AUSTRALIAN PRODUCT INFORMATION
Fuzeon (enfuvirtide)

1. NAME OF THE MEDICINE
Enfuvirtide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Fuzeon vial contains 108 mg enfuvirtide.

Reconstituted Fuzeon solution contains 90mg/mL of enfuvirtide.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM
Powder and solvent for solution for injection.

White to off-white lyophilised powder for injection.

4. CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Fuzeon (enfuvirtide) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in antiretroviral experienced patients with treatment failure due to intolerance to previous antiretroviral agents or with evidence of HIV-1 replication despite ongoing therapy. Evidence to support this indication is based on surrogate endpoints (change in viral load and CD4 count) in controlled studies following 48 weeks of treatment (see section 5.1 Pharmacodynamic properties, Clinical trials).

4.2 DOSE AND METHOD OF ADMINISTRATION
Dosage

Fuzeon should be administered only by subcutaneous injection.

Adults

The recommended dose of Fuzeon is 90 mg twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen. The injection should be given at a site different from the preceding injection site and where there is no current injection site reaction.

Special populations

Children

There are insufficient data available to establish a dose recommendation of Fuzeon in paediatric patients below the age of 6 years. In paediatric patients 6 years through 16 years of age, the recommended dosage of Fuzeon is 2.0 mg/kg twice daily up to a maximum dose of 90 mg bid injected subcutaneously into the upper arm, anterior thigh or abdomen. The injection should be given at a site different from the preceding injection site and where there is no current injection site reaction. Paediatric dosing guidelines for Fuzeon based on body weight are included in Table 1. Weight should be monitored periodically and the Fuzeon dose adjusted accordingly.

Table 1: Paediatric Dosing Guidelines

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

Renal impairment
No dose adjustment is recommended for patients with impaired renal function including those receiving haemodialysis.

Hepatic Impairment
No data are available to establish a dose recommendation for patients with hepatic impairment.

Method of Administration
Instructions for use and handling and disposal
Patients and caregivers must be instructed in the use of aseptic techniques when administering Fuzeon in order to avoid injection site infections. Appropriate instructions for reconstitution and self-injection must be given, including a careful review of the detailed instructions given in the patient information leaflet provided with the medicine. It is recommended that the first injection be performed under the supervision of an appropriately qualified healthcare professional. It is also recommended that the patient and/or caregiver's understanding and use of aseptic self-injection techniques and procedures be periodically re-evaluated.

Patients and caregivers should be instructed in the proper techniques for preparation, injection and disposal of needles and syringes in order to avoid needle stick injuries. Patients must be cautioned against the re-use of needles or syringes, instructed in safe disposal procedures including the use of a puncture-resistant container for disposal of used needles and syringes. Patients must be instructed on the safe disposal of full containers as per local requirements and to keep this container out of reach of children. Caregivers who experience an accidental needle stick after patient injection should contact a healthcare provider immediately.

Fuzeon must only be reconstituted with 1.1 mL of Sterile Water for Injections. After adding sterile water, the vial should be gently tapped for 10 seconds and then gently rolled between the hands to avoid foaming and to ensure all particles of drug are in contact with the liquid and no drug remains on the vial wall. The vial should then be allowed to stand until the powder goes completely into solution, which could take up to 45 minutes. Reconstitution time can be reduced by gently rolling the vial between the hands until the powder is completely dissolved. Before the solution is withdrawn for administration, the vial should be inspected visually to

ensure that the contents are fully dissolved in solution, and that the solution is clear, colourless and without bubbles or particulate matter. If there is evidence of particulate matter, the vial must not be used and should be discarded or returned to the pharmacy.

The solvent vials contain 2 mL of 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 of solvent.

Fuzeon contains no preservative. Once reconstituted 1.0 mL of 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 and the vial should be inspected visually again to ensure that the contents are fully dissolved in solution and that the solution is clear, colourless and without bubbles or particulate matter.

The reconstituted solution should be injected subcutaneously in the upper arm, abdomen or anterior thigh. The injection should be given at a site different from the preceding injection site and only where there is no current injection site reaction. Also, do not inject into moles, scar tissue, bruises or the navel.

A vial is for use in one patient on one occasion only.

4.3 CONTRAINDICATIONS

Fuzeon is contraindicated in patients with known hypersensitivity to enfuvirtide or any of its components.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

As with other antiretrovirals, Fuzeon must be taken as part of a combination regimen.

Patients should be informed that Fuzeon is not a cure for HIV-1 infection and its use does not preclude the need to maintain practices and behaviour designed to prevent transmission of HIV.

