



**FUZEON<sup>®</sup>**

**(enfuvirtide)**

**for Injection**

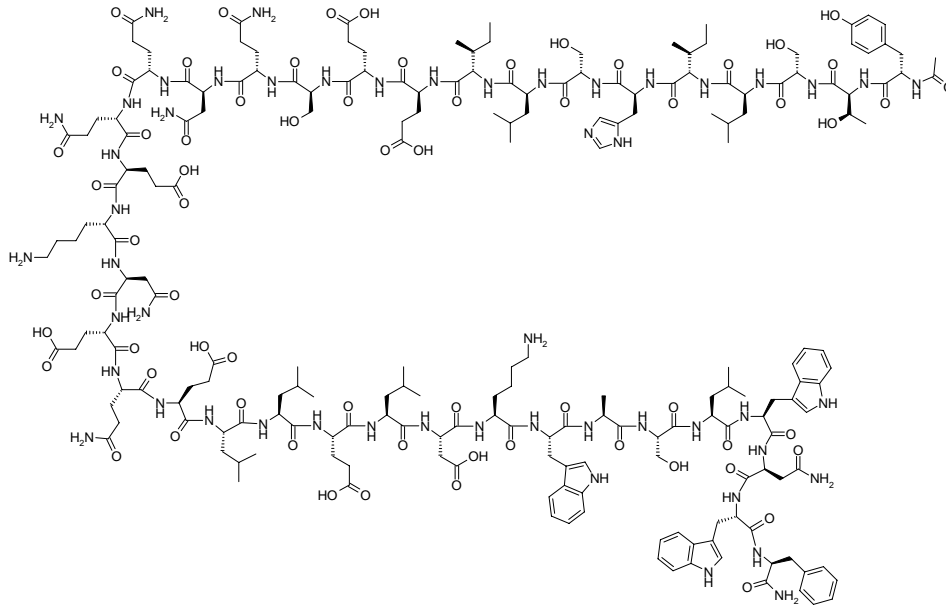
**R<sub>x</sub> only**

## **DESCRIPTION**

FUZEON (enfuvirtide) is an inhibitor of the fusion of HIV-1 with CD4<sup>+</sup> cells. Enfuvirtide is a linear 36-amino acid synthetic peptide with the N-terminus acetylated and the C-terminus is a carboxamide. It is composed of naturally occurring L-amino acid residues.

Enfuvirtide is a white to off-white amorphous solid. It has negligible solubility in pure water and the solubility increases in aqueous buffers (pH 7.5) to 85-142 g/100 mL. The empirical formula of enfuvirtide is C<sub>204</sub>H<sub>301</sub>N<sub>51</sub>O<sub>64</sub>, and the molecular weight is 4492. It has the following primary amino acid sequence:

CH<sub>3</sub>CO-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<sub>2</sub> and the following structural formula:



17

18 The drug product, FUZEON (enfuvirtide) for Injection, is a white to off-white, sterile,  
19 lyophilized powder. Each single-use vial contains 108 mg of enfuvirtide for the delivery  
20 of 90 mg. Prior to subcutaneous administration, the contents of the vial are reconstituted  
21 with 1.1 mL of Sterile Water for Injection giving a volume of approximately 1.2 mL to  
22 provide the delivery of 1 mL of the solution. Each 1 mL of the reconstituted solution  
23 contains approximately 90 mg of enfuvirtide with approximate amounts of the following  
24 excipients: 22.55 mg of mannitol, 2.39 mg of sodium carbonate (anhydrous), and sodium

25 hydroxide and hydrochloric acid for pH adjustment as needed. The reconstituted solution  
26 has an approximate pH of 9.0.

## 27 **MICROBIOLOGY**

### 28 **Mechanism of Action**

29 Enfuvirtide interferes with the entry of HIV-1 into cells by inhibiting fusion of viral and  
30 cellular membranes. Enfuvirtide binds to the first heptad-repeat (HR1) in the gp41  
31 subunit of the viral envelope glycoprotein and prevents the conformational changes  
32 required for the fusion of viral and cellular membranes.

### 33 **Antiviral Activity In Vitro**

34 The in vitro antiviral activity of enfuvirtide was assessed by infecting different CD4<sup>+</sup> cell  
35 types with laboratory and clinical isolates of HIV-1. The IC<sub>50</sub> values for baseline clinical  
36 isolates ranged from 0.089 to 107 nM (0.4 to 480 ng/mL) by the cMAGI assay (n=130)  
37 and from 1.56 to 1680 nM (7 to 7530 ng/mL) by a recombinant phenotypic entry assay  
38 (n=627). Enfuvirtide was similarly active in vitro against clades A, AE, C, D, E, F, and G  
39 (range 5.1 to 10.5 nM), and R5, X4, and dual tropic viruses. Enfuvirtide has no activity  
40 against HIV-2.

41 Enfuvirtide exhibited additive to synergistic effects in cell culture assays when combined  
42 with individual members of various antiretroviral classes, including lamivudine,  
43 zidovudine, indinavir, nelfinavir, and efavirenz.

### 44 **Drug Resistance**

45 HIV-1 isolates with reduced susceptibility to enfuvirtide have been selected in vitro.  
46 Genotypic analysis of the in vitro-selected resistant isolates showed mutations that  
47 resulted in amino acid substitutions at the enfuvirtide binding HR1 domain positions 36  
48 to 38 of the HIV-1 envelope glycoprotein gp41. Phenotypic analysis of site-directed  
49 mutants in positions 36 to 38 in an HIV-1 molecular clone showed a 5-fold to 684-fold  
50 decrease in susceptibility to enfuvirtide.

51 In clinical trials, HIV-1 isolates with reduced susceptibility to enfuvirtide have been  
52 recovered from subjects failing a FUZEON containing regimen. Posttreatment HIV-1  
53 virus from 277 subjects experiencing protocol defined virological failure at 48 weeks  
54 exhibited a median decrease in susceptibility to enfuvirtide of 33.4-fold (range 0.4-6318-  
55 fold) relative to their respective baseline virus. Of these, 249 had decreases in  
56 susceptibility to enfuvirtide of greater than 4-fold and all but 3 of those 249 exhibited  
57 genotypic changes in the codons encoding gp41 HR1 domain amino acids 36 to 45.  
58 Substitutions in this region were observed with decreasing frequency at amino acid  
59 positions 38, 43, 36, 40, 42, and 45.

