# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

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

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 108 mg enfuvirtide.

Each ml of reconstituted solution contains 90 mg enfuvirtide.

Excipient with known effect: sodium. Contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White to off-white lyophilised powder.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

In deciding on a new regimen for patients who have failed an antiretroviral regimen, careful consideration should be given to the treatment history of the individual patient

and the patterns of mutations associated with different medicinal products. Where available, resistance testing may be appropriate (see sections 4.4 and 5.1).

## 4.2 Posology and method of administration

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

Posology

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

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

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

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

**Table 1: Paediatric Dosing**

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

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

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

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

Method of Administration

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

## 4.3 Contraindications

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

## 4.4 Special warnings and precautions for use

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

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

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

Hypersensitivity reactions have occasionally been associated with therapy with enfuvirtide and in rare cases hypersensitivity reactions have recurred on rechallenge. Events included rash, fever, nausea and vomiting, chills, rigors, low blood pressure and elevated serum liver transaminases in various combinations, and possibly primary immune complex reaction, respiratory distress and glomerulonephritis. Patients developing signs/symptoms of a systemic hypersensitivity reaction should discontinue enfuvirtide treatment and should seek medical evaluation immediately. Therapy with enfuvirtide should not be restarted following systemic signs and symptoms consistent with a hypersensitivity reaction considered related to enfuvirtide. Risk factors that may predict the occurrence or severity of hypersensitivity to enfuvirtide have not been identified.

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

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

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

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

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

Osteonecrosis:

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

## 4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

Influence of enfuvirtide on metabolism of concomitant medicinal products: In an in-vivo human metabolism study enfuvirtide, at the recommended dose of 90 mg twice daily, did not

inhibit the metabolism of substrates by CYP3A4 (dapsone), CYP2D6 (debrisoquine), CYP1A2 (caffeine), CYP2C19 (mephenytoin), and CYP2E1 (chlorzoxazone).

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

## 4.6 Fertility, pregnancy and lactation

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

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

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

***a. Summary of the safety profile***

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

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

***b. Tabulated list of adverse reactions***

Table 2 presents events seen at a higher rate among patients receiving Fuzeon + OB regimen than among patients on the OB alone regimen with an exposure adjusted

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

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

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

| | |
|---|---|
| Very common | Weight decreased |
| Common | Influenza like illness, asthenia |

**c. Description of selected adverse reactions**

**Injection site reactions**

Injection site reactions (ISRs) were the most frequently reported adverse reaction and occurred in 98% of the patients (Table 3). The vast majority of ISRs occurred within the first week of Fuzeon administration and were associated with mild to moderate pain or discomfort at the injection site without limitation of usual activities. The severity of the pain and discomfort did not increase with treatment duration. The signs and symptoms generally lasted equal to or less than 7 days. Infections at the injection site (including abscess and cellulitis) occurred in 1.5% of patients.

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

| | **n=663** | | |
|---|---|---|---|
| Withdrawal Rate due to ISRs | 4% | | |
| **Event Category** | **Fuzeon +Optimised background[a]** | **% of Event comprising Grade 3 reactions** | **% of Event comprising Grade 4 reactions** |
| Pain / discomfort | 96.1% | 11.0%[b] | 0%[b] |
| Erythema | 90.8% | 23.8%[c] | 10.5%[c] |
| Induration | 90.2% | 43.5%[d] | 19.4%[d] |
| Nodules and cysts | 80.4% | 29.1%[e] | 0.2%[e] |
| Pruritus | 65.2% | 3.9%[f] | NA |
| Ecchymosis | 51.9% | 8.7%[g] | 4.7%[g] |

[a]Any severity grade.
[b]Grade 3= severe pain requiring analgesics (or narcotic analgesics for ≤ 72 hours) and/or limiting usual activities; Grade 4= severe pain requiring hospitalisation or prolongation of hospitalisation, resulting in death, or persistent or significant disability/incapacity, or life-threatening, or medically significant.
[c]Grade 3= ≥ 50 mm but < 85 mm average diameter; Grade 4= ≥ 85 mm average diameter.
[d]Grade 3= ≥ 25 mm but < 50 mm average diameter; Grade 4= ≥ 50 mm average diameter.
[e]Grade 3= ≥ 3 cm; Grade 4= If draining.
[f]Grade 3= refractory to topical treatment or requiring oral or parenteral treatment; Grade 4= not defined.
[g]Grade 3= > 3 cm but ≤ 5 cm; Grade 4= > 5 cm.