Local injection site reactions

The most common adverse events associated with Fuzeon use are local injection site reactions. Manifestations may include pain and discomfort, induration, erythema, nodules and cysts, pruritus, and ecchymosis. Eleven percent of patients had local reactions that required analgesics or limited usual activities (see section 4.8 Adverse effects (Undesirable effects)). Reactions are often present at more than one injection site. Patients must be familiar with the Fuzeon injection instructions in order to inject Fuzeon appropriately and how to monitor carefully for signs or symptoms of cellulitis or local infection.

Bacterial pneumonia and other infections

A higher rate of pneumonia (primarily bacterial) has been observed in patients treated with Fuzeon in the Phase III clinical trials compared to the control arm. Risk factors for pneumonia included low initial CD4 lymphocyte count, high initial viral load, intravenous drug use,

smoking and prior history of lung disease. Patients should be monitored closely for signs and symptoms of pneumonia especially if they have underlying conditions which may predispose them to pneumonia.

In phase III studies there were trends to higher rates of sinusitis, skin infections (not at injection site), abscess, cellulitis and sepsis in patients treated with Fuzeon compared to the control arm, although differences were not statistically significant. Patients should be monitored for signs and symptoms of these infections.

Hypersensitivity reactions
Hypersensitivity reactions have been occasionally associated with enfuvirtide therapy 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, glomerulonephritis and anaphylaxis. Patients developing signs/symptoms suggestive 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.

Administration of Fuzeon to non-HIV-1 infected individuals (e.g. post exposure prophylaxis) 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; a confirmatory Western blot and RNA testing would be expected to be negative.

Immune Reconstitution Syndrome (also referred to as Immune Reactivation Syndrome, Immune Restoration Disease, or Immune Reconstitution Inflammation Syndrome)
Immune Reconstitution Syndrome has been reported in patients treated with combination antiretroviral therapy, including Fuzeon. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), tuberculosis or others), which may necessitate immediate evaluation and treatment.

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

Use in the Elderly
Clinical studies of Fuzeon did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, and/or cardiac function and of concomitant disease or other drug therapy.

Paediatric use
The safety and pharmacokinetics of Fuzeon have not been established in paediatric patients below 6 years of age. Limited efficacy data is available in paediatric patients greater than 6 years of age.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

There are no clinically significant pharmacokinetic interactions between enfuvirtide and concomitantly given drugs metabolized by CYP450 enzymes.

Influence of Enfuvirtide on Metabolism of Concomitant Drugs
Based on the results from an *in vitro* human microsomal study enfuvirtide is not an inhibitor of CYP450 enzymes and therefore will not alter the metabolism of drugs metabolized by CYP450 enzymes. In an *in vivo* human metabolism study enfuvirtide, at the recommended dose of 90 mg bid, did not inhibit the metabolism of substrates by CYP3A4 (dapsone), CYP2D6 (debrisoquine), CYP1A2 (caffeine), CYP2C19 (mephenytoin) and CYP2E1 (chlorzoxazone).

Influence of Concomitant Drugs on Enfuvirtide Metabolism
In separate pharmacokinetic interaction studies, co-administration of rifampicin, ritonavir or saquinavir in combination with a booster dose of ritonavir, did not result in clinically significant pharmacokinetic interactions with enfuvirtide. In the case of the ritonavir study, a 22% increase in AUC and a 24 % increase in C_{max} of enfuvirtide was observed (see Table 2).

Table 2: Effect of Ritonavir, Saquinavir/Ritonavir, and Rifampin on the Steady-State Pharmacokinetics of Enfuvirtide (90 mg bd) *

Coadministered drug	**Dose of coadministered drug**	**n**	**% change of enfuvirtide pharmacokinetic parameters† (90 % CI)**		
			C_{max}	**AUC**	**C_{trough}**
Ritonavir	200 mg, q12h, 4 days	12	↑ 24 (↑ 9 to ↑ 14)	↑ 22 (↑ 8 to ↑ 37)	↑ 14 (↑ 2 to ↑ 28)
Saquinavir/ ritonavir	1000/100 mg, q12h, 4 days	12	⇔	↑ 14 (↑ 5 to ↑ 24)	↑ 26 (↑ 17 to ↑ 35)
Rifampicin	600 mg, qd, 10 days	12	⇔	⇔	↓ 15 (↓ 22 to ↓ 7)

** All studies were performed in HIV-1+ subjects using a sequential crossover design.*
† ↑= Increase; ↓ = Decrease; ⇔ = No Effect (↑or ↓ <10%)

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility
Enfuvirtide produced no adverse effects on fertility in male or female rats at subcutaneous doses up to 15 mg/kg bid (1.6x the adult clinical dose, adjusted for body surface area).

