Store at 15-30°C
Reconstituted solution: Store in refrigerator (2-8°C) for no longer than 24 hours

Unused portions of FUZEON remaining in the single-use vial should be discarded. The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems” if available in your location.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition:

FUZEON is a white to off-white, sterile, lyophilized powder. Each single-use vial contains 108 mg enfuvirtide. Reconstitution with sterile water for injection yields a 90 mg/mL solution of enfuvirtide. The non-medicinal ingredients are hydrochloric acid, mannitol, sodium carbonate, and sodium hydroxide.

Availability:

FUZEON powder for solution for subcutaneous injection is supplied in single-use vials containing 108 mg enfuvirtide.

FUZEON is available as institutional or convenience kits containing:

- 60 vials of FUZEON, 60 vials containing 2 mL of diluent (Sterile Water for Injection), reconstitution-syringes*, and administration syringes*.

*Syringes manufactured by Terumo (Philippines) Corp., 124 East Main Ave., Laguna Technopark, Binan, Laguna, Philippines.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

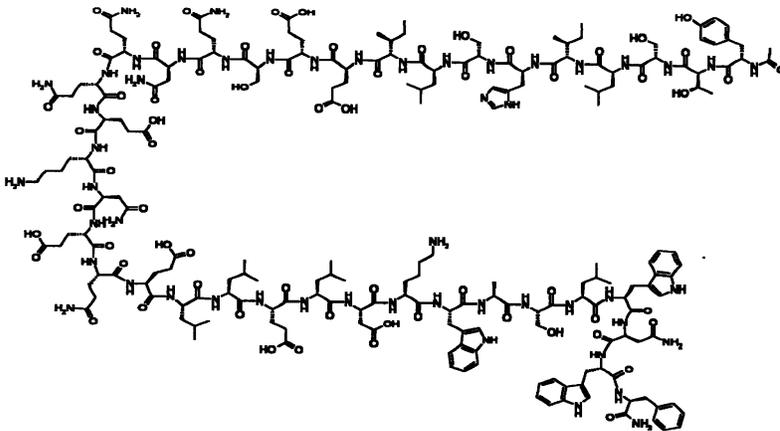
Drug Substance

Common Name Enfuvirtide

Chemical Name Enfuvirtide is a linear 36-amino acid synthetic peptide, composed of naturally-occurring L-amino acid residues. Enfuvirtide has the following primary amino acid sequence:

Ac-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

Structural Formula



Molecular Mass 4,492 Da

Molecular Formula C₂₀₄H₃₀₁N₅₁O₆₄

Physical Form Enfuvirtide is a white to off-white amorphous solid.

Solubility Enfuvirtide is insoluble to very slightly soluble in most organic solvents, exceptions being dimethylformamide and glacial acetic acid. Enfuvirtide is more soluble in dimethylformamide than in glacial acetic acid. Enfuvirtide has similar solubility in the presence of ammonium and sodium cations over potassium. In general, the solubility decreases slightly as the buffer concentration increases. Enfuvirtide has negligible solubility in pure water.

pH	Enfuvirtide is insoluble at low pH and solubility increases with increasing pH with a dramatic inflection at about pH 6.1. Extrapolation of the data from pH 6.40 to pH 8.61 indicates that enfuvirtide has an expected solubility of 296 mg/mL at a pH of 11.0.
Melting point	Enfuvirtide does not melt but decomposes upon heating with onset of decomposition at about 189°C.

CLINICAL TRIALS

Studies in Antiretroviral Experienced Patients

Studies TORO-1 and TORO-2 were randomized, controlled, open-label, multi-center trials in HIV-1 infected subjects with 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 viremia and documented resistance or intolerance to at least one member in each of the NRTI, NNRTI and PI class.

All patients received an individualized background regimen consisting of 3 to 5 antiretroviral agents selected on the basis of the patient's prior treatment history, as well as baseline genotypic and phenotypic viral resistance measurements. Patients were then randomized at a 2:1 ratio to FUZEON (enfuvirtide) 90 mg bid with background regimen or background regimen alone.

Demographic characteristics for Studies TORO-1 and TORO-2 are shown in Table 7. Subjects had prior exposure to a median of 12 antiretrovirals for a median of 7 years.

Table 7: TORO-1 and TORO-2 Pooled Subject Demographics

	FUZEON+Background Regimen	Background Regimen
	N=661	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)	5.2 (3.5-6.7)	5.1 (3.7-7.1)
Median Baseline CD4 Cell Count (cells/mm ³)	88 (1-994)	97 (1-847)

The proportion of patients achieving viral load of <400 copies/mL at week 48 was 34% for patients receiving FUZEON plus background regimen compared to 13% for subjects receiving background regimen only (see Table 8).

Table 8: Outcomes of Randomized Treatment at Week 48 (Pooled Studies TORO-1 and TORO-2)

Outcomes	FUZEON + Background Regimen 90 mg bid	Background Regimen
	N=661	N=334
HIV-1 RNA Log Change from Baseline (log ₁₀ copies/mL) ^{*∇}	-1.4	-0.5
CD4+ cell count Change from Baseline (cells/mm ³) ^{#∇}	+91	+45
HIV RNA ≥ 1 log below Baseline ^{**∇}	304 (46%)	61 (18%)
HIV RNA <400 copies/mL ^{**∇}	225 (34%)	44 (13%)
HIV RNA <50 copies/mL ^{**∇}	154 (23%)	27 (8%)
Time to Virological Failure ^{##} (weeks)	32	11
Discontinued due to adverse reactions/intercurrent illness/labs [†]	9%	11%
Discontinued due to injection site reactions [†]	4%	N/A
Discontinued due to other reasons ^{†§ø}	13%	25%

* Based on results from pooled data of TORO-1 and TORO-2 on ITT population (week 48 viral load for subjects who were lost to follow-up, discontinued therapy, or switched from their original randomization, is replaced by their baseline value).

Last value carried forward

Protocol defined virological failure (not meeting 0.5 log decline by week 8, not meeting 1.0 log decline by week 16, or having a 1.0 log rebound after a 2.0 log decline); each criteria confirmed by a second viral load ≥ 2 weeks after the initial value.

† Percentages based on safety population FUZEON+background (N=663) and background (N=334). Denominator for non-switch patients: N=112.

§ As per the judgment of the investigator.

ø Includes discontinuations from loss to follow-up, treatment refusal, and other reasons.

∇ p<0.0001

** FDA Algorithm

Pediatric Clinical Trials

Fifty-six HIV-1 infected pediatric subjects ages 3 through 16 years have received FUZEON in two open-label, single-arm clinical trials. Adverse experiences were similar to those observed in adult patients.