### 60 **Cross-resistance**

61 HIV-1 clinical isolates resistant to nucleoside analogue reverse transcriptase inhibitors  
62 (NRTI), non-nucleoside analogue reverse transcriptase inhibitors (NNRTI), and protease  
63 inhibitors (PI) were susceptible to enfuvirtide in cell culture.

## 64 **CLINICAL PHARMACOLOGY**

### 65 **Pharmacokinetics**

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

#### 68 **Absorption**

69 Following a 90-mg single subcutaneous injection of FUZEON into the abdomen in 12  
70 HIV-1 infected subjects, the mean ( $\pm$ SD)  $C_{\max}$  was  $4.59 \pm 1.5$   $\mu\text{g/mL}$ , AUC was  $55.8$   
71  $\pm 12.1$   $\mu\text{g}\cdot\text{h/mL}$  and the median  $T_{\max}$  was 8 hours (ranged from 3 to 12 h). The absolute  
72 bioavailability (using a 90-mg intravenous dose as a reference) was  $84.3\% \pm 15.5\%$ .  
73 Following 90-mg bid dosing of FUZEON subcutaneously in combination with other  
74 antiretroviral agents in 11 HIV-1 infected subjects, the mean ( $\pm$ SD) steady-state  $C_{\max}$  was  
75  $5.0 \pm 1.7$   $\mu\text{g/mL}$ ,  $C_{\text{trough}}$  was  $3.3 \pm 1.6$   $\mu\text{g/mL}$ ,  $\text{AUC}_{0-12\text{h}}$  was  $48.7 \pm 19.1$   $\mu\text{g}\cdot\text{h/mL}$ , and the  
76 median  $T_{\max}$  was 4 hours (ranged from 4 to 8 h).

77 Absorption of the 90-mg dose was comparable when injected into the subcutaneous tissue  
78 of the abdomen, thigh or arm.

#### 79 **Distribution**

80 The mean ( $\pm$ SD) steady-state volume of distribution after intravenous administration of a  
81 90-mg dose of FUZEON (N=12) was  $5.5 \pm 1.1$  L.

82 Enfuvirtide is approximately 92% bound to plasma proteins in HIV-infected plasma over  
83 a concentration range of 2 to 10  $\mu\text{g/mL}$ . It is bound predominantly to albumin and to a  
84 lower extent to  $\alpha$ -1 acid glycoprotein.

#### 85 **Metabolism/Elimination**

86 As a peptide, enfuvirtide is expected to undergo catabolism to its constituent amino acids,  
87 with subsequent recycling of the amino acids in the body pool.

88 Mass balance studies to determine elimination pathway(s) of enfuvirtide have not been  
89 performed in humans.

90 In vitro studies with human microsomes and hepatocytes indicate that enfuvirtide  
91 undergoes hydrolysis to form a deamidated metabolite at the C-terminal phenylalanine  
92 residue, M3. The hydrolysis reaction is not NADPH dependent. The M3 metabolite is  
93 detected in human plasma following administration of enfuvirtide, with an AUC ranging  
94 from 2.4% to 15% of the enfuvirtide AUC.

95 Following a 90-mg single subcutaneous dose of enfuvirtide (N=12) the mean  $\pm$ SD  
96 elimination half-life of enfuvirtide is  $3.8 \pm 0.6$  h and the mean  $\pm$ SD apparent clearance  
97 was  $24.8 \pm 4.1$  mL/h/kg. Following 90-mg bid dosing of FUZEON subcutaneously in  
98 combination with other antiretroviral agents in 11 HIV-1 infected subjects, the mean  $\pm$ SD  
99 apparent clearance was  $30.6 \pm 10.6$  mL/h/kg.

## 100 Special Populations

### 101 *Hepatic Insufficiency*

102 Formal pharmacokinetic studies of enfuvirtide have not been conducted in patients with  
103 hepatic impairment.

### 104 *Renal Insufficiency*

105 Formal pharmacokinetic studies of enfuvirtide have not been conducted in patients with  
106 renal insufficiency. However, analysis of plasma concentration data from subjects in  
107 clinical trials indicated that the clearance of enfuvirtide is not affected in patients with  
108 creatinine clearance greater than 35 mL/min. The effect of creatinine clearance less than  
109 35 mL/min on enfuvirtide clearance is unknown.

### 110 *Gender and Weight*

#### 111 GENDER

112 Analysis of plasma concentration data from subjects in clinical trials indicated that the  
113 clearance of enfuvirtide is 20% lower in females than males after adjusting for body  
114 weight.

#### 115 WEIGHT

116 Enfuvirtide clearance decreases with decreased body weight irrespective of gender.  
117 Relative to the clearance of a 70-kg male, a 40-kg male will have 20% lower clearance  
118 and a 110-kg male will have a 26% higher clearance. Relative to a 70-kg male, a 40-kg  
119 female will have a 36% lower clearance and a 110-kg female will have the same  
120 clearance.

121 No dose adjustment is recommended for weight or gender.

### 122 *Race*

123 Analysis of plasma concentration data from subjects in clinical trials indicated that the  
124 clearance of enfuvirtide was not different in Blacks compared to Caucasians. Other  
125 pharmacokinetic studies suggest no difference between Asians and Caucasians after  
126 adjusting for body weight.

### 127 *Pediatric Patients*

128 The pharmacokinetics of enfuvirtide have been studied in 23 pediatric subjects aged 6  
129 through 16 years at a dose of 2 mg/kg. Enfuvirtide pharmacokinetics were determined in  
130 the presence of concomitant medications including antiretroviral agents. A dose of  
131 2 mg/kg bid (maximum 90 mg bid) provided enfuvirtide plasma concentrations similar to  
132 those obtained in adult patients receiving 90 mg bid.

133 In the 23 pediatric subjects receiving the 2 mg/kg bid dose, the mean  $\pm$ SD steady-state  
134 AUC was  $56.3 \pm 22.3 \mu\text{g}\cdot\text{h/mL}$ ,  $C_{\text{max}}$  was  $6.3 \pm 2.4 \mu\text{g/mL}$ ,  $C_{\text{trough}}$  was  $3.1 \pm 1.5 \mu\text{g/mL}$ ,  
135 and apparent clearance was  $40 \pm 17 \text{ mL/h/kg}$ .