Use in Pregnancy - Category B2
After subcutaneous administration of radiolabelled enfuvirtide to pregnant rats on gestation day 18, radioactivity representing enfuvirtide and/or its metabolites was detected in foetuses.

In embryo-foetal development studies with enfuvirtide subcutaneous doses up to 250 mg/kg bid in rats and up to 15 mg/kg bid in rabbits (relative systemic exposures, based in AUC, of 8.9x and 3.2x, respectively), there were no adverse embryo-foetal effects. Peri-postnatal development was unaffected in rats at subcutaneous doses up to 15 mg/kg bid (1.6x the adult clinical dose, adjusted for body surface area).

There are no adequate and well-controlled studies in pregnant women. Enfuvirtide should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation
After subcutaneous administration of radiolabelled enfuvirtide to lactating rats, it was estimated that approximately 3% of the total radioactivity was secreted in milk over 48 h, with small amounts of enfuvirtide detectable up to 1 h, and only metabolites thereafter. 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 both the potential for HIV transmission and any possible adverse effects in nursing infants.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No studies have been conducted on the ability to drive or operate machinery while taking enfuvirtide. 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 Adverse effects (Undesirable effects)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)
Clinical Trials
The overall safety profile of Fuzeon is based on 2120 patients who received at least one dose of enfuvirtide during various clinical trials. The safety population consisted of 2051 adults (including 1181 adults who were exposed to the recommended dose for ≥24 weeks and 631 adults who were exposed for ≥48 weeks) and 69 paediatric patients (including 44 children who were exposed to Fuzeon for ≥24 weeks and 27 children who were exposed for ≥48 weeks).

At week 48 of the study the cumulative exposure on the Fuzeon + OB regimen was 557 patient-years, and on the OB alone regimen the cumulative exposure was 162 patient-years. Due to this difference in exposure, the adjusted safety results are expressed as the number of patients with an adverse event per 100 patient-years of exposure (except for injection site reactions).

<u>Local injection site reactions</u>
The most frequently reported adverse reactions following enfuvirtide administration were local injection site reactions (ISRs), which occurred in 98% of the 663 Fuzeon-treated patients in TORO-1 and TORO-2 (Table 3). Four percent of patients discontinued use of Fuzeon due to ISRs. The vast majority (85.6% in TORO-1 and TORO-2) 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 associated with ISRs did not increase with treatment duration. The signs and symptoms characterising the injection site reactions generally lasted less than 7 days. Seventy two percent (72%) of patients had lesions evident on at least one of the given study visits; the number of lesions evident at any given visit was ≤5. Infection at the injection site (including abscess and cellulitis) occurred in 1.5% of patients.

Table 3: Summary of Individual Signs/Symptoms Characterizing 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 + OB regimen [a]	% of events comprising Grade 3 reactions	% of events comprising Grade 4 reactions
Pain/discomfort [b]	96.1 %	11.0 %	0 %
Erythemia [c]	90.8 %	23.8 %	10.5 %
Induration [d]	90.2 %	43.5 %	19.4 %
Nodules and cysts [e]	80.4 %	29.1 %	0.2 %
Pruitus [f]	65.2 %	3.9 %	N.A.
Ecchymosis [g]	51.9 %	8.7 %	4.7 %

[a] *Any severity grade*

[b] *Grade 3= severe pain requiring analgesics (or narcotic analgesics for ≤72 hours) and/or limiting usual activities; Grade 4=severe pain requiring hospitalization or prolongation of hospitalization, resulting in death, or persistent or significant disability/incapacity, or life-threatening, or medically significant.*

[c] *Grade 3= ≥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 events most frequently reported in subjects receiving the Fuzeon+OB regimen (n=663), excluding injection site reactions, were diarrhoea (38 patients with event per 100 patient years) and nausea (27 patients with event per 100 patient years). These events were also commonly observed among subjects that received the OB alone regimen (n=334): diarrhoea (73 patients with event per 100 patient years) and nausea (50 patients with event per 100 patient years). The addition of Fuzeon to background antiretroviral therapy generally did not increase the frequency or severity of most adverse events.

Shown in Table 4 are events seen more commonly among patients receiving Fuzeon +OB regimen (n=663) than among patients on the OB alone regimen (n=334) (excluding injection site reactions), with an exposure adjusted rate of at least 2 patients with event per 100 patient-years (data from clinical trials TORO-1 and TORO-2). Rates of adverse events for patients who switched to Fuzeon after virological failure were similar. The only adverse events with a

statistically significant risk ratio between the Fuzeon regimen and the OB alone regimen, were pneumonia and lymphadenopathy. Most adverse events were of mild or moderate intensity.