Study T20-204 was an open-label, multicenter trial that evaluated the safety and antiviral activity of FUZEON in treatment-experienced pediatric subjects. Fourteen subjects from 3 to 12 years were enrolled (median age of 8 years). Median baseline CD4 cell count was 523 cells/ μ L and the median baseline HIV-1 RNA was 4.5 log₁₀ copies/mL.

Eleven of the 14 study subjects completed 48 weeks of chronic therapy. By week 48, 6/14 (43%) subjects had ≥ 1 log₁₀ decline in HIV-1 RNA and 4/14 (29%) 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 1.24 log₁₀ copies/mL and 237 cells/ μ L, respectively.

Study T20-310 is an ongoing, open-label, multicenter trial evaluating the pharmacokinetics, safety, and antiviral activity of FUZEON in treatment-experienced pediatric subjects and adolescents. Forty-two subjects from 5 through 16 years were enrolled (median age of 12 years). Median baseline CD4 cell count was 94 cells/ μ L and the median baseline HIV-1 RNA was 5.0 log₁₀ copies/mL. The evaluation of the antiviral activity is ongoing.

In addition to the above studies, 13 pediatric patients received FUZEON in ongoing safety studies.

DETAILED PHARMACOLOGY

Nonclinical Pharmacokinetics

The pharmacokinetic profiles of enfuvirtide in the rat and the monkey are similar, both being characterized by small volumes of distribution, low systemic clearances, and short terminal elimination half-lives. One metabolite of enfuvirtide, Ro 50-6343, has been identified as the hydrolysis product of the amide group on the C-terminal phenylalanine residue. The pharmacokinetic and metabolic characteristics of enfuvirtide in animals are comparable to those observed in humans.

Intravenous bolus dose administration of enfuvirtide in both the rat and monkey resulted in biphasic plasma concentration-time profiles with terminal phase half-lives of 1.4 to 2.4 hours and 2.9 to 3.8 hours, respectively. Enfuvirtide is readily absorbed in the monkey, as in humans, after SC injection with peak concentrations occurring within 1-3 hours after dosing. Absolute bioavailability in primates ranged from 54 to 133%. In the rat, enfuvirtide absorption after SC injection is dose-dependent, with a decreasing fraction absorbed with increasing dose.

The extent of plasma protein binding of enfuvirtide was 95 to 99% in plasma of healthy volunteers, and 92% in HIV+ plasma. Albumin was the primary binding constituent (95%); relatively low binding (37 to 59%) was associated with α_1 -acid glycoprotein. Enfuvirtide did not show significant protein binding displacement interactions with warfarin, midazolam, itraconazole or several anti-HIV medications. *In vitro* studies using human hepatic microsomes indicated no significant inhibitory effects of enfuvirtide on the metabolic activities of several P450 isozymes. There was a slight decrease in CYP2C19 activity at a high concentration of enfuvirtide. These protein binding and metabolic interactions studies suggest that the potential for drug interactions involving enfuvirtide is minimal.

The distribution and excretion profile of radioactivity from mass balance studies following administration of ³H-enfuvirtide in the rat suggests that enfuvirtide and its catabolites are widely distributed in the body. Relatively low amounts of radioactivity are slowly eliminated at a constant rate in the urine and feces suggesting that the radiolabel is incorporated into intermediary pathways as either a radiolabeled fragment or amino acid. A significant fraction of radioactivity was also captured in expired air.

MICROBIOLOGY

Antiviral Activity *In Vitro*: The *in vitro* antiviral activity of enfuvirtide has been demonstrated for acute infection of T-lymphoblastoid cell lines, monocyte/macrophage cells, and primary peripheral blood mononuclear cells (PBMC) by laboratory and clinical HIV-1 isolates. Enfuvirtide susceptibility for 130 baseline PBMC virus isolates from patients in Phase II clinical studies was determined in a cMAGI assay. Enfuvirtide had a geometric mean EC₅₀ of 16 ng/mL (SD 57) and a range of 0.4 to 480 ng/mL against these virus isolates. Enfuvirtide also inhibited HIV-1 envelope mediated cell cell fusion with IC₅₀ values reported in the range 0.5 ng/mL to 25 ng/mL for a variety of assay protocols.

The relationship between the *in vitro* susceptibility of HIV-1 to enfuvirtide and inhibition of HIV-1 replication in humans has not been established.

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 zidovudine, lamivudine, nelfinavir, indinavir and efavirenz.

Resistance *In Vitro*: HIV-1 isolates with reduced susceptibility to enfuvirtide have been selected *in vitro* which harbor substitutions in amino acids 36 to 38 of the gp41 ectodomain. These substitutions were correlated with varying levels of reduced enfuvirtide susceptibility in HIV site-directed mutants. 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.

Resistance *In Vivo*: In clinical trials, HIV-1 isolates with reduced susceptibility to enfuvirtide have been recovered from subjects treated with FUZEON in combination with other antiretroviral agents. Post treatment HIV-1 virus from 246 subjects experiencing protocol defined virological failure exhibited decreases in susceptibility to enfuvirtide ranging from 4-fold to 6318-fold relative to their respective baseline virus and exhibited genotypic changes in gp41 amino acids 36 to 45. Substitutions in this region, presented in order of decreasing frequency, were observed at amino acid positions 38, 43, 36, 40, 42 and 45 and the most common specific amino acids observed were V38A, N43D, G36D and Q40H. Substitutions of other amino acid residues were observed at positions 36, 38 and 43 which were also associated with varying degrees of reduced 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. Cross-resistance to other fusion inhibitors are still being evaluated.

TOXICOLOGY

Acute Toxicity: The acute toxicity of enfuvirtide was assessed after single intravenous and intraperitoneal doses in rats and in a single-dose intravenous study in cynomolgus monkeys. The results of these studies are presented in Table 9.

Multi-dose Toxicity: The toxicity and toxicokinetic profile of enfuvirtide after repeated administration were assessed in rats and monkeys.

Chronic toxicology studies revealed no adverse systemic toxicities after administration of doses up to 30 mg/kg/day in rodents for 6 months, and 20 mg/kg/day in primates for 9 months, using the therapeutic route and regimen (i.e., twice daily SC injection). Plasma exposures were 0.7 and 2.8 times higher than estimated therapeutic exposures in rats and primates, respectively. Enfuvirtide was also well tolerated in 28-day toxicity studies using the intravenous route of administration. Additional rat and primate studies evaluated enfuvirtide batches prepared by different synthetic routes, and the impact of prior treatment with another fusion inhibitor (T-1249) on enfuvirtide safety.

