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. 1 ml of reconstituted solution contains 90 mg enfuvirtide.

Excipient(s):

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'. For a 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.

Fuzeon is only to be administered by subcutaneous injection.

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.

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 ongoing clinical trials the dosage regimen in table 1 below is being 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 creatinine clearance above 35 ml/min. No data are available to establish a dose recommendation for patients with creatinine clearance below 35 ml/min or 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)

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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 must be advised that antiretroviral therapies including enfuvirtide have not been proved to prevent the risk of transmission to HIV to others through sexual contact or blood contamination. They must continue to use appropriate precautions. Patients should also 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). An increased rate of some bacterial infections, most notably a higher rate of pneumonia, has been seen in patients treated with Fuzeon. Patients should be monitored closely for signs and symptoms of pneumonia. (See section 4.8)

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 or in patients with severe renal impairment and only limited data in patients with moderate renal impairment. 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.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions 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 Pregnancy and lactation

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.

It is not known whether enfuvirtide is secreted in human milk. Mothers should be instructed not to breast-feed if they are receiving enfuvirtide because of the potential for HIV transmission 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

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 event per 100 patient-years of exposure (except for injection site reactions).

Injection site reactions

Injection site reactions (ISRs) were the most frequently reported adverse reaction and occurred in 98% of the patients (Table 2). 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 2: 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.

Other adverse reactions

The addition of Fuzeon to background antiretroviral therapy generally did not increase the frequency or severity of most adverse events. The most frequently reported events occurring in the TORO 1 and TORO 2 studies were diarrhoea (38 versus 73 patients with event per 100 patient years for Fuzeon + OB versus OB) and nausea (27 versus 50 patients with event per 100 patient years for Fuzeon + OB versus OB).

The following list 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. These events are then designated frequency estimation ("very common" (≥1/10), or "common" (≥1/100, <1/10)). A statistically significant increase was seen for pneumonia and lymphadenopathy. Most adverse events were of mild or moderate intensity.

Infections and Infestations
Common (≥1/100, <1/10): - sinusitis, skin papilloma, influenza, pneumonia, ear infection.

Blood and Lymphatic System Disorders
Common (≥1/100, <1/10): - lymphadenopathy.

Metabolism and Nutrition Disorders

Common (≥1/100, <1/10): - appetite decreased, anorexia, hypertriglyceridaemia, diabetes mellitus.

Psychiatric Disorders
Common ((≥1/100, <1/10): - anxiety, nightmare, irritability.

Nervous System Disorders
Very Common (≥1/10): - peripheral neuropathy.
Common (≥1/100, <1/10): -hypoaesthesia, disturbance in attention, tremor.

Eye Disorders
Common (≥1/100, <1/10): - conjunctivitis.

Ear and Labyrinth disorders
Common (≥1/100, <1/10): - vertigo.

Respiratory, Thoracic and Mediastinal Disorders
Common (≥1/100, <1/10): - nasal congestion.

Gastrointestinal Disorders
Common (≥1/100, <1/10): - pancreatitis, gastro-oesophageal reflux disease.

Skin and Subcutaneous Tissue Disorders
Common (≥1/100, <1/10): - dry skin, eczema seborrhoeic, erythema, acne.

Musculoskeletal, Connective Tissue and Bone Disorders
Common (≥1/100, <1/10): - myalgia.

Renal and Urinary Disorders
Common (≥1/100, <1/10): - Calculus renal.

General Disorders and Administration Site Conditions
Common (≥1/100, <1/10): - influenza like illness, weakness.

Investigations
Very Common (≥1/10): - weight decreased
Common (≥1/100, <1/10): - blood triglycerides increased, haematuria present.

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)

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 (see section 4.4).

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 3. 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 3: 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

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 events that were not seen with the recommended dose. In an Early Access Program study, one patient administered 180 mg of Fuzeon as a single dose on one occasion. He did not experience an adverse event 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: antivirals for systemic use, other antivirals, ATC code: J05A X07

This medicinal product has been authorised under "Exceptional Circumstances". This means that for scientific reasons it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency (EMEA) will review any new information which may become available every year and this SPC will be updated as necessary.

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 5)

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 4)

Table 4 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

Outcomes	FUZEON +OB 90 mg bid (N=661)	OB (N=334)	Treatment Difference	95% Confidence Interval	p-value
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 5)

Table 5 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.

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

Renal Insufficiency: A specific pharmacokinetic study has not been conducted in patients with renal impairment or those receiving dialysis. However 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.

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 Blacks compared to Whites. Other PK studies suggest no difference between Asians and Whites after adjusting exposure for body weight.

Paediatric Patients: 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
3 years

Solvent
3 years

Shelf life after reconstitution

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
This medicinal product does not require any special storage conditions.
After reconstitution: Store in a refrigerator (2°C – 8°C). Keep the vial in the outer carton in order to protect from light. For storage conditions of the reconstituted 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: aluminum seal with flip-off cap

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

Pack sizes

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

Pack 2
60 vials powder for solution for injection
60 vials solvent

6.6 Special precautions for disposal

Any unused 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 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 Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/252/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 May 2003

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Fuzeon 90 mg/ml powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s):

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.
Fuzeon is a 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 treatment history of the individual patient and the patterns of mutations associated with different drugs. 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.

Fuzeon is only to be administered by subcutaneous injection.

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.