Table 4: Adverse drug reactions, comparing Fuzeon+OB regimen to OB alone regimen, excluding injection site reactions, and with a report of at least 2 patients with event per 100 patient years of exposure

Adverse Event (by system organ class)	**Fuzeon + OB regimen per 100 pt yrs**	**OB alone regimen per 100 pt yrs**
Total Exposure (in patient years)	**557.0**	**162.1**
Nervous system disorders		
Peripheral neuropathy	15.4	13.6
Hypoesthesia	2.9	1.9
Disturbance in attention	2.3	1.9
Tremor	2.2	1.9
Psychiatric disorders		
Anxiety	7.5	6.8
Nightmare	2.3	1.2
Irritability	2.3	1.9
Respiratory, thoracic and mediastinal disorders		
Nasal congestion	3.1	2.5
Investigations		
Weight decreased	11.1	10.5
Blood triglycerides increased	2.9	1.9
Haematuria present	2.2	1.9
Metabolism and nutrition disorders		
Appetite decreased	8.6	4.9
Anorexia	3.8	3.1
Hypertriglyceridemia	2.0	1.9
Diabetes mellitus	2.0	0.6
Infections and infestations		
Sinusitis	9.5	6.2
Influenza	6.5	6.2
Skin papilloma	6.6	3.1
Pneumonia	3.9	0.6
Ear infection	2.2	1.2
General disorders and administration site conditions		
Influenza like illness	4.5	3.7
Weakness	2.7	0.6
Skin and subcutaneous tissue disorders		
Dry skin	5.0	4.3
Eczema seborrhoeic	2.3	1.9
Erythema	2.2	1.2
Acne	2.0	0.6
Musculoskeletal, connective tissue and bone disorders		
Myalgia	7.0	5.6

Adverse Event (by system organ class)	Fuzeon + OB regimen per 100 pt yrs	OB alone regimen per 100 pt yrs
Total Exposure (in patient years)	**557.0**	**162.1**
Gastrointestinal disorders		
Pancreatitis	3.6	2.5
Gastro-oesophageal reflux disease	2.7	2.5
Eye disorders		
Conjunctivitis	4.1	2.5
Blood and lymphatic system disorders		
Lymphadenopathy	5.9	1.2
Ear and labyrinth disorders		
Vertigo	3.6	0.6
Renal and urinary disorders		
Calculus renal	2.3	1.2

Hypersensitivity Reactions

In addition there have been a small number of hypersensitivity reactions attributed to Fuzeon and in some cases recurrence has occurred upon re-challenge (see section 4.4 Special warnings and precautions for use). 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, glomerulonephritis and anaphylaxis.

Laboratory Testing

The majority of patients had no change in the toxicity grade of any laboratory parameter during the study. Table 5 shows the treatment emergent laboratory abnormalities that occurred at a rate of at least 2 patients per 100 patient-years of exposure and that occurred more frequently (either as a grade 3 or 4 laboratory abnormality) among patients receiving Fuzeon+OB regimen than among patients on the OB alone regimen, to week 48 of the pooled studies TORO 1 and TORO 2.

Through week 48, treatment-emergent eosinophilia [greater than the Upper Limit of Normal (ULN) of > 0.7 x 10^9/L] occurred at a higher rate among patients in the Fuzeon containing group (12.4 per 100 patient years) compared with OB alone regimen (5.6 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 5: Exposure adjusted Grade 3 and 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+ Background Regimen	Background Regimen
Treatment Exposure (patient-years)		**557.0**	**162.1**
Eosinophilia			
1-2 X ULN (0.7 x 10^9/L)	0.7-1.4 x 10^9/L	10.8	3.7
>2 X ULN (0.7 x 10^9/L)	>1.4 x 10^9/L	2.2	1.8

Laboratory Parameters	Grading	Fuzeon+ Background Regimen	Background Regimen
ALT			
Gr. 3	>5-10 x ULN	4.8	4.3
Gr. 4	>10 x ULN	1.4	1.2
Creatine kinase (U/L)			
Gr. 3	>5-10 x ULN	8.3	8.0
Gr. 4	>10 x ULN	3.1	8.6
Haemoglobin (g/dL)			
Gr. 3	6.5-7.9 g/dL	2.0	1.9
Gr. 4	<6.5 g/dL	0.7	1.2

Additional adverse events or laboratory abnormalities

The following additional adverse events or laboratory abnormalities were reported from the 24 week analysis of the two pivotal studies as occurring in >2% of patients and more frequently in patients receiving Fuzeon+OB regimen than in those taking OB alone regimen. A causal relationship of these events to Fuzeon has not been established.

