ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fuzeon 90 mg/ml powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 108 mg enfuvirtide.
Each ml of reconstituted solution contains 90 mg enfuvirtide.
Excipient with known effect: sodium. Contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
White to off-white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fuzeon is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected patients who have received treatment with and failed on regimens containing at least one medicinal product from each of the following antiretroviral classes: protease inhibitors, non-nucleoside reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitors, or who have intolerance to previous antiretroviral regimens (see section 5.1).

In deciding on a new regimen for patients who have failed an antiretroviral regimen, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different medicinal products. Where available, resistance testing may be appropriate (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Fuzeon should be prescribed by physicians who are experienced in the treatment of HIV infection.

Posology

Adults and adolescents ≥ 16 years: The recommended dose of Fuzeon is 90 mg twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen.

In case a Fuzeon dose is missed, patients should be instructed to administer the dose as soon as possible. However, if it is less than 6 hours before the next regular dose, the missed dose should be skipped

Elderly: There is no experience in patients > 65 years old.

Children ≥ 6 years and adolescents: The experience in children is limited (see section 5.2). In clinical trials the dosage regimen in Table 1 below was used:

Table 1: Paediatric Dosing

Weight (kg)	Dose per bid injection (mg/dose)	Injection volume (90 mg enfuvirtide per ml)
11.0 to 15.5	27	0.3 ml
15.6 to 20.0	36	0.4 ml
20.1 to 24.5	45	0.5 ml
24.6 to 29.0	54	0.6 ml
29.1 to 33.5	63	0.7 ml
33.6 to 38.0	72	0.8 ml
38.1 to 42.5	81	0.9 ml
≥42.6	90	1.0 ml

Fuzeon is not recommended for use in children below age 6 due to insufficient data on safety and efficacy (see section 5.2).

Renal impairment: No dose adjustment is required for patients with renal impairment including those receiving dialysis (see sections 4.4 and 5.2).

Hepatic impairment: No data are available to establish a dose recommendation for patients with hepatic impairment (see sections 4.4 and 5.2).

Method of Administration

Fuzeon is only to be administered by subcutaneous injection. For instructions on reconstitution before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Fuzeon must be taken as part of a combination regimen. Please also refer to the respective summary of product characteristics of the other antiretroviral medicinal products used in the combination. As with other antiretrovirals, enfuvirtide should optimally be combined with other antiretrovirals to which the patient's virus is sensitive (see section 5.1).

Patients should be informed that Fuzeon is not a cure for HIV-1 infection.

Animal studies have shown that enfuvirtide may impair some immune functions (see section 5.3). In clinical trials, an increased rate of some bacterial infections, most notably a higher rate of pneumonia, was seen in patients treated with Fuzeon; however, an increased risk of bacterial pneumonia related to the use of Fuzeon has not been confirmed by subsequent epidemiological data.

Hypersensitivity reactions have occasionally been associated with therapy with enfuvirtide and in rare cases hypersensitivity reactions have recurred on rechallenge. Events included rash, fever, nausea and vomiting, chills, rigors, low blood pressure and elevated serum liver transaminases in various combinations, and possibly primary immune complex reaction, respiratory distress and glomerulonephritis. Patients developing signs/symptoms of a systemic hypersensitivity reaction should discontinue enfuvirtide treatment and should seek medical evaluation immediately. Therapy with

enfuvirtide should not be restarted following systemic signs and symptoms consistent with a hypersensitivity reaction considered related to enfuvirtide. Risk factors that may predict the occurrence or severity of hypersensitivity to enfuvirtide have not been identified.

Liver disease: The safety and efficacy of enfuvirtide has not been specifically studied in patients with significant underlying liver disorders. Patients with chronic hepatitis B and C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events. Few patients included in the phase III trials were co-infected with hepatitis B/C. In these the addition of Fuzeon did not increase the incidence of hepatic events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Administration of Fuzeon to non-HIV-1 infected individuals may induce anti-enfuvirtide antibodies that cross-react with HIV gp41. This may result in a false positive HIV test with the anti-HIV ELISA test.

There is no experience in patients with reduced hepatic function. Data is limited in patients with moderate to severe renal impairment, and in patients maintained on dialysis. Fuzeon should be used with caution in these populations (see sections 4.2 and 5.2).

Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and can occur many months after initiation of treatment.

Osteonecrosis:

Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

No clinically significant pharmacokinetic interactions are expected between enfuvirtide and concomitantly given medicinal products metabolised by CYP450 enzymes.

Influence of enfuvirtide on metabolism of concomitant medicinal products: In an *in-vivo* human metabolism study enfuvirtide, at the recommended dose of 90 mg twice daily, did not inhibit the metabolism of substrates by CYP3A4 (dapsone), CYP2D6 (debrisoquine), CYP1A2 (caffeine), CYP2C19 (mephenytoin), and CYP2E1 (chlorzoxazone).

Influence of concomitant medicinal products on enfuvirtide metabolism: In separate pharmacokinetic interaction studies, co-administration of ritonavir (potent CYP3A4 inhibitor) or saquinavir in combination with a booster dose of ritonavir or rifampicin (potent CYP34A inducer) did not result in clinically significant changes of the pharmacokinetics of enfuvirtide.

4.6 Fertility, pregnancy and lactation

Pregnancy: There are no adequate and well-controlled studies in pregnant women. Animal studies do not indicate harmful effects with respect to foetal development. Enfuvirtide should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding: It is not known whether enfuvirtide is secreted in human milk. It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV and any possible undesirable effects in breast-fed infants.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. There is no evidence that enfuvirtide may alter the patient's ability to drive and use machines, however, the adverse event profile of enfuvirtide should be taken into account (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

Safety data mainly refer to 48-week data from studies TORO 1 and TORO 2 combined (see section 5.1). Safety results are expressed as the number of patients with an adverse reaction per 100 patient-years of exposure (except for injection site reactions).