The major observations in both species when enfuvirtide was given subcutaneously were local changes at the injection sites indicative of inflammation and mechanical trauma. Enfuvirtide evoked an immunogenic response in primates manifested as the development of antibodies to the molecule. There was no evidence that the antibodies reduced systemic exposures to the enfuvirtide. The animal profile of general tolerance of enfuvirtide with adverse effects limited to the injection site is generally consistent with observations in HIV patients.

The multi-dose studies performed, and their results are presented in Tables 10-11.

Special Toxicity Studies and Safety Pharmacology Studies: Studies to address specific safety concerns related to enfuvirtide administration were focussed on the potential for hypersensitivity reactions, and potential pharmacological actions of the molecule on the cardiovascular and central nervous systems were also assessed in standard models. In addition, the minipig was investigated as a potential animal model for injection site reactions, the most common clinical adverse finding.

A positive skin sensitization response to enfuvirtide was observed in guinea pigs, indicating a potential for causing delayed contact hypersensitivity.

Slight, transient changes in hemodynamic and respiratory parameters, and changes in the QRS complex and ST-segment, were observed in dogs after intravenous administration enfuvirtide doses that produced high peak plasma concentrations (> 86 times the human plasma concentration following a clinical dose of 90 mg bid). Importantly, no change in the QT or QTC interval were observed. Enfuvirtide did not affect the central nervous system in mouse observational studies.

A summary of these studies is presented in Table 12.

Reproductive Toxicity: Fertility, teratology and pre- and postnatal development studies were conducted to provide information on the effect of enfuvirtide on all phases of mammalian reproduction and development, including immediate and latent effects through one complete life cycle (i.e., to the F₂ generation).

Enfuvirtide produced no adverse effects on embryofetal development after administration of doses up to 500 mg/kg/day in rats, and 30 mg/kg/day in rabbits. Plasma exposures were 8.9 and 3.2 times higher than estimated therapeutic exposures in rats and rabbits, respectively. No adverse effects on fertility or pre- and postnatal development were seen in rats treated with up to 30 mg/kg/day enfuvirtide. The risk of enfuvirtide for causing genetic or chromosomal damage is low.

The reproductive toxicity studies performed, and their results are presented in Table 13.

Carcinogenicity: Long-term animal carcinogenicity studies of enfuvirtide are ongoing.

Mutagenicity: 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.

A summary of the studies performed, and their results are presented in Table 14.

Table 9: Summary of Acute Toxicity Studies

Study Type	Species/ Strain	N (sex/gp)	Rte	Dose (mg/kg/day)	C _{max} (µg/mL)	AUC (µg·hr/mL)	Findings
Single dose toxicity in rat	Rat/ Fischer	5	IV	0 10 20 50 100	NM	NM	Clinical signs of toxicity and lethality at 100 mg/kg; Congestion and hemorrhage in lung at ≥ 20 mg/kg; MNLD = 50 mg/kg
		3	IP	100			
Single dose toxicity in primate	Cyno Monkey	1 (females only)	IV	0 5 10 25 50	NM	NM	All doses well-tolerated; mild intolerance (including slow recovery from anesthesia and pale mucous membranes) at 50 mg/kg.

NM = not measured

Table 10: Summary of Multiple-Dose Toxicity Studies in Rats

Study Type	Species/ Strain	N (sex/gp)	Rte	Dose (mg/kg/day) [regimen]	C _{max} (µg/mL)	AUC _{0-12hr} (µg.hr/mL)	Findings
28-Day toxicity in rat	Rat/ Fisher	Terminal: 10; Recovery: 5	IV	0 1 3 10 [QD]	NM	NM	Well-tolerated at all doses; slight ↓ leukocytes and reversible ↑ thyroid/parathyroid wts at 10 mg/kg; slight ↑ RBC, Hct, Hb, ↓ MCH, MCHC after recovery at 10 mg/kg.
7-Day bridging toxicity in rat	Rat/ Fischer	MTD Phase: 2 Repeat Dose Phase: 5	IV	0, 50, 75, 100, 110, 125 0, 2, 7, 15 [QD]	NM	NM	Lethality at 110 (F-moc material) or 125 (t-Boc material); <u>F-moc</u> : Slight ↓ RBC, Hb, ↑ MCV at ≥ 2 mg/kg; ↓ Hct, ↑ MCH at ≥ 7 mg/kg; <u>t-Boc</u> : Slight ↓ RBC, HB, Hct at ≥ 7 mg/kg.
6-Month toxicity and toxicokinetics in rat	Rat/ Sprague- Dawley (CrI:CD)	Interim: 10; Terminal: 15; Recovery: 5	SC	0 2.76/2.4 10.35/9.0 34.5/30.0 [BID]	(day 36) 1.84 3.82 8.27	(day 36) 8.0 20.1 39.1	All doses well-tolerated; no adverse systemic toxicities; gross and microscopic injection site changes in all groups.

Table 11: Summary of Multiple Dose Toxicity Studies in Primates

Study Type	Species/ Strain	N (sex/gp)	Rte	Dose (mg/kg/day) [regimen]	C _{max} (µg/mL)	AUC (µg.hr/mL)	Findings		
28-Day toxicity and toxico-kinetics in primate	Cyno Monkey	4	IV	0 0.4 1.2 4.0 [BID]	(day 7) 3.8 11.9 41.2	(day 7) ^a 5.7 17.7 48.4	Well-tolerated at all doses; antibody response at 4 mg/kg/day.		
28-Day bridging toxicity and toxico-kinetics in primate	Cyno monkey	2	SC	0 10 20 [BID]	(day 28)		(day 28) ^b		All doses well-tolerated; no adverse systemic toxicities; Local gross and microscopic changes at 20 mg/kg; slightly more severe with Rte 1 material.
					Rt1 22 45	Rt2 18 33	Rt1 104 218	Rt2 100 168	
9-Month toxicity and toxico-kinetics in primate	Cyno monkey	Interim: 2-3; Terminal: 3-4; Recovery: 1	SC	0 10 20 [BID]	(day 272) 15.0 20.0	(day 272) ^c 161.2 158.1	All doses well-tolerated; no adverse systemic toxicities; isolated ↑ eosinophils and leukocytes; antibody response at both dose levels; injection site changes in all groups, but more significant in enfuvirtide groups.		
28-day toxicity in primates	Cyno Monkey	6	SC	T1249: 12.5, 25 [QD]			All treatments well-tolerated; no adverse systemic toxicities; gross and microscopic changes at enfuvirtide injection sites		
		2		ENF: 50 [BID]	(day 49) 59.2	(day 49) ^c 342.0			