136 *Geriatric Patients*

137 The pharmacokinetics of enfuvirtide have not been studied in patients over 65 years of  
138 age.

139 *Drug Interactions*

140 *Influence of FUZEON on the Metabolism of Concomitant Drugs*

141 Based on the results from an in vitro human microsomal study, enfuvirtide is not an  
142 inhibitor of CYP450 enzymes. In an in vivo human metabolism study (N=12), FUZEON  
143 at the recommended dose of 90 mg bid did not alter the metabolism of CYP3A4,  
144 CYP2D6, CYP1A2, CYP2C19 or CYP2E1 substrates.

145 *Influence of Concomitant Drugs on the Metabolism of Enfuvirtide*

146 As indicated in Table 1, pharmacokinetic interaction studies were conducted between  
147 FUZEON and the following drugs: ritonavir, saquinavir/ritonavir, and rifampin.

148 **Table 1**            **Effect of Ritonavir, Saquinavir/Ritonavir, and Rifampin on**  
149 **the Steady-State Pharmacokinetics of Enfuvirtide (90 mg**  
150 **bid)\***

Coadministered Drug	Dose of Coadministered Drug	N	% Change of Enfuvirtide Pharmacokinetic Parameters <sup>†x</sup> (90% CI)		
			C <sub>max</sub>	AUC	C <sub>trough</sub>
Ritonavir	200 mg, q12h, 4 days	12	↑24 (↑9 to ↑41)	↑22 (↑8 to ↑37)	↑14 (↑2 to ↑28)
Saquinavir/ Ritonavir	1000/100 mg, q12h, 4 days	12	↔	↑14 (↑5 to ↑24)	↑26 (↑17 to ↑35)
Rifampin	600 mg, qd, 10 days	12	↔	↔	↓15 (↓22 to ↓7)

151 \* All studies were performed in HIV-1+ subjects using a sequential crossover design.

152 † ↑= Increase; ↓ = Decrease; ↔ = No Effect (↑ or ↓ <10%)

153 <sup>x</sup> No interactions were clinically significant.

154 **INDICATIONS AND USAGE**

155 FUZEON in combination with other antiretroviral agents is indicated for the treatment of  
156 HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication  
157 despite ongoing antiretroviral therapy.

158 This indication is based on results from two controlled studies of 48 weeks duration.  
159 Subjects enrolled were treatment-experienced adults; many had advanced disease. There  
160 are no studies of FUZEON in antiretroviral naive patients.

161 **Description of Clinical Studies**

162 **Studies in Antiretroviral Experienced Patients**

163 Studies T20-301 and T20-302 were randomized, controlled, open-label, multicenter trials  
164 in HIV-1 infected subjects. Subjects were required to have either (1) viremia despite 3 to  
165 6 months prior therapy with a nucleoside reverse transcriptase inhibitor (NRTI), non-  
166 nucleoside reverse transcriptase inhibitor (NNRTI), and protease inhibitor (PI) or (2)  
167 viremia and documented resistance or intolerance to at least one member in each of the  
168 NRTI, NNRTI, and PI classes.

169 All subjects received an individualized background regimen consisting of 3 to 5  
170 antiretroviral agents selected on the basis of the subject's prior treatment history and  
171 baseline genotypic and phenotypic viral resistance measurements. Subjects were then  
172 randomized at a 2:1 ratio to FUZEON 90 mg bid with background regimen or  
173 background regimen alone.

174 After week 8, patients on either treatment arm who met protocol defined criteria for  
175 virological failure were permitted to revise their background regimens; those on  
176 background regimen alone were also permitted to add FUZEON.

177 Demographic characteristics for studies T20-301 and T20-302 are shown in Table 2.  
178 Subjects had prior exposure to a median of 12 antiretrovirals for a median of 7 years.

179 **Table 2 T20-301 and T20-302 Pooled Subject Demographics**

	<b>FUZEON+Background Regimen</b>	<b>Background Regimen</b>
	<b>N=663</b>	<b>N=334</b>
Sex		
Male	90%	90%
Female	10%	10%
Race		
White	89%	89%
Black	8%	7%
Mean Age (yr) (range)	42 (16-67)	43 (24-82)
Median Baseline HIV-1 RNA (log <sub>10</sub> copies/mL) (range)	5.2 (3.5-6.7)	5.1 (3.7-7.1)
Median Baseline CD4 <sup>+</sup> Cell Count (cells/mm <sup>3</sup> ) (range)	89 (1-994)	97 (1-847)

180 The disposition and efficacy outcomes of studies T20-301 and T20-302 are shown in  
 181 Table 3.

182 **Table 3 Outcomes at Week 48 (Pooled Studies T20-301 and T20-302)**

<b>Outcomes</b>	<b>FUZEON+Background Regimen 90 mg bid N=663</b>	<b>Background Regimen N=334</b>	
Virological Responder (at least 1 log <sub>10</sub> below baseline)	304 (46%)	61 (18%)	
Virological Non-responder:			
• Switch	0	220 (66%)	
• Completed 48 weeks randomized regimen*	191 (29%)	12 (4%)	
		<b>Continued Background Regimen (N=112)</b>	<b>Switched to FUZEON (N=220)</b>
Discontinued due to insufficient treatment response <sup>#</sup>	37 (5%)	13 (12%)	22 (10%)
Discontinued due to	46 (7%)	9 (8%)	13 (6%)

adverse reactions/intercurrent illness/labs			
Deaths	15 (2%)	5 (4%)	2 (1%)
Discontinued due to injection:			
• Injection site reactions	27 (4%)	NA	10 (5%)
• Difficulty with injecting Fuzeon <sup>##</sup>	18 (3%)	NA	2 (1%)
Discontinued due to other reasons <sup>†</sup>	25 (4%)	14 (13%)	6 (3%)

183 \*Includes never responded, rebound, and missing RNA data.

184 <sup>#</sup>Includes study discontinuation for virological failure and insufficient response as per the  
185 judgment of the investigator.

186 <sup>##</sup>Includes difficulties with injection, such as injection fatigue and inconvenience.

187 <sup>†</sup>Includes lost to follow-up, treatment refusal, and non-compliance.

188 At 48 weeks, 154 (23%) of subjects in the FUZEON+background regimen and 27 (8%)  
189 in the background regimen alone had HIV RNA levels <50 copies/mL, and 225 (34%) of  
190 subjects receiving FUZEON+background regimen had HIV RNA levels <400 copies/mL  
191 compared to 44 (13%) in the background regimen alone. Subjects achieving HIV RNA  
192 levels <50 copies/mL were included in the <400 copies/mL category and both categories  
193 were incorporated in the overall virologic responder category of achieving HIV RNA at  
194 least 1 log<sub>10</sub> below baseline.