The most frequently reported events were injection site reactions, diarrhoea and nausea. The addition of Fuzeon to background antiretroviral therapy generally did not increase the frequency or severity of most adverse reactions.

b. Tabulated list of adverse reactions

Table 2 presents events seen at a higher rate among patients receiving Fuzeon + OB regimen than among patients on the OB alone regimen with an exposure adjusted increase of at least 2 patients with event per 100 patient-years. A statistically significant increase was seen for pneumonia and lymphadenopathy. Most adverse reactions were of mild or moderate intensity. Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 2: Adverse reactions attributed to treatment with Fuzeon in studies TORO 1 and TORO 2 combined

System organ class **Frequency**	***Adverse reaction***
Infections and infestations Common	Sinusitis, skin papilloma, influenza, pneumonia, ear infection
Blood and lymphatic system disorders Common	Lymphadenopathy
Metabolism and nutrition disorders Common	Appetite decreased, anorexia, hypertriglyceridaemia, blood triglycerides increased, diabetes mellitus
Psychiatric disorders Common	Anxiety, nightmare, irritability
Nervous system disorders Very common Common	Peripheral neuropathy Hypoaesthesia, disturbance in attention, tremor
Eye disorders Common	Conjunctivitis
Ear and labyrinth disorders Common	Vertigo
Respiratory, thoracic and mediastinal disorders Common	Nasal congestion
Gastrointestinal disorders Common	Pancreatitis, gastro-oesophageal reflux disease
Skin and subcutaneous tissue disorders Common	Dry skin, eczema seborrhoeic, erythema, acne
Musculoskeletal, connective tissue and bone disorders Common	Myalgia
Renal and Urinary Disorders Common	Nephrolithiasis, haematuria
General disorders and administration site conditions Very common Common	Weight decreased Influenza like illness, asthenia

c. Description of selected adverse reactions

Injection site reactions

Injection site reactions (ISRs) were the most frequently reported adverse reaction and occurred in 98% of the patients (Table 3). The vast majority of ISRs occurred within the first week of Fuzeon administration and were associated with mild to moderate pain or discomfort at the injection site

without limitation of usual activities. The severity of the pain and discomfort did not increase with treatment duration. The signs and symptoms generally lasted equal to or less than 7 days. Infections at the injection site (including abscess and cellulitis) occurred in 1.5% of patients.

Table 3: Summary of individual signs/symptoms characterising local injection site reactions in studies TORO 1 and TORO 2 combined (% of patients)

	n=663		
Withdrawal Rate due to ISRs	4%		
Event Category	**Fuzeon +Optimised background[a]**	**% of Event comprising Grade 3 reactions**	**% of Event comprising Grade 4 reactions**
Pain / discomfort	96.1%	11.0%[b]	0%[b]
Erythema	90.8%	23.8%[c]	10.5%[c]
Induration	90.2%	43.5%[d]	19.4%[d]
Nodules and cysts	80.4%	29.1%[e]	0.2%[e]
Pruritus	65.2%	3.9%[f]	NA
Ecchymosis	51.9%	8.7%[g]	4.7%[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 hospitalisation or prolongation of hospitalisation, resulting in death, or persistent or significant disability/incapacity, or life-threatening, or medically significant.
[c]Grade 3= ≥ 50 mm but < 85 mm average diameter; Grade 4= ≥ 85 mm average diameter.
[d]Grade 3= ≥ 25 mm but < 50 mm average diameter; Grade 4= ≥ 50 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.

In addition there have been a small number of hypersensitivity reactions attributed to enfuvirtide and in some cases recurrence has occurred upon re-challenge (see section 4.4).

Other adverse reactions

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

As a peptide, enfuvirtide can cause cutaneous amyloidosis at the injection site.

Laboratory abnormalities

The majority of patients had no change in the toxicity grade of any laboratory parameter during the study except for those listed in Table 4. Through week 48, eosinophilia [greater than the Upper Limit of Normal of > 0.7 x 10^9/l] occurred at a higher rate amongst patients in the Fuzeon containing group (12.4 patients with event per 100 patient-years) compared with OB alone regimen (5.6 patients with event per 100 patient-years). When using a higher threshold for eosinophilia (>1.4 x 10^9/l), the patient exposure adjusted rate of eosinophilia is equal in both groups (1.8 patients with event per 100 patient-years).

Table 4: Exposure adjusted Grade 3 & 4 laboratory abnormalities among patients on Fuzeon+OB and OB alone regimens, reported at more than 2 patients with event per 100 patient years

Laboratory Parameters Grading	**Fuzeon+OB regimen Per 100 patient years**	**OB alone regimen Per 100 patient years**
n (Total Exposure patient years)	**663 (557.0)**	**334 (162.1)**
ALAT		
Gr. 3 (>5-10 x ULN)	4.8	4.3
Gr. 4 (>10 x ULN)	1.4	1.2
Haemoglobin		
Gr. 3 (6.5-7.9 g/dL)	2.0	1.9
Gr. 4 (<6.5 g/dL)	0.7	1.2
Creatinine phosphokinase		
Gr. 3 (>5-10 x ULN)	8.3	8.0
Gr. 4 (>10 x ULN)	3.1	8.6

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported. 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 reactions that were not seen with the recommended dose. In an Early Access Program study, one patient was administered 180 mg of Fuzeon as a single dose on one occasion. He did not experience an adverse reaction as a result.

There is no specific antidote for overdose with enfuvirtide. Treatment of overdose should consist of general supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antivirals, ATC code: J05AX07

Mechanism of Action: Enfuvirtide is a member of the therapeutic class called fusion inhibitors. It is an inhibitor of the structural rearrangement of HIV-1 gp41 and functions by specifically binding to this virus protein extracellularly thereby blocking fusion between the viral cell membrane and the target cell membrane, preventing the viral RNA from entering into the target cell.