a = AUC 0 ∞

b = AUC 0 8hr

c = AUC 0 12hr

Table 12: Summary of Special Toxicity and Safety Pharmacology Studies

Study Type	Species/ Strain	N (sex/gp)	Rte	Dose	C _{max} (µg/mL)	AUC (µg.hr/mL)	Findings
Skin Sensitization	Guinea pig/ Dunkin Hartley	Con: 5 Test: 10 (males only)	derm top	25 mg/ml 50 mg/ml	NM	NM	Positive skin sensitization response
Skin Sensitization	Guinea pig/ Dunkin Hartley	Con: 5 Test: 10 (males only)	derm top	50 mg/ml 100 mg/ml	NM	NM	Positive skin sensitization response; more severe response with Tris
14 Day Minipig Dose Response Study	Minipig/ Hanford	1M 2F	SC	50 mg/ml (4 inj/day); 100 mg/ml (2 inj/day)	NM	NM	SC masses beginning day 5; acute and chronic inflammation, foreign body giant cells, granuloma, fibrosis, collagen degeneration seen microscopically. Most prominent changes at sites injected 4X daily with vehicle or T-20.
14 Day Minipig Formulation Comparison	Minipig/ Hanford	3M	SC	50 mg/ml (4 inj/day); 100 mg/ml (2 inj/day)	NM	NM	SC masses beginning on day 4. Well-defined granulomas in most T-20 treated sites (none in vehicle sites). Tris formulation appeared to cause the most severe reaction. Other microscopic changes as in previous study.
Locomotor activity in mice (single dose study)	Mice ICR CD-1	10M	SC	0, 5, 15, 50 mg/kg	NM	NM	No effect of enfuvirtide
General behavior in mice (single dose study)	Mice ICR CD-1	4M	SC	0, 5, 15, 50 mg/kg	NM	NM	No effect of enfuvirtide
Cardio-vascular and respiratory function in dog (single dose study)	Beagle dogs	1M 3 F 3M 3F	IV	0 mg/kg 5 " 15 " 50 "	108 396 1240	NM	Slight, transient ↓ MAP, ↑ HR, LV dp/dt, ↓ QRS amplitude, resp rate, min vol at ≥ 15 mg/kg; slight ↓ LV SP, tidal volume at 50 mg/kg; one ST-segment elevation at 50 mg/kg. No changes in QT or QTc

NM = not measured

Table 13: Summary of Reproductive Toxicity Studies

Study Type	Species/ Strain	N (sex/gp)	Rte	Dose	C _{max} (µg/mL)	AUC (µg.hr/mL)	Findings
Rat Fertility and Early Embryonic Development	Rat/ Sprague- Dawley CrI:CD	25	SC	0 2.4 9.0 30.0 [BID]	NM	NM	No adverse effects on fertility or early embryonic development
Rat Embryofetal Development	Rat/ Sprague- Dawley CrI:CD	25F	SC	0 2.4 9.0 30.0 [BID]	NM	NM	No adverse effects on maternal generation or embryofetal development
Rat Embryofetal Development	Rat/ Sprague- Dawley CrI:CD	22F	SC	0 125 250 500 [BID]	(day 11) 49.4 64.0 62.2	(day 11) 325 546 499	No adverse effects on maternal generation or embryofetal development
Rabbit Embryofetal Development	Rabbit/ New Zealand White	4F	SC	0 1.0 3.0 10.0 30.0 [BID]	NM	NM	No adverse effects on maternal generation or embryofetal development
Rabbit Embryofetal Development	Rabbit/ New Zealand White	20F 6F	SC	0 3.0 10.0 30.0 [BID]	<u>day 11</u> NM 8.4 27.0	<u>day 11</u> NM 33 177	No adverse effects on maternal generation or embryofetal development
Rat Pre- and Postnatal Development	Rat/ Sprague- Dawley CrI:CD	25F (F ₀) 25F (F ₁)	SC	0 2.4 9.0 30.0 [BID]	NM	NM	No adverse effects on the maternal generation or the peri- and postnatal development of the offspring

NM = not measured

Table 14: Summary of Genetic Toxicity Studies

Study Type	Species/ Strain	N (sex/gp)	Dose	Rte	Findings
Bacterial Reverse Gene Mutation (Ames Test)	TA1535 TA1537 TA98 TA100 TA102 WP2 <i>uvrA</i>		16.7, 50, 167, 500, 1670, 5000 µg/plate		Non-mutagenic
Forward Gene Mutation Assay in Mammalian Cells	AS52 Chinese Hamster Ovary Cells		10, 50, 100, 250, 500, 750, 1000 µg/ml		Non-mutagenic
<i>In vivo</i> micronucleus	Mice CrI:CD1 (ICR)	5/sex at 24, 48, 72 hr	100 500 1000 mg/kg	IV	Non-clastogenic

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PART III: CONSUMER INFORMATION

PrFUZEON[®]
enfuvirtide for injection

This leaflet is part III of a three-part "Product Monograph" published when FUZEON was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FUZEON. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

- FUZEON is a type of medicine called an HIV (human immunodeficiency virus) fusion inhibitor.
- FUZEON is always used in combination with other anti-HIV medicines to treat people with HIV infection.

What it does:

FUZEON blocks HIV's ability to infect healthy CD4 cells. When used in combination with other anti-HIV medicines, FUZEON has been shown to reduce the amount of HIV in the blood and increase the number of CD4 cells keeping your immune system as healthy as possible, so it can help fight infection.

FUZEON does **not** cure HIV infection or AIDS.

FUZEON does **not** reduce the risk of passing HIV to other people through unprotected sex, sharing used needles, or contaminated blood. For your own health and the health of others, it is important to continue to practice safe sex. Use a latex or polyurethane condom or other barrier to reduce the risk of sexual contact with semen, vaginal secretions, or blood. Do not use or share dirty needles.

When it should not be used:

Do not use FUZEON if you are allergic to any of the ingredients in FUZEON (see the end of this section for a list of ingredients in FUZEON).

What the medicinal ingredient is:

The medicinal ingredient found in FUZEON is enfuvirtide.

What the non-medicinal ingredients are:

FUZEON contains the following non-medicinal ingredients: hydrochloric acid, mannitol, sodium carbonate, and sodium hydroxide.

What dosage forms it comes in:

FUZEON is available in powder supplied in single-use vials, for reconstitution with sterile water for injection. Each vial contains 108 mg of the active ingredient enfuvirtide.

FUZEON is packaged in convenience kits containing FUZEON vials, diluent (sterile water for injection), reconstitution syringes[†], and administration syringes[†].