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 ongoing clinical trials the dosage regimen in Table 1 below is being 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 creatinine clearance above 35 ml/min. No data are available to establish a dose recommendation for patients with creatinine clearance below 35 ml/min or 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)

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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 must be advised that antiretroviral therapies including enfuvirtide have not been proved to prevent the risk of transmission to HIV to others through sexual contact or blood contamination. They must continue to use appropriate precautions. Patients should also 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). An increased rate of some bacterial infections, most notably a higher rate of pneumonia, has been seen in patients treated with Fuzeon. Patients should be monitored closely for signs and symptoms of pneumonia. (See section 4.8)

Hypersensitivity reactions have occasionally been associated with therapy with enfuvirtide and in rare cases hypersensitivity reactions have recurred on re-challenge. 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 gp-41. 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 or in patients with severe renal impairment and only limited data in patients with moderate renal impairment. 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.

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 enfuviritide, 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 Pregnancy and lactation

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.

It is not known whether enfuvirtide is secreted in human milk. Mothers should be instructed not to breast-feed if they are receiving enfuvirtide because of the potential for HIV transmission 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 enfuviritide 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

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 event per 100 patient-years of exposure (except for injection site reactions).

Injection site reactions

Injection site reactions (ISRs) were the most frequently reported adverse reaction and occurred in 98% of the patients (Table 2). 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 2: 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.

Other adverse reactions

The addition of Fuzeon to background antiretroviral therapy generally did not increase the frequency or severity of most adverse events. The most frequently reported events occurring in the TORO 1 and TORO 2 studies were diarrhoea (38 versus 73 patients with event per 100 patient years for Fuzeon + OB versus OB) and nausea (27 versus 50 patients with event per 100 patient years for Fuzeon + OB versus OB).

The following list 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. These events are then designated frequency estimation ("very common" (≥1/10), or "common" (≥1/100, <1/10)). A statistically significant increase was seen for pneumonia and lymphadenopathy. Most adverse events were of mild or moderate intensity.

Infections and Infestations
Common (≥1/100, <1/10): - sinusitis, skin papilloma, influenza, pneumonia, ear infection.

Blood and Lymphatic System Disorders
Common (≥1/100, <1/10): - lymphadenopathy.

Metabolism and Nutrition Disorders

Common (≥1/100, <1/10): - appetite decreased, anorexia, hypertriglyceridaemia, diabetes mellitus.

Psychiatric Disorders
Common (≥1/100, <1/10): - anxiety, nightmare, irritability.

Nervous System Disorders
Very Common (≥1/10): - peripheral neuropathy.
Common (≥1/100, <1/10): - hypoaesthesia, disturbance in attention, tremor.

Eye Disorders
Common (≥1/100, <1/10): - conjunctivitis.

Ear and Labyrinth disorders
Common (≥1/100, <1/10): - vertigo.

Respiratory, Thoracic and Mediastinal Disorders
Common (≥1/100, <1/10): - nasal congestion.

Gastrointestinal Disorders
Common (≥1/100, <1/10): - pancreatitis, gastro-oesophageal reflux disease.

Skin and Subcutaneous Tissue Disorders
Common (≥1/100, <1/10): - dry skin, eczema seborrhoeic, erythema, acne.

Musculoskeletal, Connective Tissue and Bone Disorders
Common (≥1/100, <1/10): - myalgia.

Renal and Urinary Disorders
Common (≥1/100, <1/10): - Calculus renal.

General Disorders and Administration Site Conditions
Common (≥1/100, <1/10): - influenza like illness, weakness.

Investigations
Very Common (≥1/10): - weight decreased
Common (≥1/100, <1/10): - blood triglycerides increased, haematuria present.

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)

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 (see section 4.4).

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 3. Through week 48, eosinophilia [greater than the Upper Limit of Normal of $> 0.7 \times 10^9$/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 ($>1.4 \times 10^9$/l), the patient exposure adjusted rate of eosinophilia is equal in both groups (1.8 patients with event per 100 patient-years).

Table 3: 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

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 events that were not seen with the recommended dose. In an Early Access Program study, one patient administered 180 mg of Fuzeon as a single dose on one occasion. He did not experience an adverse event 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: antivirals for systemic use, other antivirals, ATC code: J05A X07

This medicinal product has been authorised under "Exceptional Circumstances". This means that for scientific reasons it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency (EMEA) will review any new information which may become available every year and this SPC will be updated as necessary.

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 5)

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, multicenter, 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 4)

Table 4 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

Outcomes	FUZEON +OB 90 mg bid (N=661)	OB (N=334)	Treatment Difference	95% Confidence Interval	p-value
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 5)

Table 5 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.

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

Renal Insufficiency: A specific pharmacokinetic study has not been conducted in patients with renal impairment or those receiving dialysis. However 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.

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 Blacks compared to Whites. Other PK studies suggest no difference between Asians and Whites after adjusting exposure for body weight.

Paediatric Patients: 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

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

3 years

Shelf life after reconstitution:

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 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

After reconstitution: Store in a refrigerator (2°C – 8°C). Keep the vial in the outer carton in order to protect from light. For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

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

Pack sizes
Each pack contains 60 vials of Fuzeon.

6.6 Special precautions for disposal

Any unused 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 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.

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 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 Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/252/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 May 2003

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

- **OTHER CONDITIONS**

The Marketing Authorisation Holder will continue to submit 6 monthly PSURs.

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the annual reassessment of the benefit/risk profile.