Nervous system disorders: headache, dizziness (excl. Vertigo), taste disturbance

Psychiatric disorders: Insomnia, depression

Respiratory, thoracic and mediastinal disorders: Cough

Investigations: Increased gamma-glutamyltransferase, amylase, lipase, AST

Infections and infestations: Oral candidiasis, herpes simplex, folliculitis

General disorders and administration site conditions: Asthenia

Skin and subcutaneous tissue disorders: Pruritus, night sweats, sweating increased

Musculoskeletal, connective tissue and bone disorders: arthralgia, back pain, pain in limb, muscle cramps

Gastrointestinal disorders: Abdominal pain upper, constipation, sore throat

Post-Marketing Experience

Skin and subcutaneous tissue disorders: cutaneous amyloidosis at the injection site.

Post-marketing observational study in bacterial pneumonia

A higher rate of pneumonia (primarily bacterial) has been observed in patients treated with Fuzeon in the Phase III clinical trials compared to the control arm. Because it was unclear whether the higher rate of pneumonia was related to Fuzeon use, an observational study in 1150 HIV-infected patients (740 Fuzeon arm with 2,045 patient-years of observation and 1110 comparator population with 3,501 patient-years of observation) was conducted to carefully evaluate the risk of pneumonia from Fuzeon while controlling for other known risk factors. The incidence of pneumonia was 3.82 events/100 patient-years in the Fuzeon treatment arm and 2.31 events/100 patient-years in the non-exposed cohort. The adjusted risk ratio for incidence of pneumonia was 0.989 for confirmed pneumonia only, and 1.228 for confirmed or

probable pneumonia, with the lower limit of the 95% confidence interval of 0.437 and 0.862, respectively.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There are no reports of overdose with Fuzeon in humans. The highest dose administered to 12 patients in a clinical trial was 180 mg as a single dose subcutaneously. These patients did not experience any adverse events that were not seen with the recommended dose.

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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 that functions by specifically binding to this virus protein extracellularly and thereby blocking the virus from entering the cell. The antiviral activity of enfuvirtide results from its association with a heptad-repeat motif, HR1, within native gp41 on the viral surface.

Microbiology

Antiviral activity in vitro

The *in vitro* antiviral activity of enfuvirtide has been demonstrated for acute infection of T-lymphoblastoid cell lines, monocyte/macrophage cells, and primary peripheral blood mononuclear cells (PBMC) by laboratory and clinical HIV-1 isolates. Enfuvirtide demonstrated selective anti-HIV-1 activity against both prototypic and primary virus isolates. Enfuvirtide susceptibility for 130 PBMC baseline virus isolates from enfuvirtide treated patients in Phase II clinical studies was determined in a cMAGI cell assay (CCR5 expressing derivative of the Multinuclear Activation of a Galactosidase Indicator cell line). Enfuvirtide had a geometric mean EC_{50} of 0.016 µg/mL (SD = 0.057) against these virus isolates. Enfuvirtide also inhibited HIV-1 envelope mediated cell-cell fusion. Drug combination studies of enfuvirtide with representative members of the various antiretroviral classes (nucleoside reverse transcriptase inhibitor, non-nucleoside reverse transcriptase inhibitors and protease inhibitors; namely zidovudine, lamivudine, nelfinavir, indinavir, and efavirenz) exhibited additive to synergistic effects in cell culture assays. The relationship between the *in vitro* susceptibility of HIV-1 to enfuvirtide and inhibition of HIV-1 replication in humans has not been established. The *in vitro* antiviral activity of enfuvirtide against HIV-2 isolates is low.

Viral Resistance

In Vitro Resistance to enfuvirtide

HIV-1 isolates with reduced susceptibility to enfuvirtide have been selected *in vitro*. These isolates harboured substitutions in amino acids 36-38 of the gp41 ectodomain and these substitutions were correlated with varying levels of reduced enfuvirtide susceptibility in HIV site-directed mutants.

Mutations in gp41 amino acids 36-45 were observed with clinical isolates exhibiting decreased *in vitro* susceptibility to enfuvirtide in comparison to their respective baseline (i.e. pretreatment) isolate. Site directed mutagenesis in the HIV-1 NL4-3 molecular clone confirmed that mutations in gp41 amino acid residues 36-45 could confer decreased *in vitro* sensitivity to enfuvirtide.

In Vivo Resistance to enfuvirtide

Post-treatment HIV-1 virus from 246 subjects experiencing protocol defined virological failure exhibited decreases in susceptibility to enfuvirtide ranging from 4 fold to 6318 fold relative to respective baseline virus and exhibited genotypic changes in gp41 amino acids 36 to 45. The substitutions observed in decreasing frequency were at amino acid positions 38, 43, 40, and 36. In isolates from subjects experiencing virological failure in Phase III clinical studies the two most common amino acid substitutions were V38A and N43D.