Antiviral activity *in vitro*: The susceptibility to enfuvirtide of 612 HIV recombinants containing the env genes from HIV RNA samples taken at baseline from patients in Phase III studies gave a geometric mean EC_{50} of 0.259 μg/ml (geometric mean + 2SD = 1.96 μg/ml) in a recombinant phenotype HIV entry assay. Enfuvirtide also inhibited HIV-1 envelope mediated cell-cell fusion. Combination studies of enfuvirtide with representative members of the various antiretroviral classes exhibited additive to synergistic antiviral activities and an absence of antagonism. The relationship between the *in vitro* susceptibility of HIV-1 to enfuvirtide and inhibition of HIV-1 replication in humans has not been established.

Antiretroviral drug resistance: Incomplete viral suppression may lead to the development of drug resistance to one or more components of the regimen.

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

In Vivo resistance to enfuvirtide: In phase III clinical studies HIV recombinants containing the env genes from HIV RNA samples taken up to week 24 from 187 patients showed > 4 fold reduced susceptibility to enfuvirtide compared with the corresponding pre-treatment samples. Of these, 185 (98.9%) env genes carried specific substitutions in region of aa 36 - 45 of gp41. The substitutions observed in decreasing frequency were at aa positions 38, 43, 36, 40, 42 and 45. Specific single substitutions at these residues in gp41 each resulted in a range of decreases from baseline in recombinant viral susceptibility to enfuvirtide. The geometric mean changes ranged from 15.2 fold for V38M to 41.6 fold for V38A. There were insufficient examples of multiple substitutions to determine any consistent patterns of substitutions or their effect on viral susceptibility to enfuvirtide. The relationship of these substitutions to *in vivo* effectiveness of enfuvirtide has not been established. Decrease in viral sensitivity was correlated to the degree of pre-treatment resistance to background therapy. (see Table 6).

Cross-resistance: Due to its novel viral target enfuvirtide is equally active *in vitro* against both wild-type laboratory and clinical isolates and those with resistance to 1, 2 or 3 other classes of antiretrovirals (nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors). Conversely, mutations in aa 36-45 of gp41 which give resistance to enfuvirtide would not be expected to give cross resistance to other classes of antiretrovirals.

Clinical Pharmacodynamic data

Studies in Antiretroviral Experienced Patients: The clinical activity of Fuzeon (in combination with other antiretroviral agents) on plasma HIV RNA levels and CD4 counts have been investigated in two randomised, multicentre, controlled studies (TORO 1 and TORO 2) of Fuzeon of 48 weeks duration. 995 patients comprised the intent-to-treat population. Patient demographics include a median baseline HIV-1 RNA of 5.2 $\log_{10}$ copies/ml and 5.1 $\log_{10}$ copies/ml and median baseline CD4 cell count of 88 cells/mm^3 and 97 cells/mm^3 for Fuzeon + OB and OB, respectively. Patients had prior exposure to a median of 12 antiretrovirals for a median of 7 years. All patients received an optimised background (OB) 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.

The proportion of patients achieving viral load of <400 copies/ml at week 48 was 30.4% among patients on the Fuzeon + OB regimen compared to 12% among patients receiving OB regimen only. The mean CD4 cell count increase was greater in patients on the Fuzeon + OB regimen than in patients on OB regimen only (see Table 5).

Table 5 Outcomes of Randomised Treatment at Week 48 (Pooled Studies TORO 1 and TORO 2, ITT)

Outcomes	Fuzeon + OB 90 mg bid (N=661)	OB (N=334)	Treatment Difference	95% Confidence Interval	p-value
HIV-1 RNA Log Change from baseline (log_{10} copies/ml)*	-1.48	-0.63	LSM -0.85	-1.073, -0.628	<.0001
CD4+ cell count Change from baseline (cells/mm^3)#	+91	+45	LSM 46.4	25.1, 67.8	<.0001
HIV RNA ≥1 log below Baseline**	247 (37.4%)	57 (17.1%)	Odds Ratio 3.02	2.16, 4.20	<.0001
HIV RNA <400 copies/ml**	201 (30.4%)	40 (12.0%)	Odds Ratio 3.45	2.36, 5.06	<.0001
HIV RNA <50 copies/ml**	121 (18.3%)	26 (7.8%)	Odds Ratio 2.77	1.76, 4.37	<.0001
Discontinued due to adverse reactions/intercurrent illness/labs†	9%	11%			
Discontinued due to injection site reactions†	4%	N/A			
Discontinued due to other reasons†ϕ§	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 had virological failure replaced by their last observation (LOCF).

\# Last value carried forward.

** M-H test: Discontinuations or virological failure considered as failures.

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

ϕ As per the judgment of the investigator.

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

Fuzeon + OB therapy was associated with a higher proportion of patients reaching <400 copies/ml (or <50 copies/ml) across all subgroups based on baseline CD4, baseline HIV-1 RNA, number of prior antiretrovirals (ARVs) or number of active ARVs in the OB regimen. However, subjects with baseline CD4 >100 cells/mm^3, baseline HIV-1 RNA <5.0 log_{10} copies/ml, ≤ 10 prior ARVs, and/or other active ARVs in their OB regimen were more likely to achieve a HIV-1 RNA of <400 copies/ml (or <50 copies/ml) on either treatment (see Table 6).