If you run out of supplies (for example, if you run out of syringes, sharps container, etc.) call your doctor's office or pharmacy where you originally obtained your supplies.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Allergic reactions have been associated with the use of FUZEON in clinical trials (see ‘Allergic Reactions’ below).

BEFORE you use FUZEON talk to your doctor or pharmacist if:

- you are allergic to FUZEON or any of its ingredients.
- you are pregnant or plan to become pregnant while using FUZEON. The effects of FUZEON on pregnant women or on the fetus are not known.
- you are breast-feeding. It is recommended that HIV-positive mothers using FUZEON not breast-feed their infants. Experts advise against breast-feeding if you are HIV-positive. Breast-feeding carries the risk of passing HIV to your baby. Also, it is not known if FUZEON passes into human breast milk.
- you have any other medical conditions.
- you use any other medicines, including prescription and nonprescription medicines, or nutritional, herbal, and dietary supplements

Be sure to purchase antiseptic pads at the time FUZEON is dispensed as they are not included in the FUZEON kit (see FUZEON Injection Directions for antiseptic pad use).

This information will help your doctor and you decide whether you should use FUZEON and what extra care may need to be taken while you are on the medication. If you have any doubts about your health condition or about using FUZEON, talk to your doctor.

INTERACTIONS WITH THIS MEDICATION

- FUZEON has been shown not to interact with other anti-HIV medicines. You can decide to use FUZEON at the same times or at different times than your other anti-HIV medicines.
- FUZEON has been shown not to interact with rifampicin (known also as rifampin).
- FUZEON has not been tested with all medicines including nonprescription medicines, and it has not been tested with nutritional, herbal or dietary supplements. It is important to discuss with your doctor all of the medications and nutritional, herbal or dietary supplements you are using or are planning to use before you begin treatment with FUZEON.

PROPER USE OF THIS MEDICATION

Your doctor has prescribed FUZEON after carefully studying your case. Other people may not benefit from taking this medicine, even though their problems may seem similar to yours. Do not give your FUZEON to anyone else.

- You should be under a doctor's care when using FUZEON.
- FUZEON must be used in combination with other anti-HIV medicines.
- Before you begin using FUZEON, make sure you understand all of the information provided with your medicine. You or your caregiver should be properly trained before injecting FUZEON. If you do not understand some of the information, talk with your doctor or nurse about your questions or concerns.
- Be sure to read the consumer information for the other products your doctor may prescribe for use with FUZEON.
- FUZEON is injected under the skin two times a day. Complete, step-by-step instructions about injecting FUZEON are given in the **FUZEON Injection Directions** provided with your medicine.
- You must use FUZEON every day exactly as your doctor prescribed it. Do not change your dose or stop using FUZEON without first talking with your doctor.
- When your supply of FUZEON runs low, be sure to have it refilled. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. If you miss or skip doses of FUZEON, HIV may develop resistance to FUZEON and become harder to treat.

- It is important that you properly discard your used syringes after injecting FUZEON. Discard all used syringes into your sharps waste container. Your doctor or nurse will give you additional instructions about the safe disposal of your used syringes.

Usual dose:

The recommended dose of FUZEON in adults is 90 mg (1 mL) twice daily injected under the skin. Refer to the FUZEON Injection Directions for step-by-step instructions about injecting FUZEON.

FUZEON can be injected before or after a meal.

The dosage for children is based on weight and will be determined by the doctor.

Overdose:

As with any prescription medicine, if you use more than the recommended dosage, seek medical attention immediately. Experience of FUZEON overdose is unknown, and there is no specific antidote for overdose with this drug.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of FUZEON, you should take the missed dose as soon as possible and then take your next dose as scheduled. If you have missed a dose of FUZEON and it is close to the time when you are supposed to take your next dose, wait and take the next dose as regularly scheduled. Do not take two doses of FUZEON at once.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Unwanted effects are possible with all medicines. Talk to your doctor or pharmacist if you are worried about side effects or find them very bothersome, and report any new or continuing symptoms to your doctor immediately. Your doctor will be able to tell you what to do and may be able to help you with these side effects.

This list of side effects is not complete. If you have questions about side effects, ask your doctor, nurse, or pharmacist. Report any new or worsening symptoms to your doctor immediately.

Allergic Reactions

There have been a small number of allergic reactions reported in patients using FUZEON. Symptoms of an allergic reaction could include the following (either alone or in combination): difficulty breathing; fever with vomiting and skin rash; blood in your urine; or swelling of your feet. **If you develop any of these symptoms, you should call your doctor immediately.**

Injection Site Reactions

- You will probably experience one or more of the following mild to moderate reactions at the location where you inject your medicine: itchiness, swelling, redness, pain or tenderness, hardened skin, or bumps. You may experience more severe pain, discomfort or other symptoms requiring pain medications or limiting your usual activities.
- Injection site reactions can appear within the first week of treatment with FUZEON and generally do not get worse with continued use of FUZEON. Reactions at an individual injection site usually last for fewer than 7 days but can last 14 days or longer. Discuss ways to help manage your injection site reactions with your healthcare professional.
- Injection site reactions may be worse when injections are repeated in the same place on the body, or when the injection is given deeper than intended (for example, into the muscle).
- Remember that reactions at injection sites are a common side effect of using FUZEON. In studies, most patients said that these reactions were tolerable and very few stopped using FUZEON because of them. If you experience reactions at an injection site, it is important *not* to stop using FUZEON until you have talked with your doctor about any concerns you may have.
- In rare instances, patients experienced an infection at an individual injection site. To reduce the risk of

infection, it is important that you follow the FUZEON Injection Instructions provided with your medicine. When should you contact your doctor about injection site reactions? You should call your doctor if there is evidence of infection at the site of injection such as drainage or increasing heat, swelling, redness or pain.

Almost all patients using FUZEON have injection site reactions. If you are worried about the reaction you are having, call your doctor or nurse to help you decide if you need medical attention. If the injection site reaction you are having is severe (defined as a Grade 3 or 4 below), call your doctor immediately.

This scale will help you judge the seriousness of your injection site reaction. The scale will also help you explain your reaction when you talk to your doctor or nurse:

- Grade 1: mild soreness at the injection site
- Grade 2: pain at the injection site that does not limit your daily activities
- Grade 3: severe pain at the injection site that requires pain medicine* or limits usual activities
- Grade 4: severe pain requiring hospitalization

* Your doctor can recommend which pain medicine will work best for you.