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

**Other adverse reactions**

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported;

however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

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

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

**Laboratory abnormalities**

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

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

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

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions (see details below).

**United Kingdom**

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

### 4.9 Overdose

No case of overdose has been reported. The highest dose administered to 12 patients in a clinical trial was 180 mg as a single dose subcutaneously. These patients did not experience any adverse reactions that were not seen with the recommended dose. In an Early Access Program study, one patient was administered 180 mg of Fuzeon as a single dose on one occasion. He did not experience an adverse reaction as a result.

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

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antivirals, ATC code: J05AX07

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

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

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

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

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

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

Clinical Pharmacodynamic data

Studies in Antiretroviral Experienced Patients: The clinical activity of Fuzeon (in combination with other antiretroviral agents) on plasma HIV RNA levels and CD4 counts have been investigated in two randomised, multicentre, controlled studies (TORO 1 and TORO 2) of Fuzeon of 48 weeks duration. 995 patients comprised the intent-to-treat population. Patient demographics include a median baseline HIV-1 RNA of 5.2 $\log_{10}$ copies/ml and 5.1 $\log_{10}$ copies/ml and median baseline CD4 cell count of 88 cells/$mm^3$ and 97 cells/$mm^3$ for Fuzeon + OB and OB, respectively. Patients had prior exposure to a median of 12 antiretrovirals for a median of 7 years. All patients received an optimised background (OB) regimen consisting of 3 to 5 antiretroviral agents selected on the basis of the patient's prior treatment history, as well as baseline genotypic and phenotypic viral resistance measurements.

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

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

| Outcomes | Fuzeon + OB 90 mg bid (N=661) | OB (N=334) | Treatment Difference | 95% Confidence Interval | p-value |
|---|---|---|---|---|---|
| HIV-1 RNA Log Change from baseline ($log_{10}$ copies/ml)* | -1.48 | -0.63 | LSM -0.85 | -1.073, -0.628 | <.0001 |
| CD4+ cell count Change from baseline (cells/$mm^3$)# | +91 | +45 | LSM 46.4 | 25.1, 67.8 | <.0001 |
| HIV RNA ≥1 log below Baseline** | 247 (37.4%) | 57 (17.1%) | Odds Ratio 3.02 | 2.16, 4.20 | <.0001 |
| HIV RNA <400 copies/ml** | 201 (30.4%) | 40 (12.0%) | Odds Ratio 3.45 | 2.36, 5.06 | <.0001 |
| HIV RNA <50 copies/ml** | 121 (18.3%) | 26 (7.8%) | Odds Ratio 2.77 | 1.76, 4.37 | <.0001 |
| Discontinued due to adverse reactions/intercurrent illness/labs† | 9% | 11% | | | |
| Discontinued due to injection site reactions† | 4% | N/A | | | |
| Discontinued due to other reasons†ϕ§ | 13% | 25% | | | |

* Based on results from pooled data of TORO 1 and TORO 2 on ITT population, week 48 viral load for subjects who were lost to follow-up, discontinued therapy, or had virological failure replaced by their last observation (LOCF).

\# Last value carried forward.

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

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

ϕ As per the judgment of the investigator.

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

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

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

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

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

## 5.2 Pharmacokinetic properties

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

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

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

Biotransformation: As a peptide, enfuvirtide is expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool. *In vitro* human microsomal studies and in *in vivo* studies indicate that enfuvirtide is not an inhibitor of CYP450 enzymes. In *in vitro* human microsomal and hepatocyte studies, hydrolysis of the amide group of the C-terminus amino acid, phenylalanine results in a deamidated metabolite and the formation of this metabolite is not NADPH dependent. This metabolite is detected in human plasma following administration of enfuvirtide, with an AUC ranging from 2.4 to 15% of the enfuvirtide AUC.