195 The mean log change in HIV-1 RNA from baseline was -1.4 log<sub>10</sub> copies/mL in subjects  
196 receiving FUZEON+background and -0.5 in those receiving background alone. The mean  
197 change in CD4<sup>+</sup> cell count from baseline to week 48 was +91 cells/mm<sup>3</sup> in the  
198 FUZEON+background arm and +45 cells/mm<sup>3</sup> in the background alone arm.

199 Subjects in the FUZEON+background arm achieved a better virologic and immunologic  
200 outcome than subjects in the background alone arm across all subgroups based on  
201 baseline CD4<sup>+</sup> cell count, baseline HIV-1 RNA, number of prior ARVs or number of  
202 active ARVs in the background regimen.

## 203 **CONTRAINDICATIONS**

204 FUZEON is contraindicated in patients with known hypersensitivity to FUZEON or any  
205 of its components (see **WARNINGS**).



## 206 **WARNINGS**

### 207 **Local Injection Site Reactions (ISRs)**

208 The majority of patients (98%) receiving FUZEON in the Phase 3 clinical trials had at  
209 least one local injection site reaction; ISRs occurred throughout treatment with FUZEON.  
210 Manifestations may include pain and discomfort, induration, erythema, nodules and cysts,  
211 pruritus, and ecchymosis (see **ADVERSE REACTIONS**). Reactions are often present at  
212 more than one injection site. Patients must be familiar with the FUZEON *Injection*  
213 *Instructions* in order to know how to inject FUZEON appropriately and how to monitor  
214 carefully for signs or symptoms of cellulitis or local infection.

### 215 **Pneumonia**

216 An increased rate of bacterial pneumonia was observed in subjects treated with FUZEON  
217 in the Phase 3 clinical trials compared to the control arm (see **ADVERSE**  
218 **REACTIONS**). It is unclear if the increased incidence of pneumonia is related to  
219 FUZEON use. However, because of this finding, patients with HIV infection should be  
220 carefully monitored for signs and symptoms of pneumonia, especially if they have  
221 underlying conditions which may predispose them to pneumonia. Risk factors for  
222 pneumonia included low initial CD4<sup>+</sup> cell count, high initial viral load, intravenous drug  
223 use, smoking, and a prior history of lung disease (see **ADVERSE REACTIONS**).

### 224 **Hypersensitivity Reactions**

225 Systemic hypersensitivity reactions have been associated with FUZEON therapy and may  
226 recur on re-challenge. Hypersensitivity reactions have occurred in <1% of patients  
227 studied and have included combinations of: rash, fever, nausea and vomiting, chills,  
228 rigors, hypotension, and/or elevated serum liver transaminases. Other adverse events that  
229 may be immune mediated and have been reported in subjects receiving FUZEON include  
230 primary immune complex reaction, respiratory distress, glomerulonephritis, and Guillain-  
231 Barre syndrome. Patients developing signs and symptoms suggestive of a systemic  
232 hypersensitivity reaction should discontinue FUZEON and should seek medical  
233 evaluation immediately. Therapy with FUZEON should not be restarted following  
234 systemic signs and symptoms consistent with a hypersensitivity reaction. Risk factors that  
235 may predict the occurrence or severity of hypersensitivity to FUZEON have not been  
236 identified (see **ADVERSE REACTIONS**).

## 237 **PRECAUTIONS**

### 238 **Non-HIV Infected Individuals**

239 There is a theoretical risk that FUZEON use may lead to the production of anti-  
240 enfuvirtide antibodies which cross react with HIV gp41. This could result in a false  
241 positive HIV test with an ELISA assay; a confirmatory western blot test would be  
242 expected to be negative. FUZEON has not been studied in non-HIV infected individuals.

### 243 **Immune Reconstitution Syndrome**

244 Immune reconstitution syndrome has been reported in patients treated with combination  
245 antiretroviral therapy, including FUZEON. During the initial phase of combination

246 antiretroviral treatment, patients whose immune system responds may develop an  
247 inflammatory response to indolent or residual opportunistic infections (such as  
248 *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia  
249 [PCP] or tuberculosis), which may necessitate further evaluation and treatment.

### 250 **Administration with Biojector® 2000**

251 Nerve pain (neuralgia and/or paresthesia) lasting up to 6 months associated with  
252 administration at anatomical sites where large nerves course close to the skin, bruising  
253 and hematomas (see **ADVERSE REACTIONS**) have occurred with use of the Biojector  
254 2000 needle-free device for administration of FUZEON. Patients receiving anticoagulants  
255 or persons with hemophilia, or other coagulation disorders, may have a higher risk of  
256 post-injection bleeding.

### 257 **Information for Patients**

258 To assure safe and effective use of FUZEON, the following information and instructions  
259 should be given to patients:

- 260 • Patients should be informed that injection site reactions occur in almost all patients  
261 taking FUZEON. Patients must be familiar with the FUZEON *Injection Instructions*  
262 for instructions on how to appropriately inject FUZEON and how to carefully monitor  
263 for signs or symptoms of cellulitis or local infection. Patients should be instructed  
264 when to contact their healthcare provider about these reactions.
- 265 • Patients should be made aware that an increased rate of bacterial pneumonia was  
266 observed in subjects treated with FUZEON in Phase 3 clinical trials compared to the  
267 control arm. Patients should be advised to seek medical evaluation immediately if  
268 they develop signs or symptoms suggestive of pneumonia (cough with fever, rapid  
269 breathing, shortness of breath) (see **WARNINGS**).
- 270 • Patients should be advised of the possibility of a systemic hypersensitivity reaction to  
271 FUZEON. Patients should be advised to discontinue therapy and immediately seek  
272 medical evaluation if they develop signs/symptoms of systemic hypersensitivity such  
273 as combinations of rash, fever, nausea and vomiting, chills, rigors, and/or hypotension  
274 (see **WARNINGS**).
- 275 • FUZEON is not a cure for HIV-1 infection and patients may continue to contract  
276 illnesses associated with HIV-1 infection. The long-term effects of FUZEON are  
277 unknown at this time. FUZEON therapy has not been shown to reduce the risk of  
278 transmitting HIV-1 to others through sexual contact or blood contamination.
- 279 • FUZEON must be taken as part of a combination antiretroviral regimen. Use of  
280 FUZEON alone may lead to rapid development of virus resistant to FUZEON and  
281 possibly other agents of the same class.
- 282 • Patients and caregivers must be instructed in the use of aseptic technique when  
283 administering FUZEON in order to avoid injection site infections. Appropriate  
284 training for FUZEON reconstitution and self-injection must be given by a healthcare  
285 provider, including a careful review of the FUZEON Patient Package Insert and

286 FUZEON *Injection Instructions*. The first injection should be performed under the  
287 supervision of an appropriately qualified healthcare provider. It is recommended that  
288 the patient and/or caregiver's understanding and use of aseptic injection techniques  
289 and procedures be periodically re-evaluated.