Table 6 Proportion of Patients achieving <400 copies/ml and <50 copies/ml at Week 48 by subgroup (pooled TORO 1 and TORO 2, ITT)

Subgroups	HIV-1 RNA < 400 copies/ml		HIV-1 RNA < 50 copies/ml	
	Fuzeon + OB 90 mg bid (N=661)	OB (N=334)	Fuzeon + OB 90 mg bid (N=661)	OB (N=334)
BL HIV-1 RNA < 5.0 log_{10}[1] copies/ml	118/269 (43.9%)	26/144 (18.1%)	77/269 (28.6%)	18/144 (12.5%)
BL HIV-1 RNA ≥ 5.0 log_{10}[1] copies/ml	83/392 (21.2%)	14/190 (7.4%)	44/392 (11.2%)	8/190 (4.2%)
Total prior ARVs ≤ 10[1]	100/215 (46.5%)	29/120 (24.2%)	64/215 (29.8%)	19/120 (15.8%)
Total prior ARVs > 10[1]	101/446 (22.6%)	11/214 (5.1%)	57/446 (12.8%)	7/214 (3.3%)
0 Active ARVs in background[1,2]	9/112 (8.0%)	0/53 (0%)	4/112 (3.5%)	0/53 (0%)
1 Active ARV in background[1,2]	56/194 (28.9%)	7/95 (7.4%)	34/194 (17.5%)	3/95 (3.2%)
≥ 2 Active ARVs in background[1,2]	130/344 (37.8%)	32/183 (17.5%)	77/334 (22.4%)	22/183 (12.0%)

[1]Discontinuations or virological failures considered as failures.
[2]Based on GSS score.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of enfuvirtide have been evaluated in HIV-1-infected adult and paediatric patients.

Absorption: The absolute bioavailability after subcutaneous administration of enfuvirtide 90 mg in the abdomen was 84.3 ± 15.5%. Mean (± SD) C_{max} was 4.59 ± 1.5 μg/ml, AUC was 55.8 ± 12.1 μg*hr/ml The subcutaneous absorption of enfuvirtide is proportional to the administered dose over the 45 to 180 mg dose range. Subcutaneous absorption at the 90 mg dose is comparable when injected into abdomen, thigh or arm. In four separate studies (N = 9 to 12) the mean steady state trough plasma concentration ranged from 2.6 to 3.4 μg/ml.

Distribution: The steady state volume of distribution with intravenous administration of a 90 mg dose of enfuvirtide was 5.5 ± 1.1 l. Enfuvirtide is 92% bound to plasma proteins in HIV infected plasma over a plasma concentration range of 2 to 10 μg/ml. It is bound predominantly to albumin and to a lower extent to α-1 acid glycoprotein. In *in vitro* studies, enfuvirtide was not displaced from its binding sites by other medicinal products, nor did enfuvirtide displace other medicinal products from their binding sites. In HIV patients, enfuvirtide levels in the cerebrospinal fluid have been reported to be negligible.

Biotransformation: 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 vitro* human microsomal studies and in *in vivo* studies indicate that enfuvirtide is not an inhibitor of CYP450 enzymes. 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 and the formation of this metabolite 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.

Elimination: Clearance of enfuvirtide after intravenous administration 90 mg was 1.4 ± 0.28 l/h and the elimination half-life was 3.2 ± 0.42 h. Following a 90 mg subcutaneous dose of enfuvirtide the half-life of enfuvirtide is 3.8 ± 0.6 h. Mass balance studies to determine elimination pathway(s) of enfuvirtide have not been performed in humans.

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

Renal impairment: 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 mild to moderate renal impairment. In a renal impairment study AUC of enfuvirtide was increased on average by 43-62% in patients with severe or end stage renal disease compared to patients with normal renal function. Haemodialysis did not significantly alter enfuvirtide clearance. Less than 13% of the dose was removed during haemodialysis. No dose adjustment is required for patients with impaired renal function.

Elderly: The pharmacokinetics of enfuvirtide have not been formally studied in elderly 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 irrespective of weight 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 Afro-Americans compared to Caucasians. Other PK studies suggest no difference between Asians and Caucasians after adjusting exposure for body weight.

Paediatric population: The pharmacokinetics of enfuvirtide have been studied in 37 paediatric patients. A dose of 2 mg/kg bid (maximum 90 mg bid) provided enfuvirtide plasma concentrations similar to those obtained in adult patients receiving 90 mg bid dosage. In 25 paediatric patients ranging in age from 5 to 16 years and receiving the 2 mg/kg bid dose into the upper arm, anterior thigh or abdomen, the mean steady-state AUC was 54.3 ± 23.5 μg*h/ml, C_{max} was 6.14 ± 2.48 μg/ml, and C_{trough} was 2.93 ± 1.55 μg/ml.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and late embryonal development. Long-term animal carcinogenicity studies have not been performed.

Studies in guinea pigs indicated a potential for enfuvirtide to produce delayed contact hypersensitivity. In a rat model on the resistance to influenza infection, an impairment of IFN-γ production was observed. The resistance to influenza and streptococcal infection in rats was only weakly compromised. The clinical relevance of these findings is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Sodium carbonate
Mannitol
Sodium hydroxide
Hydrochloric Acid

Solvent

Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Powder

4 years

Solvent

4 years

Shelf life after reconstitution

After reconstitution: Store in a refrigerator (2°C – 8°C).
Chemical and physical in-use stability has been demonstrated for 48 hours at 5°C when protected from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Powder

Keep the vial in the outer carton in order to protect from light. For storage conditions after reconstitution of the medicinal product, see section 6.3.

Solvent

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Powder

Vial:	3 ml vial, colourless glass type 1
Closure:	lyophilisate stopper, rubber (latex free)
Seal:	aluminium seal with flip-off cap

Solvent

Vial:	2 ml vial, colourless glass type 1
Closure:	rubber stopper (latex free)
Seal:	aluminium seal with flip-off cap

Pack sizes

60 vials powder for solution for injection
60 vials solvent
60 3 ml syringes
60 1 ml syringes
180 alcohol swabs

6.6 Special precautions for disposal and reconstitution

Any unused medicinal product should be disposed of in accordance with local requirements.

Patients should be instructed on the use and administration of Fuzeon by a healthcare professional before using for the first time.