Clinical

SOB 005
The MAH commits to discuss further clinical studies if potential immunotoxicity cannot be excluded by other means, including functionality of neutrophils, antigen presenting cells and complement activity. It must be further discussed whether an expanded clinical program is sufficient for this purpose, after submission of a plan to perform *ex-vivo* immunotoxicity studies. The MAH's proposal to perform *ex vivo* studies on the effect of enfuvirtide on INF-γ production was accepted. The MAH has submitted a draft protocol and a timeframe for submission of the final study report.
Pending evaluation of the submitted study protocol and the completion of *ex vivo* studies on the effect of enfuvirtide on INF-γ, the SOB 005 remains outstanding.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR PACK 1

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 Fuzeon 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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 Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

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

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

IMMEDIATE OUTER CARTON FOR FUZEON VIALS WITHIN PACK 1

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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 Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

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

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 WITHIN PACK 1

1. NAME OF THE MEDICINAL PRODUCT

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
Please read the package leaflet before use for full instructions on preparation and administration

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

Keep out of the reach and sight 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 Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

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

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

Water for Injections
Subcutaneous use

2. METHOD OF ADMINISTRATION

Please 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

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR PACK 2

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 solution contains 90 mg of enfuvirtide.

3. LIST OF EXCIPIENTS

Each vial with powder 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 this box:
60 vials with powder for solution for injection
60 vials with solvent

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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 Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/252/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

IMMEDIATE OUTER CARTON FOR FUZEON VIALS WITHIN PACK 2

1. NAME OF THE MEDICINAL PRODUCT

Fuzeon 90 mg/ml powder for solution for injection
Enfuvirtide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each Fuzeon vial contains 108 mg enfuvirtide.
1 ml of reconstituted solution contains 90 mg 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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 Limited
6 Falcon Way
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United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/252/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

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 WITHIN PACK 2

1. NAME OF THE MEDICINAL PRODUCT

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 reconstitution of Fuzeon 90 mg/ml powder for solution for injection to obtain a solution for subcutaneous use
Please read the package leaflet before use for full instructions on preparation and administration

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

Keep out of the reach and sight 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 Limited
6 Falcon Way
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Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/252/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

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

Water for Injections
Subcutaneous use

2. METHOD OF ADMINISTRATION

Please 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

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR PACKAGE TO CONTAIN FUZEON VIALS ONLY

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 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/252/003

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

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

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

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

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you personally. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT FUZEON IS AND WHAT IT IS USED FOR

What Fuzeon is
Fuzeon inhibits the entry of the human immunodeficiency virus (HIV) into the cells that HIV attacks (called CD4 or T-cells) in your blood. It works by preventing the HIV from making contact with the affected cell membrane. This means that the HIV cannot enter the cell and then it cannot multiply. This is because HIV needs the DNA in the host cell so it can multiply.

When Fuzeon should be used
Fuzeon is used in combination with other antiretroviral medicinal products by persons who are infected with HIV, the virus which causes AIDS. Your doctor has prescribed Fuzeon to help control your HIV infection. Fuzeon is not a cure for HIV infection. Never use or share dirty needles.

2. BEFORE YOU USE FUZEON

Do not use Fuzeon
- if you are allergic (hypersensitive) to enfuvirtide or any of the other ingredients of Fuzeon.

Take special care with Fuzeon:

Tell your doctor
- if you have any other medical conditions,
- if you have had any lung disease in the past; are currently, or have been, an intravenous drug user; are a smoker,
- if you have a history of any kidney problems.

Fuzeon does not reduce the risk of passing HIV to others through sexual contact or blood contamination. It is important to continue to take appropriate precautions to prevent passing HIV to others. Fuzeon is not a cure for HIV infection.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, 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 an improvement in the body's immune response,

enabling 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.

Taking other medicines
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed. Fuzeon has been shown not to interact with your other anti-HIV medicines or rifampicin (an antibiotic).

Using Fuzeon with food and drink
You can take Fuzeon with or without food but you still need to follow the instructions given in the package leaflets for your other medicines.

Pregnancy and breast-feeding
Pregnant women and breast-feeding mothers should not take Fuzeon unless specifically directed to by their doctor. Be sure to tell your doctor immediately if you are or may be pregnant or if you are breast-feeding a baby. It is recommended that HIV-infected women should not breast-feed their infants because of the possibility that your baby can be infected with HIV through your breast milk. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Fuzeon has not been specifically tested for its possible effects on your ability to drive a car or operate machines. However, if you feel dizzy while taking Fuzeon then please do not drive.

3. HOW TO USE FUZEON

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

The usual dose is 90 mg twice a day, given as a 1 ml subcutaneous (just below the skin) injection

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

If you take more Fuzeon than you should
There is no specific antidote for overdose with Fuzeon. If you take more than the recommended dose please consult your doctor.

If you forget to take Fuzeon
Take the dose as soon as you remember and then take your next dose at its regular time. Do not take the forgotten dose if it is less than 6 hours before you are going to take your next regular dose and never take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

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

In clinical trials pneumonia was seen more commonly in patients treated with Fuzeon. It is important for you to tell your doctor if you develop a cough with a high temperature, very fast breathing and/or shortness of breath as these symptoms may mean you are developing pneumonia.

The most common side effect that you may experience when taking Fuzeon, are reactions at the place on your body where you have given yourself the injection. You will probably experience one or more of the following mild to moderate reactions at the place where you inject your medicine: itchiness, swelling, redness, pain or tenderness, hardened skin, or bumps. These reactions can appear within the

first week of treatment and generally do not get worse with continued use of Fuzeon. Reactions at an individual injection site usually last for equal to or less than 7 days.