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 classes of antiretrovirals (nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors). These isolates had genotypic resistance specifically identified for: zidovudine, lamivudine, stavudine, didanosine, zalcitabine, abacavir, nevirapine, delavirdine, efavirenz, indinavir, saquinavir, nelfinavir, ritonavir and amprenavir; all were sensitive to enfuvirtide. Conversely, mutations in amino acids 36-45 of gp41 which give resistance to enfuvirtide would not be expected to give cross resistance to other classes of antiretrovirals.

Clinical trials

Studies in Antiretroviral Experienced Patients

The clinical activity of Fuzeon (in combination with other antiretroviral agents) on surrogate markers for clinical efficacy (plasma HIV-1 RNA levels and CD4 counts) has been investigated in two randomised, multi-centre, controlled studies (TORO-1 and TORO-2). Analyses have been performed following 48 weeks of treatment.

The HIV-1 infected patients enrolled into these studies all had at least 3 to 6 months of prior treatment with (or documented resistance or intolerance to) nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors. Patients had prior exposure to a median of 12 antiretrovirals for a median of 7 years.

All patients received an optimized 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. Patients were randomized at a 2:1 ratio to Fuzeon (90 mg bid) + OB or OB alone.

There were 995 patients in the pooled intention to treat (ITT) population and demographic characteristics for patients in studies TORO-1 and TORO-2 are shown in Table 6.

Table 6: Patient Demographics (Pooled Studies TORO-1 and TORO-2)

	Fuzeon + OB n = 661	**OB n = 334**
Sex Male Female	 90 % 10 %	 90 % 10 %
Race White Black	 89% 8 %	 89% 7%
Mean age (year) (range)	42 (16 – 67)	43 (24 – 82)
Median baseline HIV-1 RNA (log_{10} copies/mL)	5.2 (3.5 – 6.7)	5.1 (3.7 – 7.1)
Median baseline CD4 cell count (cells/mm^3)	88 (1 – 994)	97 (1 – 847)

Compared to the OB treatment group, the Fuzeon + OB treatment group experienced a significantly greater decrease in plasma HIV-1 RNA with a treatment difference of 0.85 log_{10} copies/mL and a significantly greater increase in CD4 cell count after 48 weeks of treatment (see Table7).

The percentages of patients who achieved a decrease in HIV-1 RNA plasma levels of ≥1 log_{10}, and decreases to <400 copies/mL and <50 copies/mL after 48 weeks of treatment were significantly higher in the Fuzeon + OB treatment group (see Table 7).

The proportion of patients achieving viral load of <400 copies/mL at week 48 was 30% among patients on the Fuzeon+OB regimen compared to 12% among patients receiving OB regimen only (see Table 7).

Table 7: Outcomes of Randomised Treatment at Week 48 (Pooled Studies TORO 1 and TORO 2, ITT)

Outcomes	**Fuzeon + OB regimen 90 mg bid (n = 661)**	**OB alone regimen (n = 334)**	**Difference between arms**	**Confidence Interval**
HIV-1 RNA log change from baseline (log_{10} copies/mL)*	- 1.48	- 0.63	0.85***	(- 1.07, - 0.63)

CD4+ cell count change from baseline (cells/mm^3)[#]	+ 91	+ 45	+ 46[***]	(+ 25, + 68)
Decrease HIV RNA ≥1 log from baseline[**]	247 (37.4 %)	57 (17.1 %)	20.3 %[***]	(14.8 %, 25.8 %)
HIV RNA <400 copies/mL[**]	201 (30.4 %)	40 (12.0 %)	18.4 %[***]	(13.5 %, 23.3 %)
HIV RNA <50 copies/mL[**]	121 (18.3 %)	26 (7.8 %)	10.5 %[***]	(6.4 %, 14.0 %)
Time to virological failure[##] (weeks)[**]	32	11	-	-
Discontinued due to adverse reactions/intercurrent illness/labs[†]	9 %	11 %	-	-
Discontinued due to injection site reactions[†]	4 %	N/A	-	-
Discontinued due to other reasons[†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*

[**] *Discontinuations or virological failure considered as failures*

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

[†] *Percentages based on safety population Fuzeon + OB (n=663) and OB (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.*

*** *Statistically significant p<0.0001*

The studies were not designed to assess differences in AIDS defining events or mortality as patients switched from OB to Fuzeon + OB upon virological failure.