290 • Patients and caregivers should be instructed on the preferred anatomical sites for  
291 administration (upper arm, abdomen, anterior thigh). FUZEON should not be  
292 injected near any anatomical areas where large nerves course close to the skin, such  
293 as near the elbow, knee, groin or the inferior or medial sections of the buttocks, skin  
294 abnormalities, including directly over a blood vessel, into moles, scar tissue, bruises,  
295 or near the navel, surgical scars, tattoos or burn sites.

296 • Patients and caregivers should be instructed in the proper techniques for preparation,  
297 injection and disposal of needles and syringes (including not recapping needles) in  
298 order to avoid needle stick injuries. Patients should be told not to reuse needles or  
299 syringes, and be instructed in safe disposal procedures including the use of a  
300 puncture-resistant container for disposal of used needles and syringes. Patients must  
301 be instructed on the safe disposal of full containers as per local requirements.  
302 Caregivers who experience an accidental needle stick after patient injection should  
303 contact a healthcare provider immediately.

304 • Patients should contact their healthcare provider for any questions regarding the  
305 administration of FUZEON.

306 • Patients should inform their healthcare provider if they are pregnant, plan to become  
307 pregnant or become pregnant while taking this medication.

308 • Patients should inform their healthcare provider if they are breast-feeding.

309 • Patients should not change the dose or dosing schedule of FUZEON or any  
310 antiretroviral medication without consulting their healthcare provider.

311 • Patients should contact their healthcare provider immediately if they stop taking  
312 FUZEON or any other drug in their antiretroviral regimen.

313 • Patients should be told that they can obtain more information on the self-  
314 administration of FUZEON at [www.FUZEON.com](http://www.FUZEON.com) or by calling 1-877-4-FUZEON  
315 (1-877-438-9366).

316 Patients should be advised that no studies have been conducted on the ability to drive or  
317 operate machinery while taking FUZEON. If patients experience dizziness while taking  
318 FUZEON, they should be advised to talk to their healthcare provider before driving or  
319 operating machinery.

## 320 **Drug Interactions**

### 321 CYP450 Metabolized Drugs

322 Results from in vitro and in vivo studies suggest that enfuvirtide is unlikely to have  
323 significant drug interactions with concomitantly administered drugs metabolized by  
324 CYP450 enzymes (see **CLINICAL PHARMACOLOGY**).

### 325 Antiretroviral Agents

326 No drug interactions with other antiretroviral medications have been identified that would  
327 warrant alteration of either the enfuvirtide dose or the dose of the other antiretroviral  
328 medication.

## 329 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

### 330 Carcinogenesis

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

### 332 Mutagenesis

333 Enfuvirtide was neither mutagenic nor clastogenic in a series of in vivo and in vitro  
334 assays including the Ames bacterial reverse mutation assay, a mammalian cell forward  
335 gene mutation assay in AS52 Chinese Hamster ovary cells or an in vivo mouse  
336 micronucleus assay.

### 337 Impairment of Fertility

338 Enfuvirtide produced no adverse effects on fertility in male or female rats at doses up to  
339 1.6 times the maximum recommended adult human daily dose on a m<sup>2</sup> basis.

## 340 **Pregnancy**

341 Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at  
342 doses up to 27 times and 3.2 times the adult human dose on a m<sup>2</sup> basis. The animal  
343 studies revealed no evidence of harm to the fetus from enfuvirtide. There are no adequate  
344 and well-controlled studies in pregnant women. Because animal reproduction studies are  
345 not always predictive of human response, this drug should be used during pregnancy only  
346 if clearly needed.

## 347 **Antiretroviral Pregnancy Registry**

348 To monitor maternal-fetal outcomes of pregnant women exposed to FUZEON and other  
349 antiretroviral drugs, an Antiretroviral Pregnancy Registry has been established.  
350 Physicians are encouraged to register patients by calling 1-800-258-4263.

## 351 **Nursing Mothers**

352 **The Centers for Disease Control and Prevention recommends that HIV-infected**  
353 **mothers not breast-feed their infants to avoid the risk of postnatal transmission of**  
354 **HIV.** It is not known whether enfuvirtide is excreted in human milk. Because of both the  
355 potential for HIV transmission and the potential for serious adverse reactions in nursing

356 infants, **mothers should be instructed not to breast-feed if they are receiving**  
357 **FUZEON.**

358 Studies where radio-labeled  $^3\text{H}$ -enfuvirtide was administered to lactating rats indicated  
359 that radioactivity was present in the milk. It is not known whether the radioactivity in the  
360 milk was from radio-labeled enfuvirtide or from radio-labeled metabolites of enfuvirtide  
361 (ie, amino acids and peptide fragments).

### 362 **Pediatric Use**

363 The safety and pharmacokinetics of FUZEON have not been established in pediatric  
364 subjects below 6 years of age; limited efficacy data is available in pediatric subjects 6  
365 years of age and older.

366 Sixty-three HIV-1 infected pediatric subjects ages 5 through 16 years have received  
367 FUZEON in two open-label, single-arm clinical trials. Adverse experiences, including  
368 ISRs, were similar to those observed in adult patients.

369 Study T20-204 was an open-label, multicenter trial that evaluated the safety and antiviral  
370 activity of FUZEON in treatment-experienced pediatric subjects. Eleven subjects from 6  
371 to 12 years were enrolled (median age of 9 years). Median baseline  $\text{CD4}^+$  cell count was  
372 495 cells/ $\mu\text{L}$  and the median baseline HIV-1 RNA was 4.6  $\log_{10}$  copies/mL.