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 a muscle).

The side effects most frequently reported in patients receiving antiretroviral treatment with or without Fuzeon, excluding reactions at injection site, are diarrhoea and feeling sick.

Very common side effects *(in more than one in ten persons)* are pain and numbness in hands, feet or legs, and loss of weight.

Common side effects *(in more than one in a hundred but less than one in ten persons)* are inflammation of the sinuses, local swelling on the skin, pneumonia, 'flu', ear infection, swollen glands, decreased appetite, anorexia, increased blood fat values, diabetes, feeling anxious or irritated, nightmares, feeling dizzy, lack of concentration, tremor (shaking), inflamed eye lids, nasal congestion, inflammation of the pancreas, heart burn, dry skin, eczema, redness of the skin, acne, muscle pain, kidney stones, 'flu like' symptoms, feeling weak and blood in the urine.

Remember that reactions at injection sites are a common side effect *(in more than one in a hundred but less than one in ten persons)* of taking Fuzeon. If you experience reactions at an injection site, it is important not to stop taking 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 below.

Hypersensitivity (allergy) to Fuzeon is rare *(in more than one in ten thousand but less than one in a thousand persons)*. However if you develop symptoms that may suggest that you are allergic to this medicine then you must stop taking it straight away and tell your doctor as soon as possible. Symptoms that you should look out for are rash, a high temperature or chill, feeling sick or being sick and sweating and shaking. These symptoms do not definitely mean you are allergic to this medicine but you must discuss them with your doctor.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FUZEON

Keep out of the reach and sight of children.

Do not use Fuzeon 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.

The Fuzeon or the Water for Injections Vials do not require any special storage conditions.

Once the solution has been prepared for your injection it should be used immediately. If it is not used immediately it must be stored in a refrigerator (2°C – 8°C) and used within 24 hours. Keep the vial in the outer carton in order to protect from light.

Do not use Fuzeon 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.

6. FURTHER INFORMATION

What Fuzeon contains

- The active substance is 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

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

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.

Fuzeon is also available in a carton containing 60 vials of Fuzeon and 60 vials of Water for Injections.

Marketing Authorisation Holder

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

The Manufacturer responsible for batch release is

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

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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N.V. Roche S.A.
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Luxembourg/Luxemburg
(Voir/siehe Belgique/Belgien)

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Österreich
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Portugal
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Slovenija
Roche farmacevtska družba d.o.o.
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Slovenská republika
Roche Slovensko, s.r.o.
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United Kingdom
Roche Products Ltd.
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This leaflet was last approved in

This medicine has been authorised under "exceptional circumstances".

This means that for scientific reasons it has been impossible to get complete information on this medicine. The European Medicines Agency (EMEA) will review any new information on the medicine every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea. europa.eu. There are also links to other websites about rare diseases and treatments.

HOW TO USE FUZEON

Always take Fuzeon exactly as your doctor has instructed you. Check with your doctor or pharmacist if you are unsure.

The usual dose is 90 mg twice a day, given as a 1 ml subcutaneous (just below the skin) injection into the upper arm, anterior thigh or abdomen. Each injection should be given at a site different from the last place you injected and never where there is still an injection site reaction from an earlier dose. You should not inject your medicine into moles, scar tissue, bruises or your navel.

When to take Fuzeon
It is best to take Fuzeon at the same time each day if you can. Try and space the doses evenly apart whenever it is convenient for you. First thing in the morning and again in the evening are good times.

The following is a basic, step-by-step guide to injecting your medicine. Please contact your doctor or pharmacist if you have any questions about Fuzeon administration.

How long should you take Fuzeon for?
You should keep taking your medicine until your doctor tells you to stop. If you stop and interrupt your treatment with Fuzeon this may lead to the HIV in your blood becoming resistant to it quicker than if you take it regularly and without treatment interruptions. The HIV virus in your blood may eventually become resistant to Fuzeon and your blood levels of virus 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.

What to do if you are left-handed
The illustrations in this leaflet show individuals 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 thumb and forefinger of your right hand.

When to have a carer help 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 needlestick injury, you should have a carer attend an injection training session with your healthcare provider.

Your syringes
The syringes supplied with this 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.

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 provider.

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 swabs.
- 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 your medicine with tap water.
- Never inject your medicine with other injectable medicines.
- 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).
- Throw away used syringes into your dedicated waste container with a lid for the safe disposal of waste materials. Consult your doctor if you have any questions about safe disposal of these items.

GETTING STARTED

Gather Supplies

Gather all of the following supplies:

- 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
- 3 Alcohol swabs
- Dedicated waste container with a lid for the safe disposal of the waste materials.

Open Syringe Packages and Remove Vial Caps

- Throw away packages and vial caps into the rubbish.
- Place syringes and vials onto a clean surface.

Wash Hands Thoroughly

- After washing hands, do not touch anything except the injection supplies and the injection site.

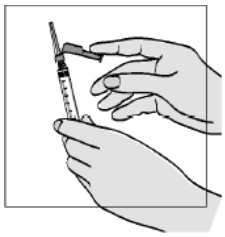
Clean the Tops of Vials

- 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.

MIXING FUZEON

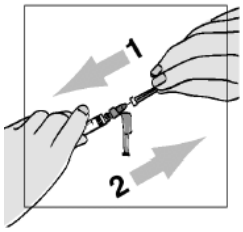
Draw Up Water for Injections

Pick up the **3 ml large syringe**. Using your index finger, push back the coloured needle protection device towards the syringe.