Virological failure was defined in the protocols as failure to achieve 0.5 log response by week 6 and 8, failure to achieve a 1.0 log response by weeks 14 and 16, or having ≥ 2 log decrease from baseline followed by >1 log rebound at any time. Overall, 301 (46%) and 236 (71%) of patients on Fuzeon + OB and OB, respectively, met virological failure criteria by week 24.

Paediatric population

Limited efficacy data is available from 39 HIV-1 infected paediatric patients age 3 through 16 years. The evaluation of the safety and antiviral activity of Fuzeon in paediatric patients in clinical trials is ongoing.

Study T20-204 is an ongoing open-label, multi-centre trial evaluating the pharmacokinetics, safety, and antiviral activity of Fuzeon in 14 paediatric patients aged 3 to 12 years. All patients had experience with at least two classes of licensed antiretrovirals.

Study T20-204 patients added either 30 or 60 mg/m^2/dose Fuzeon bid to their existing background antiretroviral regimen. After 7 days, the background regimen was changed to 3 new or sensitive antiretrovirals and Fuzeon dosing was continued. Patients had a median age of 8 years (range 3.7 through 11.9 years). Median baseline CD4 cell count was 523 cells/μL and the median baseline HIV-1 RNA was 4.4 $\log_{10}$ c/mL.

Following day 7 analysis for safety, pharmacokinetics and antiviral activity, all but 1 patient was switched to 60 mg/m^2/dose of Fuzeon. The median change from baseline HIV RNA at day 7 was -1.15 $\log_{10}$ copies/mL for 10 paediatric patients receiving the 60 mg/m^2 dose.

All but 3 patients completed 48 weeks of chronic therapy. By week 48, 6/14 (43%) patients had >1 $\log_{10}$ decline in HIV-1 RNA and 4/14 (29%) patients were below 400 copies/mL of HIV-1 RNA. The median changes from baseline in HIV-1 RNA and CD4 cell count were -1.24 $\log_{10}$ c/mL and 237 cells/μL, respectively, but no control group was included in these studies.

5.2 PHARMACOKINETIC PROPERTIES

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

Absorption

The pharmacokinetics of enfuvirtide has been explored by both intravenous (iv) and subcutaneous (sc) administration and they provide similar exposures. The absolute bioavailability (using the 90 mg iv dose as a reference) was 84.3 ± 15.5%. Following 90 mg bid dosing of enfuvirtide subcutaneously in 11 HIV-1 infected patients, the mean (± SD) steady state C_{max} was 5.0 ± 1.7 μg/mL, C_{trough} was 3.3 ± 1.6 μg/mL, $AUC_{0\text{-}12h}$ was 48.7 ± 19.1 μg*h/mL and the median T_{max} was 4 hours. 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 the 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 mean (± SD) steady state volume of distribution with intravenous administration of a 90 mg dose of enfuvirtide (n=12) 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. No data is available on distribution to semen, breast milk or vaginal secretions.

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

Metabolism

As a peptide, enfuvirtide is expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool. *In vitro* human microsomal 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 (nicotinamide adenine dinucleotide phosphate) dependent. This metabolite is detected in human plasma following administration of enfuvirtide, with an AUC ranging from 2.4 to 15 % of the enfuvirtide AUC.

Excretion

Following a 90 mg subcutaneous dose of enfuvirtide (n=12) the mean ± SD elimination half-life of enfuvirtide was 3.8 ± 0.6 h and the mean ± SD clearance was 1.7 ± 0.4 L/h. Mass balance studies to determine elimination pathway(s) of enfuvirtide have not been performed in humans.

Pharmacokinetics in Special Populations

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 creatinine clearance greater than 35mL/min. The results of a renal impairment study indicate clearance of enfuvirtide was reduced by 38% in patients with severe renal impairment and by 14-28% in patients with end stage renal disease maintained on dialysis compared to patients with normal renal function. The results were within the range seen in patients in the pivotal studies with normal renal function. Haemodialysis did not significantly alter enfuvirtide clearance. Thus, no dose adjustment is required for patients with impaired renal function.

Elderly patients

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 100kg and 20% lower in a 40 kg body weight patient relative to a 70 kg reference patient). However, these changes are not clinically significant and no dose adjustment is required.

Race

Analysis of plasma concentration data from patients in clinical trials indicated that the clearance of enfuvirtide was not different in Blacks compared to Caucasians. Other

pharmacokinetic studies suggest no difference between Asians and Caucasians after adjusting exposure for body weight.

Paediatric patients

The pharmacokinetics of enfuvirtide have been studied in 32 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 23 paediatric patients ranging in age from 6 to 16 years and receiving the 2 mg/kg bid dose into the upper arm, anterior thigh or abdomen, the mean ± SD steady-state AUC was 56.3 ± 22.3 μg*h/mL, C_{max} was 6.3 ± 2.4 μg/mL, and C_{trough} was 3.1 ± 1.5 μg/mL.