Fuzeon must only be reconstituted with 1.1 ml of Water for Injections. Patients must be instructed to add the water for injections and then gently tap the vial with their fingertip until the powder begins to dissolve. **They must never shake the vial or turn it upside down to mix—this will cause excessive foaming**. After the powder begins to dissolve they can set the vial aside to allow it to completely dissolve. The powder may take up to 45 minutes to dissolve into solution. The patient can gently roll the vial between their hands after adding the water for injections until it is fully dissolved and this may reduce the time it takes for the powder to dissolve. Before the solution is withdrawn for administration, the patient should inspect the vial visually to ensure that the contents are fully in solution, and that the solution is clear 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.

The solvent vials contain 2 ml Water for Injections, of which 1.1 ml must be withdrawn for the reconstitution of the powder. Patients should be instructed to discard the remaining volume in the solvent vials.

Fuzeon contains no preservative. Once reconstituted, the solution should be injected immediately. If the reconstituted solution cannot be injected immediately, it must be kept refrigerated until use and used within 24 hours. Refrigerated reconstituted solution should be brought to room temperature before injection.

1 ml of the reconstituted solution should be injected subcutaneously in to 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. A vial is suitable for single use only; unused portions must be discarded.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/252/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 May 2003
Date of latest renewal: 27 May 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the web site of the European Medicines Agency: http://www.ema.europa.eu/

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Roche Pharma AG, Emil-Barrell-Str. 1, D-79639 Grenzach-Wyhlen, Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2.)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Fuzeon 90 mg/ml powder and solvent for solution for injection
Enfuvirtide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 108 mg enfuvirtide.
1 ml of reconstituted solutions contains 90 mg enfuvirtide.

3. LIST OF EXCIPIENTS

Each vial with powder also contains sodium carbonate (anhydrous), mannitol, sodium hydroxide and hydrochloric acid.

Each solvent vial contains 2 ml Water for Injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents of the box:
60 vials with powder for solution for injection
60 vials with solvent
60 3 ml syringes
60 1 ml syringes
180 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton in order to protect from light

After reconstitution store in a refrigerator

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

The remaining Water for Injections in the solvent vial after withdrawal of the 1.1 ml required for reconstitution has to be discarded

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/252/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

IMMEDIATE OUTER CARTON FOR FUZEON VIALS

1. NAME OF THE MEDICINAL PRODUCT

Fuzeon 90 mg/ml powder for solution for injection
Enfuvirtide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 108 mg enfuvirtide.
1 ml of reconstituted solution contains 90 mg of enfuvirtide.

3. LIST OF EXCIPIENTS

Each vial also contains sodium carbonate (anhydrous), mannitol, sodium hydroxide and hydrochloric acid.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection

60 vials with powder for solution for injection

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton in order to protect from light
After reconstitution store in a refrigerator

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/252/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

FUZEON VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Fuzeon 90 mg/ml powder for solution for injection
Enfuvirtide
Subcutaneous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

108 mg enfuvirtide

6. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

IMMEDIATE OUTER CARTON FOR WATER FOR INJECTIONS VIALS

1. NAME OF THE MEDICINAL PRODUCT

Solvent for solution
Water for Injections

2. STATEMENT OF ACTIVE SUBSTANCE(S)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Solvent for parenteral use
Contained in this box are 60 vials of 2 ml water for injections

5. METHOD AND ROUTE(S) OF ADMINISTRATION

This water for injections is intended for the reconstitution of Fuzeon 90 mg/ml powder for solution for injection to obtain a solution for subcutaneous use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

The remaining Water for Injections in the solvent vial after withdrawal of the 1.1 ml required for reconstitution has to be discarded

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/252/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

WATER FOR INJECTIONS VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for solution
Water for Injections
Subcutaneous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Fuzeon 90 mg/ml powder and solvent for solution for injection
Enfuvirtide

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Fuzeon is and what it is used for

What Fuzeon is

Fuzeon contains the active substance enfuvirtide and belongs to a group of medicines called ‘antiretrovirals’.

What Fuzeon is used for

Fuzeon is used for the treatment of Human Immune deficiency Virus (HIV) - in combination with other antiretroviral medicines in patients infected with HIV.
- Your doctor has prescribed Fuzeon to help control your HIV infection.
- Fuzeon is not a cure for HIV infection.

How Fuzeon works

HIV attacks cells in your blood called CD4 or T-cells. The virus needs to make contact with, and get inside these cells in order for the virus to multiply. Fuzeon helps by preventing this.

2. What you need to know before you use Fuzeon

Do not use Fuzeon if

- you are allergic to enfuvirtide or any of the other ingredients of this medicine (listed in section 6).

If you are not sure, talk to your doctor, pharmacist or nurse before using Fuzeon.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Fuzeon if:
- you have ever had any lung problems
- you have ever had any kidney problems
- you have chronic hepatitis B or C or another liver disease - you are more likely to get serious liver problems while using this medicine

Signs of previous infections

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infections, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to a recovery of the body's immune system. This improvement enables the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

Signs of autoimmune disorders

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

Patients with liver disease

Patients with chronic hepatitis B or C and treated with anti-HIV therapy are at an increased risk for serious liver problems. Speak with your doctor if you have a history of liver disease.

Bone disease (osteonecrosis)

Some patients taking combination anti-HIV medicines may develop a bone disease called osteonecrosis. This is where the bone tissue dies because the blood supply has been lost (death of bone tissue caused by loss of blood supply to the bone).

- Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these signs please inform your doctor.

- Risk factors for developing this disease include: how long you have been taking anti-HIV medicines, whether you take corticosteroids, how much alcohol you drink, how well your immune system works and being overweight.

Other medicines and Fuzeon

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines. Fuzeon has been shown not to interact with your other anti-HIV medicines or rifampicin (an antibiotic).

Fuzeon with food and drink

You can use Fuzeon with or without food. However, you still need to follow the instructions given in the package leaflets for the other medicines you are taking.