Pneumonia

Patients with HIV get bacterial pneumonia more often than patients without HIV. In clinical trials, patients using FUZEON with other HIV medicines got bacterial pneumonia more often than patients not receiving FUZEON. It is unclear if this was related to the use of FUZEON. **You should contact your healthcare professional right away if you have a cough, fever or trouble breathing.** Patients are more likely to get bacterial pneumonia if they had a low number of CD4 cells, increased amount of HIV in the blood, intravenous (injected into the vein) drug use, smoking or had experienced lung disease in the past. It is unclear if pneumonia is related to FUZEON.

Immune Reconstitution Inflammatory Syndrome

Changes in your immune system can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time, or you could develop an autoimmune disease in which your immune system reacts against your own body (e.g. Grave's disease (which affects the thyroid gland), Guillain-Barre syndrome (which affects the nervous system) or polymyositis (which affects the muscles) and it may develop at any time, sometimes months later after the start of HIV therapy). Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling, or fatigue or any new symptoms contact your doctor immediately.

Additional information about possible side effects:

- The following side effects were seen more frequently in patients using FUZEON with their other anti-HIV medicines than in patients not using FUZEON with their other anti-HIV medicines: cough; headache; pain and numbness in feet or legs; dizziness; loss of sleep; depression; decreased appetite; inflamed sinuses; enlarged lymph nodes; weight decrease; weakness or loss of strength; muscle pain; constipation; and pain and inflammation of the pancreas.
- There have been other side effects in patients using FUZEON. However, these side effects may have been due to other medicines that patients were using or to HIV disease itself. Some of these side effects can be serious.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call
Common	<p><u>Injection Site Reactions</u> Symptoms: itchiness, swelling, redness, pain or tenderness of skin, hardened skin, or bumps.</p>	✓ (defined as Grade 3 or 4)		
Uncommon	<p><u>Allergic Reactions</u> Symptoms: trouble breathing, nausea, chills, shivering, fever with vomiting and skin rash, blood in your urine, swelling of feet, low blood pressure which may make you faint or feel faint.</p> <p><u>Pneumonia</u> Symptoms: cough with fever, rapid breathing, or shortness of breath.</p>		✓ ✓	

Contact your healthcare provider **immediately** if you develop any of the symptoms associated with an allergic reaction or pneumonia.

This is not a complete list of side effects. For any unexpected effects while taking FUZEON, contact your doctor or pharmacist.

HOW TO STORE IT

Unopened FUZEON vials can be stored at room temperature (15-30°C). The sterile water for injection (diluent) may be stored at room temperature.

After FUZEON has been mixed with the sterile water for injection, the vial can be stored in a refrigerator for up to 24 hours.

Do not use FUZEON or sterile water for injection after the expiration date on the vials.

Keep this and all other medications out of the reach and sight of children. Do not keep medicine that is out of date or that you no longer need. Vials of FUZEON that are not used should be returned to the pharmacy. Opened vials of FUZEON containing unused amounts of medicine should be safely discarded. For further information on the proper disposal of FUZEON and its components see section below “Discarding Used Syringes and Other Supplies”.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: [http:// www.rochecanada.com](http://www.rochecanada.com) or by contacting the sponsor, Hoffmann-La Roche Limited, at 1-888-762-4388.

This leaflet was prepared by Hoffmann-La Roche Ltd.

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⁺ Syringes manufactured by Terumo (Philippines) Corp., 124 East Main Ave., Laguna Technopark, Binan, Laguna, Philippines.



Hoffmann-La Roche Limited
Mississauga, Ontario L5N 5M8

FUZEON INJECTION DIRECTIONS

The following is a basic, step-by-step guide to injecting FUZEON (enfuvirtide). **Please read this guide in its entirety before proceeding.** Contact your healthcare professional if you have any questions about FUZEON or its administration.

These instructions are for an adult dose of 1 mL of FUZEON. If your prescription is for less than 1 mL your healthcare professional may tell you to use different syringes.

It can take up to 1 hour to prepare FUZEON - mostly time for the powder to dissolve. Be sure to plan ahead, allowing yourself enough time.

Safety Tips

Wash your hands well to reduce the risk of bacterial infections. Do not touch anything except the medicine and supplies.

- When handling the syringe, do not touch the needle. Do not touch the tops of the vials once they have been cleaned with alcohol pads.
- Make sure none of the items in your kit have been opened. Do not use opened materials.
- Never use a syringe with a bent or damaged needle.
- Never mix FUZEON with tap water. Use only the sterile water for injection provided to mix FUZEON.
- Never mix FUZEON in the same syringe with other injectable medicines.
- There should never be any particles floating in the FUZEON once it is completely mixed with the sterile water for injection. If you see any, do not use it. Contact your pharmacist.
- The only recommended route of injection is subcutaneous (under the skin). FUZEON should not be given intravenously (directly into your veins) or intramuscularly (directly into your muscle).
- Use syringes, vials of FUZEON and vials of sterile water for injection only once.
- Discard used syringes into your sharps container. Consult your doctor if you have any questions about safe disposal of these items.

When to Have a Caregiver Assist You

Certain injection sites, such as the upper arms, can be difficult to use at first. Have your partner, a friend, or a family member with you if you need help. To reduce the risk of infection to the patient or needle-stick injury to the caregiver, anyone giving or helping with injections should also attend an injection training session with your healthcare professional. Administration instructions are available from your healthcare professional.

If someone will be assisting you with your injections, purchase a supply of latex gloves for them. These should always be worn by anyone who helps you.

About the Safety Syringe⁺

The syringes supplied with your medicine have a coloured needle protection device that is attached to the needle. This safety device covers the needle after use and reduces the risk of needle-stick injuries. **Do not tear off the needle protection device from the syringe.**

Although these syringes offer this safety feature, it is important that you dispose of used syringes properly and according to the instructions given to you by your healthcare professional.

If your doctor has prescribed other syringes, please follow the instructions provided for those syringes and the mixing and administration instructions provided for FUZEON below.

Getting Ready

Gather all of the following supplies onto a clean surface:

Included in the convenience kit:

- One vial of FUZEON
- One vial of sterile water for injection
- One 3-mL syringe⁺ (larger syringe) with a 25 mm needle
- One 1-mL syringe⁺ (smaller syringe) with a 13 mm needle

****Not included in the convenience kit:***

- 3-4 alcohol or other antiseptic pads
- Sharps waste container

*You may need to purchase these items.

Washing Hands

Wash hands thoroughly with soap and water. Dry your hands with a clean paper towel and also use the paper towel to turn off the faucet. After washing hands, do not touch anything except the injection supplies and the injection site.

If you are giving the injection to someone else, be sure to wear latex gloves.