5.3 PRECLINICAL SAFETY DATA

Genotoxity

Enfuvirtide was not mutagenic in a series of assays including the Ames bacterial reverse mutation assay, a mammalian cell forward gene mutation assay in AS52 Chinese Hamster ovary cells, nor did it induce micronuclei in an *in vivo* mouse micronucleus assay.

Carcinogenicity

Long-term animal carcinogenicity studies of enfuvirtide have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium carbonate
Mannitol
Sodium hydroxide
Hydrochloric acid

6.2 INCOMPATIBILITIES

Fuzeon should not be mixed with other medicinal products except for the solvent supplied (water for injections).

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C

After reconstitution with water for injection the product may only be stored at 2 to 8°C for no longer than 24 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

Fuzeon is available in packs of 60 vials.

Fuzeon is also available as a combination pack containing the following:
60 vials powder for injection
60 vials solvent

60 3mL syringes + needle
60 1mL syringes + needle
180 alcohol swabs

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Disposal of Syringes and Sharps

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).
- Keep the sharps container out of the reach of children.
- Placing used sharps container in household waste should be avoided.
- Dispose of the full sharps container according to local requirements or as instructed by your healthcare provider.

For home use, a puncture resistant container for the disposal of used syringes and needles should be supplied to the patients.

Disposal of Medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

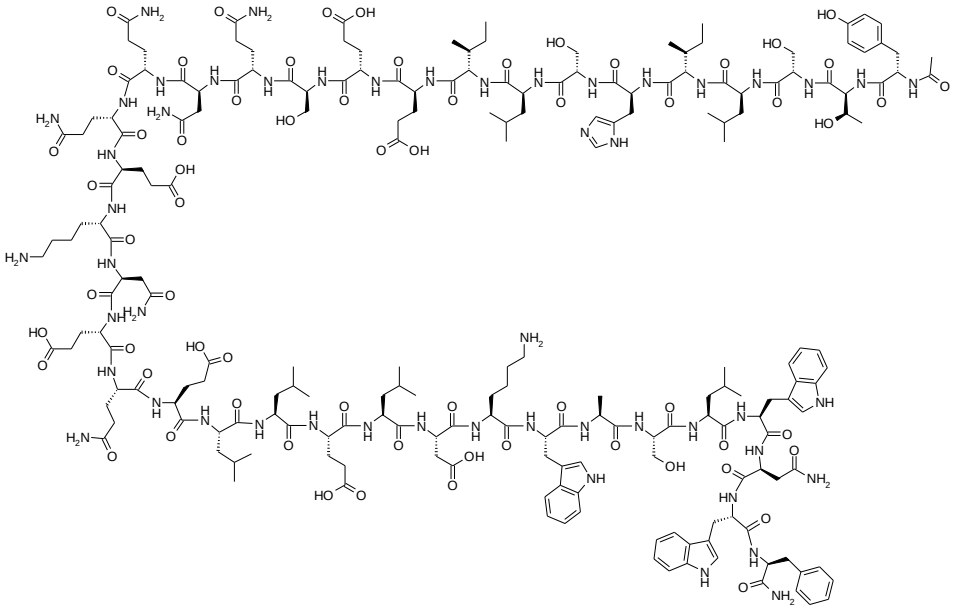
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure

The empirical formula of enfuvirtide is $C_{204}H_{301}N_{51}O_{64}$, and the molecular weight is 4,492. It has the following primary amino acid sequence:

Ac-Tyr-Thr-Ser-Leu-Ile-His-Ser-Leu-Ile-Glu-Glu-Ser-Gln-Asn-Gln-Gln-Glu-Lys-Asn-Glu-Gln-Glu-Leu-Leu-Glu-Leu-Asp-Lys-Trp-Ala-Ser-Leu-Trp-Asn-Trp-Phe-NH_2



Fuzeon (enfuvirtide) is derived from a naturally occurring motif, amino acid residues (643-678) within the gp41 transmembrane glycoprotein of human immunodeficiency virus type 1 strain LAI (HIV-1_{LAI}). Enfuvirtide is a linear 36-amino acid synthetic peptide, composed of naturally occurring L-amino acid residues.

CAS number

159519-65-0

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30-34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

2 September 2003

10. DATE OF REVISION

19 October 2020

Summary table of changes

Section Changed	Summary of new information
All	New PI format and mandatory text added
8	Sponsor address updated
4.9, 6.5, 8	Reference to New Zealand removed
6.1	Update to ingredient name