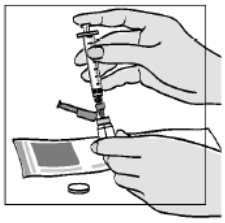
To ensure that the needle is secure, hold the clear plastic cap and tighten the needle with a gentle clockwise twist. Do not use too much force as the needle may loosen.

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



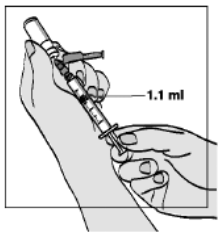
Draw back 1.1 ml of air.

Insert the syringe needle into the rubber top of the vial of water for injections and press the plunger, injecting the air.



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.

Slowly pull back the plunger until the water reaches the 1.1 ml mark. **Please be aware that the vial contains an excess of water for injections (2 ml); you only have to withdraw 1.1 ml of it to prepare your medication properly.**



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

If excess air enters the syringe, gently press the plunger to force any air back into the vial and withdraw the water again, making sure you have 1.1 ml of water for injections in the syringe.

- Remove the needle from the vial, **making sure you never touch the needle with your fingers or any other object**.

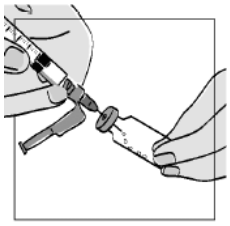
- Throw away the vial into the rubbish. The solvent vial is intended for single use only and the remaining water for injections in the vial after withdrawal of the volume required for reconstitution has to be discarded.

Injecting Water For Injections Into Fuzeon Powder

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

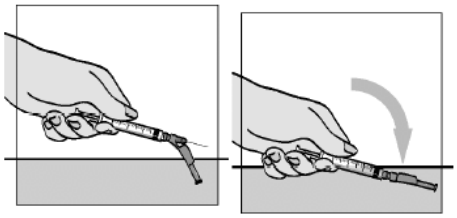
- Hold the water-filled syringe by the barrel and push the needle through the rubber top of the vial at a slight angle.

Press the syringe plunger in 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 powder to dissolve completely.**



- After all of the sterile water for injections has been added to the vial of Fuzeon, 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.**



- Throw away the syringe into the sharps container.

Mixing the Water with the Fuzeon Powder

- 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 excessive foaming**. After the powder begins to dissolve you can set the vial aside to allow it to completely dissolve. The powder may take up to 45 minutes to dissolve in to solution. The vial can also be gently rolled between your 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.

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

- Make sure the powder has dissolved completely, allowing any bubbles that may have formed to settle. If bubbles still exist, gently tap the side of the vial to help settle them.

- As with all injectable medicines, it is important to inspect the solution for particles. If you notice any particles in the solution, do not use it. You should throw away the vial into the dedicated waste container with a lid or return it to the pharmacy. Start again with a new vial of Fuzeon powder.

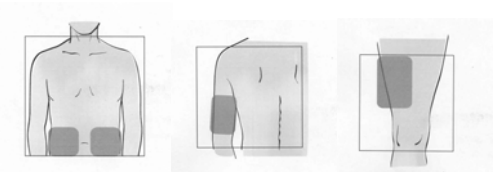
- Once a dose is mixed with water for injections, it must be used immediately or stored in a refrigerator and used within 24 hours. Allow the solution to return to room temperature before using.

- If you are preparing both of your daily doses at one time, be sure to use new syringes, water for injections, and Fuzeon for each dose.

PREPARING FOR THE INJECTION

Where to Inject

Injection sites include the abdomen, upper thighs, and upper arms. Each injection should be given at a site different from the last place you injected and never where there is still an injection site reaction from an earlier dose. You should not inject your medicine into moles, scar tissue, bruises or your navel.



Choose a different area from where you last injected yourself, and then check for any places where you may have a reaction (press the skin to see if there are any hard bumps). It is much better to avoid these areas. Also avoid areas that could become irritated by your belt or the waistline of your clothing.

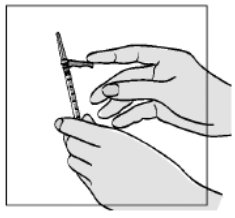
Cleansing the Injection Site

Cleanse the area for injection thoroughly with an alcohol swab in a circular motion, working outward. Allow to air-dry completely.

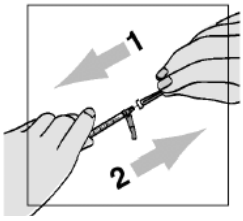
Drawing Up Fuzeon into the 1 ml Syringe

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

Pick up the **1 ml small syringe**. Using your index finger, push back the coloured needle protection device towards the syringe.



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



Draw back 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 needle into the rubber top of the Fuzeon vial and press the plunger, injecting the air. Gently turn the vial upside down.

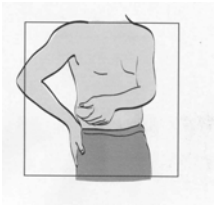
Make sure the tip of the needle is always below the surface of the solution to help keep air bubbles from entering the syringe. Slowly pull back the plunger until the solution reaches the 1.0 ml mark. Be careful not to pull the plunger too fast past the 1 ml marker and/or out of the barrel.

- Tap the syringe gently to make any air bubbles rise to the top.
- If excess air enters the syringe, gently press the plunger to inject the air back into the vial and withdraw the solution again, making sure you have 1.0 ml of solution in the syringe (whatever volume your doctor prescribed, if different). This step may be repeated until the correct amount of solution is in the syringe.
- Remove the syringe from the vial.