373 Ten of the 11 study subjects completed 48 weeks of chronic therapy. At week 48, 6/11  
374 (55%) subjects had  $\geq 1 \log_{10}$  decline in HIV-1 RNA and 4/11 (36%) subjects were below  
375 400 copies/mL of HIV-1 RNA. The median changes from baseline (for the As Treated  
376 population) in HIV-1 RNA and  $\text{CD4}^+$  cell count were -1.48  $\log_{10}$  copies/mL and +122  
377 cells/ $\mu\text{L}$ , respectively.

378 Study T20-310 was an open-label, multicenter trial that evaluated the pharmacokinetics,  
379 safety, and antiviral activity of FUZEON in treatment-experienced pediatric subjects and  
380 adolescents. Fifty-two subjects from 5 through 16 years were enrolled (median age of 12  
381 years). Median baseline  $\text{CD4}^+$  cell count was 117 cells/ $\mu\text{L}$  and the median baseline HIV-  
382 1 RNA was 5.0  $\log_{10}$  copies/mL.

383 Thirty-two of the 52 study subjects completed 48 weeks of chronic therapy. At week 48,  
384 17/52 (33%) of subjects had  $\geq 1 \log_{10}$  decline in HIV-1 RNA, 11/52 (21%) of subjects  
385 were below 400 copies/mL of HIV-1 RNA and 5/52 (10%) were below 50 copies/mL.  
386 The median changes from baseline (for the As Treated population) in HIV-1 RNA and  
387  $\text{CD4}^+$  cell count were -1.17  $\log_{10}$  copies/mL and +106 cells/ $\mu\text{L}$ , respectively.

### 388 **Geriatric Use**

389 Clinical studies of FUZEON did not include sufficient numbers of subjects aged 65 and  
390 over to determine whether they respond differently from younger subjects.

### 391 **ADVERSE REACTIONS**

392 The overall safety profile of FUZEON is based on 2131 subjects who received at least 1  
393 dose of FUZEON during various clinical trials. This includes 2051 adults, 658 of whom  
394 received the recommended dose for greater than 48 weeks, and 63 pediatric subjects.

395 Assessment of treatment-emergent adverse events is based on the pooled data from the  
396 two Phase 3 studies T20-301 and T20-302.

### 397 **Local Injection Site Reactions**

398 Local injection site reactions were the most frequent adverse events associated with the  
399 use of FUZEON. In Phase 3 clinical studies (T20-301 and T20-302), 98% of subjects had  
400 at least one local injection site reaction (ISR). A total of 7% of subjects discontinued  
401 treatment with FUZEON because of ISRs (4%) or difficulties with injecting FUZEON  
402 (3%) such as injection fatigue and inconvenience. Eighty-five percent of subjects  
403 experienced their first ISR during the initial week of treatment; ISRs continued to occur  
404 throughout treatment with FUZEON. For most subjects the severity of signs and  
405 symptoms associated with ISRs did not change during the 48 weeks of treatment. The  
406 majority of ISRs were associated with erythema, induration, the presence of nodules or  
407 cysts, and mild to moderate pain at the injection site (Table 4). In addition, the average  
408 duration of individual ISRs was between three and seven days in 41% of subjects and  
409 more than seven days in 24% of subjects. Also, the numbers of ISRs per subject at any  
410 one time was between six to 14 ISRs in 26% of subjects and more than 14 ISRs in 1.3%  
411 of subjects. Infection at the injection site (including abscess and cellulitis) was reported in  
412 1.7% of adult subjects.

413 **Table 4** Summary of Individual Signs/Symptoms Characterizing  
414 Local Injection Site Reactions to Enfuvirtide in Studies T20-  
415 301 and T20-302 Combined (% of Subjects) Through 48  
416 Weeks

Event Category	N=663		
	Any Severity Grade	% of Patients with Grade 3 Reactions	% of Patients with Grade 4 Reactions
Pain/Discomfort <sup>a</sup>	96%	11%	0%
Induration	90%	>25 but <50 mm	≥50 mm
Erythema	91%	22%	10%
		>50 but <85 mm	≥85 mm
Nodules and Cysts	80%	23%	0.2%
		>3 cm average diameter	draining
Pruritus <sup>b</sup>	65%	3%	NA
Ecchymosis	52%	5%	2%
		>3 but ≤5 cm	>5 cm

417 <sup>a</sup>Grade 3 = severe pain requiring prescription non-topical analgesics or limiting usual  
418 activities.

419 Grade 4 = severe pain requiring hospitalization or prolongation of hospitalization,  
420 resulting in death, or persistent or significant disability/incapacity, or life-threatening, or  
421 medically significant.

422 <sup>b</sup>Grade 3 = refractory to topical treatment or requiring oral or parenteral treatment; Grade  
423 4 = not applicable.

424 **Biojector 2000 Needle-Free Device**

425 Adverse events associated with the use of the Biojector 2000 needle-free device for  
426 administration of FUZEON have included: nerve pain (neuralgia and/or paresthesia)  
427 lasting up to 6 months associated with administration at anatomical sites where large  
428 nerves course close to the skin, bruising and hematomas (see **PRECAUTIONS**).

429 **Other Adverse Events**

430 Systemic hypersensitivity reactions have been attributed to FUZEON ( $\leq 1\%$ ) and in some  
431 cases have recurred upon re-challenge (see **WARNINGS**).

432 In the T20-301 and T20-302 studies, after study week 8, patients on background alone  
433 who met protocol defined criteria for virological failure were permitted to revise their  
434 background regimens and add FUZEON. Exposure on FUZEON+background was 557  
435 patient-years, and to background alone 162 patient-years. Due to this difference in  
436 exposure, safety results are expressed as the number of patients with an adverse event per  
437 100 patient-years of exposure. For FUZEON+background, adverse events are also  
438 displayed by percent of subjects.

439 The events most frequently reported in subjects receiving FUZEON+background  
440 regimen, excluding injection site reactions, were diarrhea (38 per 100 patient-years or  
441 31.7%), nausea (27 per 100 patient-years or 22.8%), and fatigue (24 per 100 patient-years  
442 or 20.2%). These events were also commonly observed in subjects that received  
443 background regimen alone: diarrhea (73 per 100 patient-years), nausea (50 per 100  
444 patient-years), and fatigue (38 per 100 patient-years).