Open Syringe Packages and Remove Vial Caps

- Discard packages and vial caps into the trash.
- Place syringes and vials onto a clean surface.

Clean the Tops of Vials

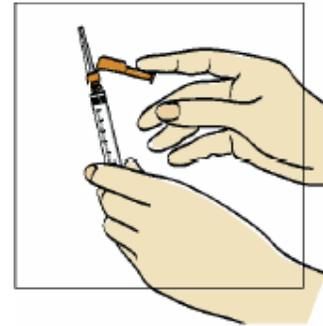
- Wipe each vial top with a fresh alcohol pad. Let the tops air-dry.
- Be sure not to touch the rubber tops after cleaning them. If you touch them, be sure to clean them again.

⁺ Syringes manufactured by Terumo (Philippines) Corp., 124 East Main Ave., Laguna Technopark, Binan, Laguna, Philippines.

Mixing FUZEON

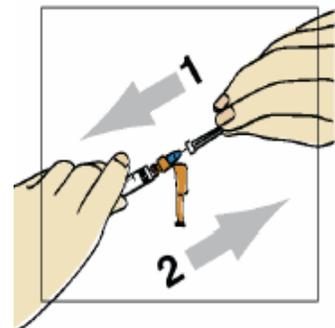
Draw Up Sterile Water for Injection

Step 1: Pick up the 3-mL, large syringe. Using your index finger, push back the coloured needle protection device towards the body of the syringe.



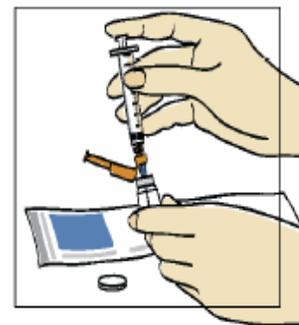
To ensure that the needle is secure, hold the clear plastic cap and tighten the needle with a gentle clockwise twist. Do not use too much force as the needle may loosen.

Step 2: Remove the clear plastic cap by pushing towards the syringe and pulling the cap off.



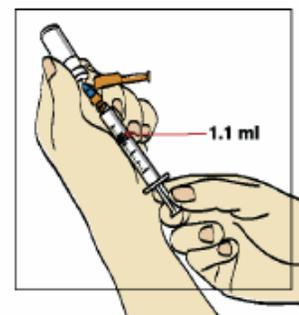
Draw back 1.1 mL of air.

Step 3: Insert the syringe needle into the rubber top of the sterile water vial and press the plunger, injecting the air.



Step 4: With the needle still in the vial, turn the vial upside down. **Make sure the tip of the needle is always below the surface of the sterile water to help keep any air bubbles from entering the syringe.**

Slowly pull the plunger past the 1.1-mL mark.



Step 5: With the needle still in the vial, tap or flick the syringe gently to make any air bubbles rise to the top.

If extra air enters the syringe, gently press the plunger to force any air back into the vial and withdraw the sterile water again, making sure you have 1.1 mL of sterile water in the syringe

Step 6: Remove the needle from the vial, making sure you never touch the needle with your fingers or any other object. If the needle touches your fingers or any other object, discard the syringe and start over with a new one.

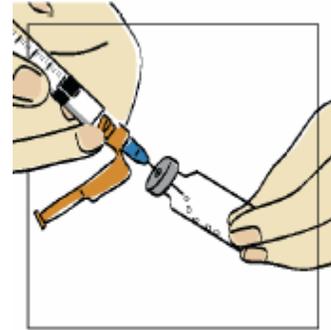
Discard the sterile water vial into the trash. The sterile water vial is intended for single use only.

Inject Sterile Water Into FUZEON

Step 7: Gently tap the FUZEON vial to loosen the powder.

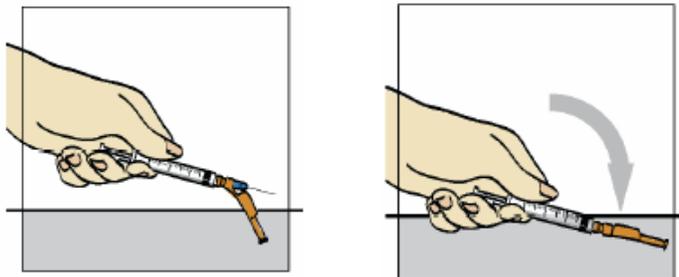
Hold the water-filled syringe by the barrel and push the needle through the rubber top of the FUZEON vial at a slight angle.

Step 8: Press the syringe plunger slowly. Allow the water to flow slowly down the inside of the vial. **Be careful not to forcefully shoot water into the powder, since this can cause foaming. If foaming occurs, it may take longer for the FUZEON to completely dissolve.**



Step 9: After all of the sterile water has been added to the FUZEON vial, remove the syringe from the vial.

Hold the barrel of the syringe with one hand and gently press the coloured needle protection device down on a **flat surface** until it covers the needle. You will hear a click. **Do not use your free hand to press the device over the needle.**



Discard the syringe into the sharps container

Mix

Step 10: Gently tap the FUZEON vial with your fingertip for 10 seconds until the powder begins to dissolve. **Never shake the vial or turn it upside down to mix—this will cause excessive foaming.**

You may also gently and slowly roll the vial between your hands.

If there are some undissolved pieces sticking to the wall of the vial above the water level, slowly roll the vial in an upright position between your hands for a short time until the pieces fall back into the water. After the powder begins to dissolve, set the vial aside to allow it to completely dissolve. The FUZEON may take up to 45 minutes to dissolve.

If you accidentally touch the rubber top, be sure to clean it again with a new alcohol pad.

Make sure the FUZEON has dissolved completely. The solution should be clear and colourless. Allow any bubbles that may have formed to settle. If bubbles still exist, gently tap the side of the FUZEON vial to help settle them.

As with all injectable medicines, it is important to inspect the FUZEON solution for particles. If you notice any particles in the FUZEON solution, discard the vial or return it to your pharmacy.

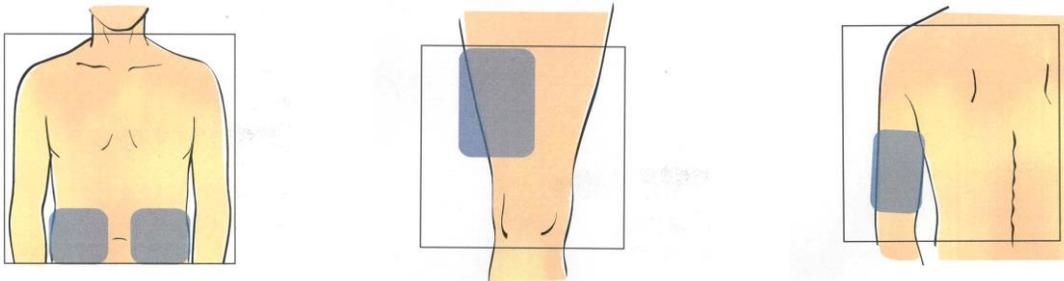
Once a dose of FUZEON is mixed with sterile water, it must be used immediately or stored in a refrigerator in the vial and used within 24 hours. Do not store FUZEON in the syringe.