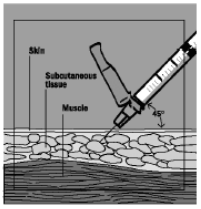
INJECTING FUZEON

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

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



- Pierce the skin at a 45-degree angle.

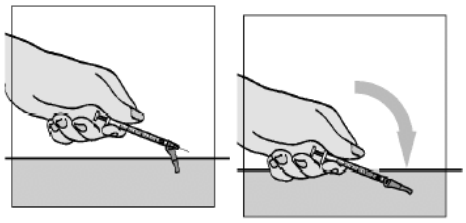


When the needle is in, release the skin, and using the same hand, hold on to the syringe barrel to help steady it and prevent shifting.

- Using the thumb, depress the plunger in to inject the solution.

  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.**



- Throw away the syringe into the dedicated waste container with a lid.

- Cover the injection site with a sticking plaster if any blood is present.

DISPOSING OF USED SUPPLIES

Throw away all used syringes directly into the dedicated waste container with a lid. Keep the cover of this container tight and keep the dedicated waste container with a lid out of the reach of children. Check with your doctor or pharmacist about proper disposal of the container.

In addition, you should safely dispose of all used alcohol swabs and vials, even if the vials contain unused amounts of medicine or water for injections. The vials of Fuzeon and water for injections should only be used once. Used supplies other than syringes (alcohol swabs and empty vials) may be disposed of into the rubbish as long as no blood is visible. If blood is visible, dispose of the items into the dedicated waste container with a lid.

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

Fuzeon 90 mg/mL powder for solution for injection
Enfuvirtide

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you personally. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT FUZEON IS AND WHAT IT IS USED FOR

What Fuzeon is
Fuzeon inhibits the entry of the human immunodeficiency virus (HIV) into the cells that HIV attacks (called CD4 or T-cells) in your blood. It works by preventing the HIV from making contact with the affected cell membrane. This means that the HIV cannot enter the cell and then it cannot multiply. This is because HIV needs the DNA in the host cell so it can multiply.

When Fuzeon should be used
Fuzeon is used in combination with other antiretroviral medicinal products by persons who are infected with HIV, the virus which causes AIDS. Your doctor has prescribed Fuzeon to help control your HIV infection. Fuzeon is not a cure for HIV infection. Never use or share dirty needles.

2. BEFORE YOU USE FUZEON

Do not use Fuzeon
- if you are allergic (hypersensitive) to enfuvirtide or any of the other ingredients of Fuzeon.

Take special care with Fuzeon:

Tell your doctor
- if you have any other medical conditions,
- if you have had any lung disease in the past; are currently, or have been, an intravenous drug user; are a smoker,
- if you have a history of any kidney problems.

Fuzeon does not reduce the risk of passing HIV to others through sexual contact or blood contamination. It is important to continue to take appropriate precautions to prevent passing HIV to others. Fuzeon is not a cure for HIV infection.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, 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 an improvement in the body's immune response,

enabling 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.

Taking other medicines
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed. Fuzeon has been shown not to interact with your other anti-HIV medicines or rifampicin (an antibiotic).

Using Fuzeon with food and drink
You can take Fuzeon with or without food but you still need to follow the instructions given in the package leaflets for your other medicines.

Pregnancy and breast-feeding
Pregnant women and breast-feeding mothers should not take Fuzeon unless specifically directed to by their doctor. Be sure to tell your doctor immediately if you are or may be pregnant or if you are breast-feeding a baby. It is recommended that HIV-infected women should not breast-feed their infants because of the possibility that your baby can be infected with HIV through your breast milk. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Fuzeon has not been specifically tested for its possible effects on your ability to drive a car or operate machines. However, if you feel dizzy while taking Fuzeon then please do not drive.

3. HOW TO USE FUZEON

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

The usual dose is 90 mg twice a day, given as a l ml subcutaneous (just below the skin) injection.

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

If you take more Fuzeon than you should
There is no specific antidote for overdose with Fuzeon. If you take more than the recommended dose please consult your doctor.

If you forget to take Fuzeon
Take the dose as soon as you remember and then take your next dose at its regular time. Do not take the forgotten dose if it is less than 6 hours before you are going to take your next regular dose and never take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

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

In clinical trials pneumonia was seen more commonly in patients treated with Fuzeon. It is important for you to tell your doctor if you develop a cough with a high temperature, very fast breathing and/or shortness of breath as these symptoms may mean you are developing pneumonia.

The most common side effect that you may experience when taking Fuzeon, are reactions at the place on your body where you have given yourself the injection. You will probably experience one or more of the following mild to moderate reactions at the place where you inject your medicine: itchiness, swelling, redness, pain or tenderness, hardened skin, or bumps. These reactions can appear within the

first week of treatment and generally do not get worse with continued use of Fuzeon. Reactions at an individual injection site usually last for equal to or less than 7 days.

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 a muscle).

The side effects most frequently reported in patients receiving antiretroviral treatment with or without Fuzeon, excluding reactions at injection site, are diarrhoea and feeling sick.

Very common side effects *(in more than one in ten persons)* are pain and numbness in hands, feet or legs, and loss of weight.