Pregnancy and breast-feeding

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. You should not use Fuzeon unless specifically told to by your doctor.
- Breast-feeding is not recommended in women living with HIV because HIV infection can be passed on to the baby in breast milk. If you are breast-feeding, or thinking about breast-feeding, you should discuss it with your doctor as soon as possible.

Driving and using machines

Fuzeon has not been tested for its effect on your ability to drive a car or use tools or machines. If you feel dizzy while using Fuzeon do not drive or use any tools or machines.

Fuzeon contains sodium

Fuzeon contains less than 1 mmol sodium (23 mg) per dose, that is to say it is essentially 'sodium-free'.

3. How to use Fuzeon

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How to prepare and inject Fuzeon

Fuzeon must be given as an injection just below the skin – called a 'subcutaneous' injection. Section 7 tells you how to prepare Fuzeon and how to give yourself an injection.

How much to use

- The recommended dose is 90 mg twice a day for adults and adolescents (16 years and older).
- This is given as a 1 ml injection just below the skin.
- It is best to use Fuzeon at the same time each day.
- Try and space the doses evenly apart at times which are good for you – for example, first thing in the morning and then in the early evening.

See further instructions on how to use Fuzeon at the end of this leaflet (see Section 7). There you will find instructions on how to prepare Fuzeon and how to give yourself an injection.

If you use more Fuzeon than you should

If you use more Fuzeon than you should, talk to a doctor or go to a hospital straight away. Take the medicine pack with you.

If you forget to use Fuzeon

- If you forget to use a dose, use it as soon as you remember it. However if it is less than 6 hours before you are going to take your next regular dose, skip the missed dose.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Fuzeon

- Keep using your medicine until your doctor tells you to stop. If you stop and there is a gap in your treatment this may speed up the chances of the HIV in your blood becoming resistant to Fuzeon. This is less likely if you use it regularly and without gaps in treatment.
- The HIV virus in your blood may eventually become resistant to Fuzeon. If this happens, your blood levels of virus may begin to rise. This is when your doctor may decide to no longer keep treating you with Fuzeon. Your doctor should discuss this with you at that time.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop using Fuzeon and see a doctor straight away, if you notice any of the following serious side effects – you may need urgent medical treatment:

- Allergic reaction (hypersensitivity) – signs may include: rash, a high temperature or chills, feeling or being sick, sweating or shaking.

This side effect is rare (affects less than 1 in 1,000 people). These signs do not definitely mean you are allergic to this medicine.

Tell your doctor if you get side effects where the injection is given

The most common side effects (affect more than 1 in 10 people), are problems at the place on your body where you have the injection. You will probably have one or more of the following mild to moderate reactions:

- redness
- swelling
- feeling itchy
- bruises
- hardened skin or bumps
- pain, feeling sore or tender

These reactions can appear in the first week of treatment and usually only last for up to 7 days. They generally do not get worse after this time. If you have any of these reactions do not stop using Fuzeon, but talk to your doctor about any concerns you have.

Reactions may be worse when injections are repeated in the same place on the body. They may also be worse when the injection is given deeper than intended (for example, into a muscle). Rarely, you may get an infection at a place where an individual injection was given. To reduce the risk of infection, it is important that you follow the instructions provided in Section 7.

Fuzeon can cause a build-up of a type of protein, called amyloid, under the skin at the injection site. This may feel like lumps under the skin. Please contact your doctor if this occurs.

Other possible side effects

Very common *(affects more than 1 in 10 people)*

- diarrhoea
- feeling sick
- weight loss
- pain and feeling numb in hands, feet or legs.

Common *(affects less than 1 in 10 people)*

- pneumonia
- ear infection
- swollen glands (lymph nodes)
- inflamed eye (conjunctivitis)
- flu or 'flu-like' symptoms
- inflamed sinuses
- nasal congestion
- anorexia
- heart burn
- inflamed pancreas
- decreased appetite
- diabetes,
- nightmares
- feeling dizzy
- shaking (tremor)
- feeling anxious or irritated
- not being able to concentrate
- decreased sensation
- acne
- redness of the skin
- eczema
- dry skin
- warts
- muscle pain
- kidney stones
- feeling weak
- blood in the urine
- changes shown in blood tests (increased blood fat)

Reporting of side effects

If you get anyside effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Fuzeon

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label of either the Fuzeon or the Water for Injections Vials after EXP. The expiry date refers to the last day of that month.

Keep the vial in the outer carton in order to protect from light.

Once the solution has been prepared for your injection it should be used immediately. If it is not used straight away it must be stored in a refrigerator (2°C – 8°C) and used within 24 hours.

Do not use this medicine if you notice any particles in the powder or the solution once the water for injection has been added. Also do not use the Water for Injections if you see any particles in the vial or if the water is cloudy.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Fuzeon contains

- The active substance is enfuvirtide. Each vial contains 108 mg enfuvirtide. After reconstitution with the solvent provided 1 ml of reconstituted solution contains 90 mg enfuvirtide.
- The other ingredients are:

Powder

Sodium Carbonate, anhydrous
Mannitol
Sodium Hydroxide
Hydrochloric Acid

Solvent

Water for Injections

See section 2 “Fuzeon contains sodium”.

What Fuzeon looks like and contents of the pack

Fuzeon powder and solvent for solution for injection comes in a carton containing:

60 vials of Fuzeon
60 vials of Water for Injections that is used to reconstitute the Fuzeon powder
60 3 ml syringes
60 1 ml syringes
180 alcohol swabs.

This pack provides you with everything you need to prepare and take your Fuzeon for 30 days of injections.

Marketing Authorisation Holder

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

The Manufacturer responsible for batch release is

Roche Pharma AG
Emil-Barell-Str. 1,
D-79639 Grenzach-Wyhlen
Germany

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

7. STEP-BY-STEP GUIDE TO INJECTING FUZEON

Always use this medicine exactly as your doctor or pharmacist has told you. You should check with your doctor, pharmacist or nurse if you are not sure.