445 Treatment-emergent adverse events, regardless of causality and excluding ISRs, from  
446 Phase 3 studies are summarized for adult subjects, in Table 5. Any Grade 2 or above  
447 events occurring at  $\geq 2$  percent of subjects and at a higher rate in subjects treated with  
448 FUZEON are summarized in Table 5; events that occurred at a higher rate in the control  
449 arms are not displayed.

450 Rates of adverse events for patients who switched to FUZEON after virological failure  
451 were similar.

452 **Table 5 Rates of Treatment-Emergent Adverse Events\* ( $\geq$ Grade 2)**  
453 **Reported in  $\geq 2$  % of Patients Treated with FUZEON\*\* (Pooled**  
454 **Studies T20-301/T20-302 at 48 Weeks)**

Adverse Event (by System Organ Class)	FUZEON+Back-ground Regimen (N=663)	FUZEON+Back-ground Regimen (N=663)	Background Regimen (N=334)
	663 patients total	557 total patient-years	162 total patient-years
	% frequency	rate/100 patient-years	rate/100 patient-years
Weight Decreased	6.6%	7.9	6.2

Adverse Event (by System Organ Class)	FUZEON+Background Regimen (N=663)	FUZEON+Background Regimen (N=663)	Background Regimen (N=334)
	663 patients total	557 total patient-years	162 total patient-years
	% frequency	rate/100 patient-years	rate/100 patient-years
Sinusitis	6.0%	7.2	4.9
Abdominal Pain	3.9%	4.7	3.7
Cough	3.9%	4.7	2.5
Herpes Simplex	3.5%	4.1	3.7
Appetite Decreased	3.2%	3.8	2.5
Pancreatitis	3.0%	3.6	2.5
Pain in Limb	2.9%	3.4	3.1
Pneumonia (see text below)	2.7%	3.2	0.6
Myalgia	2.7%	3.2	1.2
Influenza-Like Illness	2.4%	2.9	1.9
Folliculitis	2.4%	2.9	2.5
Anorexia	2.3%	2.7	1.9
Dry Mouth	2.1%	2.5	1.9
Conjunctivitis	2.0%	2.3	1.9

455 \*Excludes Injection Site Reactions

456 \*\*Events listed occurred more frequently in patients treated with FUZEON (based on  
457 rates/100 patient-years).

458 The incidence of pneumonia was 2.7% or 3.2 events/100 patient-years in subjects  
459 receiving FUZEON+background regimen. On analysis of all diagnoses of pneumonia  
460 (pneumonia, bacterial pneumonia, bronchopneumonia, and related terms) in the Phase 3  
461 clinical trials, an increased rate of bacterial pneumonia was observed in subjects treated  
462 with FUZEON compared to the control arm (6.9%, 6.7 pneumonia events per 100  
463 patient-years versus 0.6 events per 100 patient-years, respectively). Approximately half  
464 of the study subjects with pneumonia required hospitalization. Three subject deaths in the  
465 FUZEON arm were attributed to pneumonia; all three had serious concomitant AIDS-  
466 related illnesses that contributed to their deaths. Risk factors for pneumonia included low  
467 initial CD4<sup>+</sup> lymphocyte count, high initial viral load, intravenous drug use, smoking, and  
468 a prior history of lung disease. It is unclear if the increased incidence of pneumonia was  
469 related to FUZEON use. However, because of this, finding patients with HIV infection  
470 should be carefully monitored for signs and symptoms of pneumonia, especially if they  
471 have underlying conditions which may predispose them to pneumonia (see  
472 **WARNINGS**).



473 **Less Common Events**

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

476 *Immune System Disorders:* worsening abacavir hypersensitivity reaction

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

479 *Blood and Lymphatic Disorders:* thrombocytopenia; neutropenia; fever;  
480 lymphadenopathy

481 *Endocrine and Metabolic:* hyperglycemia

482 *Infections:* sepsis; herpes simplex

483 *Nervous System Disorders:* taste disturbance; Guillain-Barre syndrome (fatal); sixth  
484 nerve palsy; peripheral neuropathy

485 *Cardiac Disorders:* unstable angina pectoris

486 *Gastrointestinal Disorders:* constipation; abdominal pain upper

487 *General:* asthenia

488 *Hepatobiliary Disorders:* toxic hepatitis; hepatic steatosis

489 *Investigations:* increased amylase; increased lipase; increased AST; increased GGT;  
490 increased triglycerides

491 *Psychiatric Disorders:* insomnia; depression; anxiety; suicide attempt

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

494 *Skin and Subcutaneous Tissue Disorders:* pruritus

495 **Laboratory Abnormalities**

496 Table 6 shows the treatment-emergent laboratory abnormalities that occurred in at least 2  
497 subjects per 100 patient-years and more frequently in those receiving  
498 FUZEON+background regimen than background regimen alone from studies T20-301  
499 and T20-302.

500  
501  
502

**Table 6 Treatment-Emergent Laboratory Abnormalities in  $\geq 2$  % of Patients Receiving FUZEON\* (Pooled Studies T20-301 and T20-302 at 48 Weeks)**

Laboratory Parameters	Grading	FUZEON+Back-ground Regimen (N=663)	FUZEON+Back-ground Regimen (N=663)	Background Regimen (N=334)
		663 patients total	557 total patient-years	162 total patient-years
		% frequency	rate/100 patient-years	rate/100 patient-years
Eosinophilia				
1-2 X ULN ( $0.7 \times 10^9/L$ )	$0.7-1.4 \times 10^9/L$	9.1%	10.8	3.7
>2 X ULN ( $0.7 \times 10^9/L$ )	$>1.4 \times 10^9/L$	1.8%	2.2	1.8
ALT				
Grade 3	$>5-10 \times ULN$	4.1%	4.8	4.3
Grade 4	$>10 \times ULN$	1.2%	1.4	1.2
Creatine Phosphokinase (U/L)				
Grade 3	$>5-10 \times ULN$	6.9%	8.3	8.0
Grade 4	$>10 \times ULN$	2.6%	3.1	8.6

503 \*Events listed occurred more frequently in patients treated with FUZEON (based on  
504 rates/100 patient-years).

### 505 Adverse Events in Pediatric Patients

506 FUZEON has been studied in 63 pediatric subjects 5 through 16 years of age with  
507 duration of FUZEON exposure ranging from 1 dose to 134 weeks. Adverse experiences  
508 seen during clinical trials were similar to those observed in adult subjects, although  
509 infections at site of injection (cellulitis or abscess) were more frequent in adolescents  
510 than in adults, with 4 events occurring in 3 of 28 (11%) subjects.