Common side effects *(in more than one in a hundred but less than one in ten persons)* are inflammation of the sinuses, local swelling on the skin, pneumonia, 'flu', ear infection, swollen glands, decreased appetite, anorexia, increased blood fat values, diabetes, feeling anxious or irritated, nightmares, feeling dizzy, lack of concentration, tremor (shaking), inflamed eye lids, nasal congestion, inflammation of the pancreas, heart burn, dry skin, eczema, redness of the skin, acne, muscle pain, kidney stones, 'flu like' symptoms, feeling weak, and blood in the urine.

Remember that reactions at injection sites are a common side effect *(in more than one in a hundred but less than one in ten persons)* of taking Fuzeon. If you experience reactions at an injection site, it is important not to stop taking 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 below.

Hypersensitivity (allergy) to Fuzeon is rare *(in more than one in ten thousand but less than one in a thousand persons)*. However if you develop symptoms that may suggest that you are allergic to this medicine then you must stop taking it straight away and tell your doctor as soon as possible. Symptoms that you should look out for are rash, a high temperature or chill, feeling sick or being sick and sweating and shaking. These symptoms do not definitely mean you are allergic to this medicine but you must discuss them with your doctor.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FUZEON

Keep out of the reach and sight of children.

Do not use Fuzeon after the expiry date which is stated on the label of the Fuzeon Vials after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Once the solution has been prepared for your injection it should be used immediately. If it is not used immediately it must be stored in a refrigerator (2°C – 8°C) and used within 24 hours. Keep the vial in the outer carton in order to protect from light.

Do not use Fuzeon if you notice any particles in the powder or the solution once the water for injections has been added.

6. FURTHER INFORMATION

What Fuzeon contains

- The active substance is enfuvirtide. After reconstitution with the solvent provided 1 ml of reconstituted solution contains 90 mg enfuvirtide.
- The other ingredients are:
  Sodium Carbonate, anhydrous
  Mannitol
  Sodium Hydroxide
  Hydrochloric Acid

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

What Fuzeon looks like and contents of the pack

Fuzeon powder for solution for injection comes in a carton containing 60 vials of your medicine.

Marketing Authorisation Holder

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

The Manufacturer responsible for batch release is

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

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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Tel: +420 - 2 20382111

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Polska
Roche Polska Sp.z o.o.
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Portugal
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Tel: +351 - 21 425 70 00

Slovenija
Roche farmacevtska družba d.o.o.
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Slovenská republika
Roche Slovensko, s.r.o.
Tel: +421 - 2 52638201

Suomi/Finland
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Puh/Tel: +358 (0) 9 525 331

Sverige
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Tel: +46 (0) 8 726 1200

United Kingdom
Roche Products Ltd.
Tel: +44 (0) 1707 366000

This leaflet was last approved in

This medicine has been authorised under "exceptional circumstances".
This means that for scientific reasons it has been impossible to get complete information on this medicine. The European Medicines Agency (EMEA) will review any new information on the medicine every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu. There are also links to other websites about rare diseases and treatments.

HOW TO USE FUZEON

Always take Fuzeon exactly as your doctor has instructed you. Check with your doctor or pharmacist if you are unsure.

The usual dose is 90 mg twice a day, given as a 1 ml subcutaneous (just below the skin) injection into the upper arm, anterior thigh or abdomen. Each injection should be given at a site different from the last place you injected and never where there is still an injection site reaction from an earlier dose. You should not inject your medicine into moles, scar tissue, bruises or your navel.

When to take Fuzeon
It is best to take Fuzeon at the same time each day if you can. Try and space the doses evenly apart whenever it is convenient for you. First thing in the morning and again in the evening are good times.

The following is a basic, step-by-step guide to injecting your medicine. Please contact your doctor or pharmacist if you have any questions about Fuzeon administration.

How long should you take Fuzeon For?
You should keep taking your medicine until your doctor tells you to stop. If you stop and interrupt your treatment with Fuzeon this may lead to the HIV in your blood becoming resistant to it quicker than if you take it regularly and without treatment interruptions. The HIV virus in your blood may eventually become resistant to Fuzeon and your blood levels of virus 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.

What to do if you are left-handed
The illustrations in this leaflet show individuals 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 thumb and forefinger of your right hand.

When to have a carer help 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 needlestick injury, you should have a carer attend an injection training session with your healthcare provider.

Safety Tips

- Wash your hands well to reduce the risk of bacterial infections. Do not touch anything except the medicine and supplies.
- When handling syringes, do not touch the needle. Do not touch the tops of the vials once they have been cleaned with alcohol swabs.
- Make sure none of the items that you need for your injection have been opened. Do not use opened materials.
- Never mix your medicine with tap water.
- Never inject your medicine with other injectable medicines.
- 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).
- Discard used syringes into your dedicated container with a lid for the safe disposal of waste materials. Consult your doctor if you have any questions about safe disposal of these items.

GETTING STARTED

Gather Supplies

Gather all of the following supplies that you will need to prepare and give yourself an injection. You need to ask your pharmacist or doctor if you need to find out where to get the water for injections, the 3 ml and 1 ml syringes, alcohol swabs and dedicated waste container with a lid:

- One vial of Fuzeon
- One vial of water for injections
- One 3 ml syringe (larger syringe) with a 25 mm needle
- One 1 ml syringe (smaller syringe) with a 13 mm needle
- 3 alcohol swabs
- Dedicated waste container with a lid for the safe disposal of the waste materials.

Open Syringe Packages and Remove Vial Caps

- Throw away packages and vial caps into the rubbish.
- Place syringes and vials onto a clean surface.