What to do if you are left-handed

The pictures in this leaflet show people who are right-handed. If you are left-handed, do what comes naturally to you. You will probably find it most comfortable to:
- hold the syringe in your left hand and
- hold the vial between the thumb and forefinger of your right hand.

When to have someone to help you

It may be difficult at first to inject in some places, such as the upper arms. If you need help, ask your partner, a friend, or a family member. You may like to ask someone to come with you to an injection training session with your doctor or nurse.

Your syringes

The syringes supplied with this medicine have a coloured needle protector. This is attached to the needle and covers it after use to lower the risk of the needle accidently pricking another person. Although these syringes have this safety feature, it is still important that you dispose of used syringes properly. Follow the instructions given to you by your doctor, pharmacist or nurse.

Safety Tips

- Wash your hands well. This will reduce the risk of bacterial infections.
- Once you have washed your hands, 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 swabs.
- Do not use opened materials. Make sure none of the items in your kit have been opened before use.

- Never use or share used needles.
- Never use a syringe with a bent or damaged needle.
- Never mix your medicine with tap water.
- Never inject your medicine with other injectable medicines.
- Only inject Fuzeon under the skin (‘subcutaneous’).
- Do not inject Fuzeon into your veins (‘intravenously’) or into your muscles (‘intramuscularly’).
- Dispose of all used materials into your special waste container with a lid. Do this even if the vials contain unused amounts of medicine or Water for Injections as these are for single use only. Talk to your doctor, pharmacist or nurse if you have any questions about safe disposal of these items.

The following is a basic, step-by-step guide to injecting your medicine.

Step A: Getting Started

1. Get the following things together:
- One vial of Fuzeon (glass container with white powder inside)
- One vial of Water for Injections (glass container with clear and colourless liquid inside)
- One 3 ml syringe (larger syringe) with a 25 mm needle
- One 1 ml syringe (smaller syringe) with a 13 mm needle
- Three alcohol swabs
- Special waste container with a lid for the safe disposal of the waste materials.

2. Open syringe packs and take off vial caps.
- Dispose of packaging and vial caps into your special waste container with a lid.
- Place syringes and vials onto a clean surface.

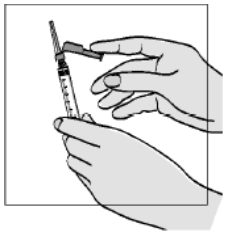
3. Wash hands thoroughly.
- After washing your hands, do not touch anything except the injection supplies and where the injection will be given.

4. Clean the tops of the vials.
- Wipe each vial top with a fresh alcohol pad. Let the tops dry in the air.
- Make sure you do not touch the rubber tops after cleaning them. If you touch them, make sure you clean them again.

Step B: Mixing Fuzeon

Draw Up Water for Injections

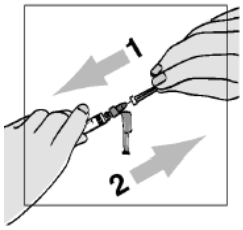
1. Pick up the **3 ml large syringe**. Using your index finger, move the coloured needle protector away from the needle.



2. To make sure that the needle is firmly on the syringe:
- hold the plastic cap under the needle protector

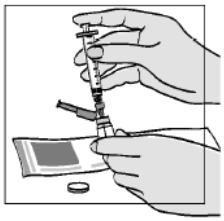
- tighten the needle and cap with a gentle clockwise twist. Do not use too much force as the needle may loosen.

3. To remove the clear plastic cap:
- push towards the syringe and then pull the cap off.



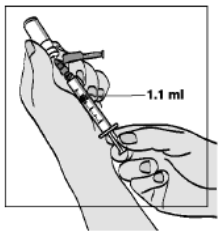
4. Draw back 1.1 ml of air.

5. Push the syringe needle into the rubber top of the vial of Water for Injections and press the plunger. This injects the air.



6. Gently turn the vial upside down. **Make sure the tip of the needle is always below the surface of the Water for Injections to help keep any air bubbles from entering the syringe.**

7. Slowly pull back the plunger until the water reaches the 1.1 ml mark. **Please be aware that the vial contains more liquid than you need (2 ml); you only have to pull out 1.1 ml to prepare your injection properly.**



8. Tap the syringe gently to make any air bubbles rise to the top.

- If too much air gets into the syringe, gently press the plunger to force any air back into the vial.
- Then pull out the water again.
- Make sure you have 1.1 ml of Water for Injections in the syringe.
- This step may be repeated until the correct amount of Water for Injections is in the syringe.

9. Take out the needle from the vial. **Make sure you never touch the needle with your fingers or anything else**.

10. Dispose of the vial and the Water for Injections into your special waste container with a lid - this vial is for single use only.

Injecting Water For Injections Into Fuzeon Powder

1. Gently tap the vial of Fuzeon to loosen the powder.

2. Hold the main part of the water-filled syringe and push the needle through the rubber top of the vial at a slight angle.

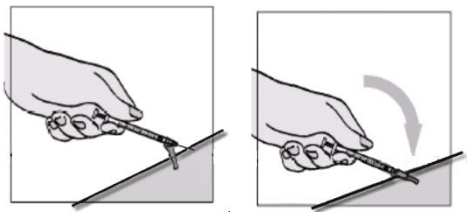
3. Press the syringe plunger in slowly.

- Let the water 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 happens, it may take longer for the powder to dissolve completely.

4. After all of the Water for Injections has been added to the vial of Fuzeon, take out the syringe from the vial.

5. Hold the main part of the syringe with one hand and gently press the coloured needle protector 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.