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

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

Renal impairment: Analysis of plasma concentration data from patients in clinical trials indicated that the clearance of enfuvirtide is not affected to any clinically relevant extent in patients with mild to moderate renal impairment. In a renal impairment study AUC of enfuvirtide was increased on average by 43-62% in patients with severe or end stage renal disease compared to patients with normal renal function. Haemodialysis did not significantly alter enfuvirtide clearance. Less than 13% of the dose was removed during haemodialysis. No dose adjustment is required for patients with impaired renal function.

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

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

Race: Analysis of plasma concentration data from patients in clinical trials indicated that the clearance of enfuvirtide was not different in Afro-Americans compared to Caucasians. Other PK studies suggest no difference between Asians and Caucasians after adjusting exposure for body weight.

Paediatric population: The pharmacokinetics of enfuvirtide have been studied in 37 paediatric patients. A dose of 2 mg/kg bid (maximum 90 mg bid) provided enfuvirtide plasma concentrations similar to those obtained in adult patients receiving 90 mg bid dosage. In 25 paediatric patients ranging in age from 5 to 16 years and receiving the 2 mg/kg bid dose into the upper arm,

anterior thigh or abdomen, the mean steady-state AUC was 54.3 ± 23.5 µg*h/ml, $C_{max}$ was 6.14 ± 2.48 µg/ml, and $C_{trough}$ was 2.93 ± 1.55 µg/ml.

### 5.3 Preclinical safety data

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

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

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Powder

Sodium carbonate

Mannitol

Sodium hydroxide

Hydrochloric Acid

Solvent

Water for Injections

### 6.2 Incompatibilities

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

## 6.3 Shelf life

Powder
4 years

Solvent
4 years

Shelf life after reconstitution
After reconstitution: Store in a refrigerator (2°C – 8°C).
Chemical and physical in-use stability has been demonstrated for 48 hours at 5°C when protected from light.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

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

Solvent
This medicinal product does not require any special storage conditions.

## 6.5 Nature and contents of container

Powder

Vial: 3 ml vial, colourless glass type 1

Closure: lyophilisate stopper, rubber (latex free)

Seal: aluminium seal with flip-off cap

Solvent

Vial: 2 ml vial, colourless glass type 1

Closure: rubber stopper (latex free)

Seal: aluminium seal with flip-off cap

Pack sizes

60 vials powder for solution for injection

60 vials solvent

60 3 ml syringes

60 1 ml syringes

180 alcohol swabs

## 6.6 Special precautions for disposal

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

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

Fuzeon must only be reconstituted with 1.1 ml of Water for Injections. Patients must be instructed to add the water for injections and then gently tap the vial with their fingertip until the powder begins to dissolve. **They must never shake the vial or turn it upside down to mix—this will cause excessive foaming**. After the powder begins to dissolve they can set the vial aside to allow it to completely dissolve. The powder may take up to 45 minutes to dissolve into solution. The patient can gently roll the vial between their hands after adding the water for injections until it is fully dissolved and this may reduce the time it takes for the powder to dissolve. Before the solution is withdrawn for administration, the patient should inspect the vial visually to ensure that the contents are fully in solution, and that the solution is clear and without bubbles or particulate matter. If there is evidence of particulate matter, the vial must not be used and should be discarded or returned to the pharmacy.

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

Fuzeon contains no preservative. Once reconstituted, the solution should be injected immediately. If the reconstituted solution cannot be injected immediately, it must be kept refrigerated until use and used within 24 hours.

Refrigerated reconstituted solution should be brought to room temperature before injection.

1 ml of the reconstituted solution should be injected subcutaneously in to the upper arm, abdomen or anterior thigh. The injection should be given at a site different from the preceding injection site and where there is no current injection site reaction. A vial is suitable for single use only; unused portions must be discarded.

## 7 MARKETING AUTHORISATION HOLDER

Roche Products Limited

6 Falcon Way, Shire Park

Welwyn Garden City

AL7 1TW

United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00031/0855

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

## 10 DATE OF REVISION OF THE TEXT

28/02/2023