### 511 OVERDOSAGE

512 There are no reports of human experience of acute overdose with FUZEON. The highest  
513 dose administered to 12 subjects in a clinical trial was 180 mg as a single dose  
514 subcutaneously. There is no specific antidote for overdose with FUZEON. Treatment of  
515 overdose should consist of general supportive measures.

### 516 DOSAGE AND ADMINISTRATION

#### 517 Adults

518 The recommended dose of FUZEON is 90 mg (1 mL) twice daily injected  
519 subcutaneously into the upper arm, anterior thigh or abdomen. Each injection should be  
520 given at a site different from the preceding injection site, and only where there is no  
521 current injection site reaction from an earlier dose. FUZEON should not be injected near

522 any anatomical areas where large nerves course close to the skin, such as near the elbow,  
523 knee, groin or the inferior or medial section of the buttocks, skin abnormalities, including  
524 directly over a blood vessel, into moles, scar tissue, bruises, or near the navel, surgical  
525 scars, tattoos or burn sites. Additional detailed information regarding the administration  
526 of FUZEON is described in the FUZEON *Injection Instructions*.

### 527 **Pediatric Patients**

528 Insufficient data are available to establish a dose recommendation of FUZEON in  
529 pediatric patients below the age of 6 years. In pediatric patients 6 years through 16 years  
530 of age, the recommended dosage of FUZEON is 2 mg/kg twice daily up to a maximum  
531 dose of 90 mg twice daily injected subcutaneously into the upper arm, anterior thigh or  
532 abdomen. Each injection should be given at a site different from the preceding injection  
533 site and only where there is no current injection site reaction from an earlier dose.  
534 FUZEON should not be injected into moles, scar tissue, bruises or the navel. Table 7  
535 contains dosing guidelines for FUZEON based on body weight. Weight should be  
536 monitored periodically and the FUZEON dose adjusted accordingly.

537 **Table 7 Pediatric Dosing Guidelines**

Weight		Dose per bid Injection (mg/dose)	Injection Volume (90 mg enfuvirtide per mL)
Kilograms (kg)	Pounds (lbs)		
11.0 to 15.5	24 to 34	27	0.3 mL
15.6 to 20.0	>34 to 44	36	0.4 mL
20.1 to 24.5	>44 to 54	45	0.5 mL
24.6 to 29.0	>54 to 64	54	0.6 mL
29.1 to 33.5	>64 to 74	63	0.7 mL
33.6 to 38.0	>74 to 84	72	0.8 mL
38.1 to 42.5	>84 to 94	81	0.9 mL
≥42.6	>94	90	1.0 mL

### 538 **Directions for Use**

539 For more detailed instructions, see FUZEON *Injection Instructions*.

#### 540 **Subcutaneous Administration**

541 FUZEON must only be reconstituted with 1.1 mL of Sterile Water for Injection. After  
542 adding sterile water, the vial should be gently tapped for 10 seconds and then gently  
543 rolled between the hands to avoid foaming and to ensure all particles of drug are in  
544 contact with the liquid and no drug remains on the vial wall. The vial should then be  
545 allowed to stand until the powder goes completely into solution, which could take up to  
546 45 minutes. Reconstitution time can be reduced by gently rolling the vial between the  
547 hands until the product is completely dissolved. Before the solution is withdrawn for  
548 administration, the vial should be inspected visually to ensure that the contents are fully  
549 dissolved in solution, and that the solution is clear, colorless and without bubbles or  
550 particulate matter. If the FUZEON is foamy or jelled, allow more time for it to dissolve.

551 If there is evidence of particulate matter, the vial must not be used and should be returned  
552 to the pharmacy.

553 FUZEON contains no preservatives. Once reconstituted, FUZEON should be injected  
554 immediately or kept refrigerated in the original vial until use. Reconstituted FUZEON  
555 must be used within 24 hours. The subsequent dose of FUZEON can be reconstituted in  
556 advance and must be stored in the refrigerator in the original vial and used within 24  
557 hours. Refrigerated reconstituted solution should be brought to room temperature before  
558 injection and the vial should be inspected visually again to ensure that the contents are  
559 fully dissolved in solution and that the solution is clear, colorless, and without bubbles or  
560 particulate matter.

561 The reconstituted solution should be injected subcutaneously in the upper arm, abdomen  
562 or anterior thigh. The injection should be given at a site different from the preceding  
563 injection site and only where there is no current injection site reaction. Also, do not inject  
564 near any anatomical areas where large nerves course close to the skin, such as near the  
565 elbow, knee, groin or the inferior or medial sections of the buttocks, skin abnormalities,  
566 including directly over a blood vessel, into moles, scar tissue, bruises or near the navel,  
567 surgical scars, tattoos or burn sites. A vial is suitable for single use only; unused portions  
568 must be discarded (see FUZEON *Injection Instructions*).

569 Patients should contact their healthcare provider for any questions regarding the  
570 administration of FUZEON. Information about the self-administration of FUZEON may  
571 also be obtained by calling the toll-free number 1-877-4-FUZEON (1-877-438-9366) or  
572 at the FUZEON website, [www.FUZEON.com](http://www.FUZEON.com). Patients should be taught to recognize the  
573 signs and symptoms of injection site reactions and instructed when to contact their  
574 healthcare provider about these reactions.

## 575 **HOW SUPPLIED**

576 FUZEON (enfuvirtide) for Injection is a white to off-white, sterile, lyophilized powder  
577 and it is packaged in a single-use clear glass vial containing 108 mg of enfuvirtide for the  
578 delivery of approximately 90 mg/1 mL when reconstituted with 1.1 mL of Sterile Water  
579 for Injection.

580 FUZEON is available in a Convenience Kit containing 60 single-use vials of FUZEON  
581 (90 mg strength), 60 vials (2 cartons of 30 each) of Sterile Water for Injection (1.1 mL  
582 per vial), 60 reconstitution syringes (3 cc), 60 administration syringes (1 cc), alcohol  
583 wipes, Package Insert, Patient Package Insert, and Injection Instruction Guide (NDC  
584 0004-0380-39).

## 585 **Storage Conditions**

586 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP  
587 Controlled Room Temperature].

588 Reconstituted solution should be stored under refrigeration at 2° to 8°C (36° to 46°F) and  
589 used within 24 hours.

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Morrisville, North Carolina 27560  
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595 27899290

596 Revised: November 2006

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