6. Throw away the syringe into the special waste container with a lid.

Mixing the Water for Injections with the Fuzeon Powder

1. Gently tap the vial with your fingertip until the powder begins to dissolve. **Never shake the vial or turn it upside down to mix—this will cause too much foaming**.

2. When the powder begins to dissolve you can put the vial aside to allow it to completely dissolve.
   - The powder may take up to 45 minutes to dissolve into solution.
   - The vial can also be gently rolled between your hands after adding the Water for Injections until it is fully dissolved.
   - This may reduce the time it takes for the powder to dissolve.

3. After the powder has dissolved completely
   - Let any bubbles that may have formed settle.
   - If the bubbles are still there, gently tap the side of the vial to help settle them.

4 It is important to check the liquid for bits (particles).
   - If you see any bits in the liquid, do not use it.
   - Dispose of the vial into the special waste container with a lid or return it to the pharmacy.

Then start again with a new vial of Fuzeon powder.

5. If you accidentally touch the rubber stopper, make sure to clean it again with a new alcohol swab

6. Once a dose is mixed with Water for Injections, it must be used straight away. If not, store in a refrigerator and use within 24 hours.

- Let the liquid get back to room temperature before using.

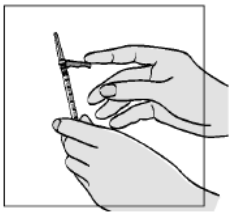
7. If you are preparing both of your daily doses at one time, make sure to use new syringes, Water for Injections, and Fuzeon for each dose.

Step C: Preparing for the injection

Drawing up Fuzeon into the 1 ml syringe

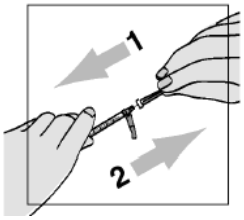
1. Wipe the top of the Fuzeon vial again with a new alcohol swab.

2. Pick up the **1 ml small syringe**. Using your index finger, move back the coloured needle protector away from the needle.



3. To make sure that the needle is firmly on the syringe:
- hold the plastic cap under the needle protector
- tighten the needle and cap by slightly turning and pushing it towards the syringe.

4. To remove the clear plastic cap:
- push towards the syringe and then pull the cap off.



5. Draw back 1 ml of air.
- Be careful not to pull the plunger too fast - it may go past the 1 ml marker or out of the syringe.

6. Push the syringe needle into the rubber top of the Fuzeon vial and press the plunger. This injects the air.

7. 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.

8. Slowly pull back the plunger until the solution reaches the 1.0 ml mark.
- Be careful not to pull the plunger too fast - it may go past the 1 ml marker or out of the syringe.

9. Tap the syringe gently to make any air bubbles rise to the top.

- If too much air enters the syringe, gently press the plunger to force the air back into the vial.

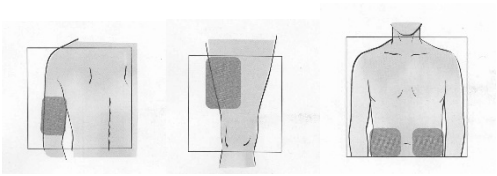
- Then pull out the liquid again.
- Make sure you have 1.0 ml of liquid in the syringe (or whatever amount your doctor prescribed, if it is different).
- This step may be repeated until the correct amount of solution is in the syringe.

10. Take out the syringe from the vial.

Step D: Injecting Fuzeon

Tip: Your doctor or nurse may suggest different injection techniques that will work best for you.

Where to Inject

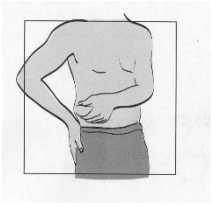


- Fuzeon is given as a 1 ml injection just below the skin – called a 'subcutaneous' injection.
- You can inject into your upper arm, upper thigh or stomach area (abdomen).
- Choose a different area from where you last injected yourself.
- Do not inject to a place where there is still a reaction from an earlier dose. Check for any places where you may have a reaction by pressing the skin to see if there are any hard bumps.
- Do not inject into areas that could become irritated by your belt or the waistline of your clothes.
- Do not inject into moles, scar tissue, bruises or your belly button (navel).

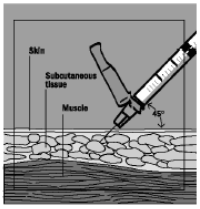
Cleansing the injection site
Clean the area for injection well with an alcohol swab. Do this in a circular motion, starting in the middle and working outward. Allow it to dry in the air completely.

Putting in the needle and injecting

1. Pinch as much of a skin fold as possible - without making yourself uncomfortable.



2. Push the needle into the skin at a 45-degree angle.



3. When the needle is in:
- release the skin
- use this free hand to hold on to the main part of the syringe – this will help steady it and stop it from moving.

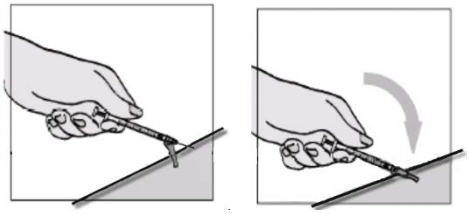
4. Using the thumb of your other hand, press the plunger to inject the liquid.

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

After pulling out the needle

1. Hold the main part of the syringe with one hand
- then gently press the coloured needle protector down on a **flat surface** until it covers the needle.
- you will hear a click.

Do not use your free hand to press the protector over the needle.



2. Dispose of the syringe into a special waste container with a lid.

3. If there is any blood where you have given the injection, cover the skin with a sticking plaster.

Step E: Disposing of used supplies

- Dispose of all used items straight into the special waste container with a lid. Do this even if the vials contain unused amounts of medicine or Water for Injections as these are for single use only.
- Keep the cover of this container tight and keep it out of the reach of children.
- Check with your doctor, pharmacist or nurse about proper disposal of the container.

. If you have any questions or concerns about the safe disposal of these materials, please talk to your doctor, pharmacist or nurse.