Wash Hands Thoroughly

- After washing hands, do not touch anything except the injection supplies and the injection site.

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.

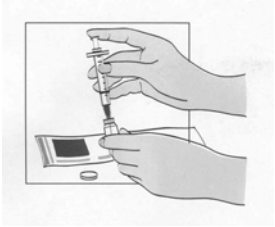
MIXING FUZEON

Draw Up Water for Injections

Pick up the **3 ml large syringe**.

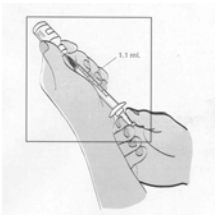
Remove the plastic cap and draw back 1.1 ml of air.

Insert the syringe needle into the rubber top of the vial of water for injections and press the plunger, injecting the air.



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 back the plunger until the water for injection reaches the 1.1 ml mark.



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

If excess air enters the syringe, gently press the plunger to force any air back into the vial and withdraw the water for injections again, making sure you have 1.1 ml of water for injections in the syringe.

- Remove the needle from the vial, **making sure you never touch the needle with your fingers or any other object**.

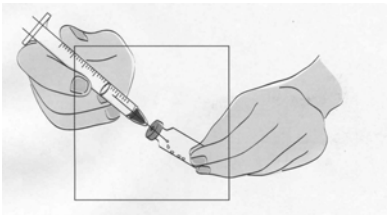
- Throw away the water for injections vial into the rubbish. The water for injections vial is intended for single use only.

Injecting Water for Injections Into the Fuzeon Powder

- Gently tap the vial of Fuzeon 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.

Press the syringe plunger in 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 powder to dissolve completely**.



- After all of the water for injections has been added to the vial of Fuzeon, throw the syringe into the dedicated waste container.

Mixing the Water For Injections with the Fuzeon Powder

- 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 excessive foaming**. After the powder begins to dissolve you can set the vial aside to allow it to completely dissolve. The powder may take up to 45 minutes to dissolve in to solution. The vial can also be gently rolled between your 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.

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

- Make sure the powder has dissolved completely, allowing any bubbles that may have formed to settle. If bubbles still exist, gently tap the side of the vial to help settle them.

- As with all injectable medicines, it is important to inspect the solution for particles. If you notice any particles in the solution, do not use it. You should throw away the vial into the

dedicated waste container with a lid or return it to the pharmacy. Start again with a new vial of Fuzeon Powder.

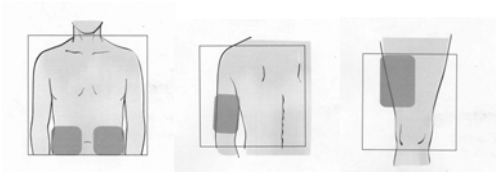
- Once a dose is mixed with water for injections, it must be used immediately or stored in a refrigerator and used within 24 hours. Allow the solution to return to room temperature before using.

- If you are preparing both of your daily doses at one time, be sure to use new syringes, water for injections and Fuzeon for each dose.

PREPARING FOR THE INJECTION

Where to Inject

Injection sites include the abdomen, upper thighs, and upper arms. Each injection should be given at a site different from the last place you injected and never where there is still an injection site reaction from an earlier dose. You should not inject your medicine into moles, scar tissue, bruises or your navel.



Choose a different area from where you last injected yourself, and then check for any places where you may have a reaction (press the skin to see if there are any hard bumps). It is much better to avoid these areas. Also avoid areas that could become irritated by your belt or the waistline of your clothing.

Cleansing the Injection Site

Cleanse the area for injection thoroughly with an alcohol swab in a circular motion, working outward. Allow to air-dry completely.

Drawing Up Fuzeon into the 1 ml syringe

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

Pick up the **1 ml small syringe**. Remove the plastic cap and draw back 1 ml of air.

Insert the syringe needle into the rubber top of the Fuzeon vial and press the plunger, injecting the air. 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 until the solution reaches the 1.0 ml mark.

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

- If excess air enters the syringe, gently press the plunger to inject the air back into the vial and withdraw the solution again, making sure you have 1.0 ml of solution in the syringe (whatever

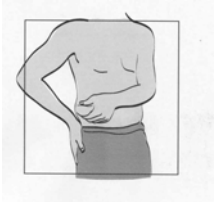
volume your doctor prescribed, if different). This step may be repeated until the correct amount of solution is in the syringe.

- Remove the syringe from the vial.

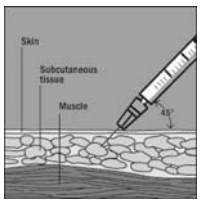
INJECTING FUZEON

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

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



- Pierce the skin at a 45-degree angle.



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.

- Using the thumb, depress the plunger in to inject the medicine. After the dose is fully delivered remove the needle from the skin.
- Discard the syringe into the dedicated waste container with a lid.
- Cover the injection site with a sticking plaster if any blood is present.

DISPOSING OF USED SUPPLIES

Throw away all used syringes directly into the dedicated waste container with a lid. Keep the cover of this container tight and keep the container out of the reach of children. Check with your doctor or pharmacist about proper disposal of the container.

In addition, you should safely dispose of all used alcohol swabs and vials, even if the vials contain unused amounts of medicine or water for injections. The vials of Fuzeon are intended for single use only. Used supplies other than syringes (alcohol swabs and empty vials) may be disposed of into the rubbish as long as no blood is visible. If blood is visible, dispose of the items into the dedicated waste container with a lid.

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