If you are preparing both of your daily doses at one time, be sure to use new syringes, a new vial of sterile water for injection, and a new vial of FUZEON for each dose. If you have refrigerated your already mixed FUZEON, let it come to room temperature and make sure that it is clear and colourless before injecting.

Giving the Injection

Select Injection Site

- Injection sites include the abdomen, upper thighs, and upper arms.



- **Choose a site that is in a different area from the site used for your previous injection and where there are no current injection site reactions.**
- With the tips of your fingers, feel for any hard bumps that may be present from past injections. Do not inject in the areas where these bumps are present. Do not inject into moles, scar tissue, bruises, your belly button, or areas that could be irritated by a belt or waistline of your clothes.

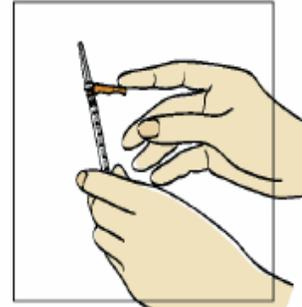
Clean the Injection Site

Clean the area for injection with an alcohol pad. Start at the center, apply pressure, and clean in a circular motion, working outward. Allow to air-dry completely.

Draw Up FUZEON

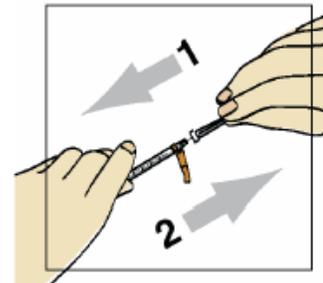
Step 1: Wipe the top of the FUZEON vial again with a new alcohol pad

Now, pick up the 1-mL, small syringe. Using your index finger, push back the coloured needle protection device towards the body of the syringe.



To ensure that the needle is secure, hold the clear plastic cap and tighten the needle with a gentle clockwise twist. Do not use too much force as the needle may loosen.

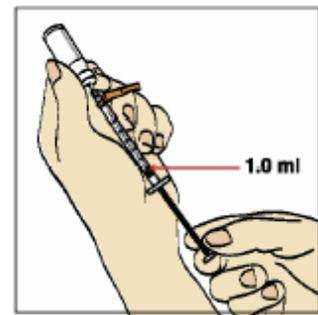
Remove the clear plastic cap by pushing towards the syringe and pulling the cap off.



Pull back the plunger to get 1 mL of air. Be careful not to pull the plunger too fast past the 1 mL marker and/or out of the barrel. Insert the syringe into the vial of mixed FUZEON.

Before turning the vial upside down, slowly inject the air into the FUZEON, and keep the needle in the vial.

Step 2: Gently turn the vial upside down. **Make sure the tip of the needle is always below the surface of the solution to help keep air bubbles from entering the syringe.** Slowly pull back the plunger to get 1.0-mL of FUZEON or the amount prescribed by your doctor. Be careful not to pull the plunger too fast past the 1 mL marker and/or out of the barrel.



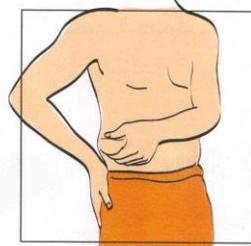
Step 3: With the needle still in the vial, tap or flick the syringe gently to make any air bubbles rise to the top.

If extra air enters the syringe, gently press the plunger to inject the air back into the vial and withdraw the FUZEON again, making sure you have 1.0 mL of FUZEON in the syringe or the amount prescribed by your doctor. This step may be repeated until the air bubbles are removed and the correct amount of FUZEON is in the syringe.

Remove the needle from the vial.

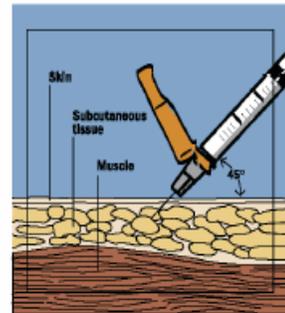
Inject FUZEON

Step 4: Choose an injection site and pinch as much of a skin fold as possible without making yourself uncomfortable.



FUZEON is injected into a thin layer of fatty tissue directly beneath the surface of the skin. Do not inject into muscle or veins.

Step 5: Pierce the skin at a 45-degree angle.



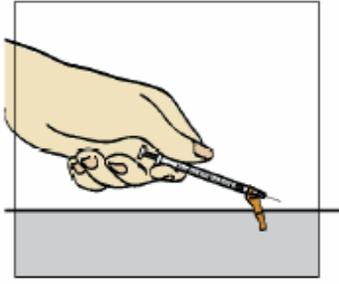
Tip: Your healthcare professional may suggest different injection techniques that will work best for you.

Step 6: When the needle is in, release the skin, and using the same hand, hold on to the syringe barrel to help steady it and prevent shifting.

Step 7: Using the thumb, depress the plunger to inject the FUZEON.

After the dose is fully delivered, remove the needle from the skin.

Hold the barrel of the syringe with one hand and gently press the coloured needle protection device down on a **flat surface** until it covers the needle. You will hear a click. **Do not use your free hand to press the device over the needle.**



Discard the syringe into the sharps waste container.

Cover the injection site with a bandage if any blood or medicine is present.

Discarding Used Syringes and Other Supplies

To minimize the release of pharmaceuticals in the environment, medicine should not be disposed via wastewater or through household waste. Discard all used syringes directly into the sharps container. Keep the cover of this container tight and keep the container out of the reach of children. Check with your healthcare professional about proper disposal of the container. **Do not overfill your sharps waste container.** If your container fills up before your next refill of FUZEON contact your physician or pharmacy.

In addition, you should safely discard all used alcohol pads and vials, even if the vials contain unused amounts of medicine or sterile water for injection. The vials of FUZEON and sterile water for injection are intended for single use only. Used supplies other than syringes (alcohol pads and vials) may be discarded into the trash as long as no blood is visible. If blood is visible, discard the items into the sharps waste container.

If you have any questions or concerns about the safe disposal of these materials, please call your healthcare professional.

This guide does not provide all known information about FUZEON. If you have any questions or concerns about your treatment, please speak with your doctor or pharmacist.