



FUZEON[®]

(enfuvirtide)

for Injection

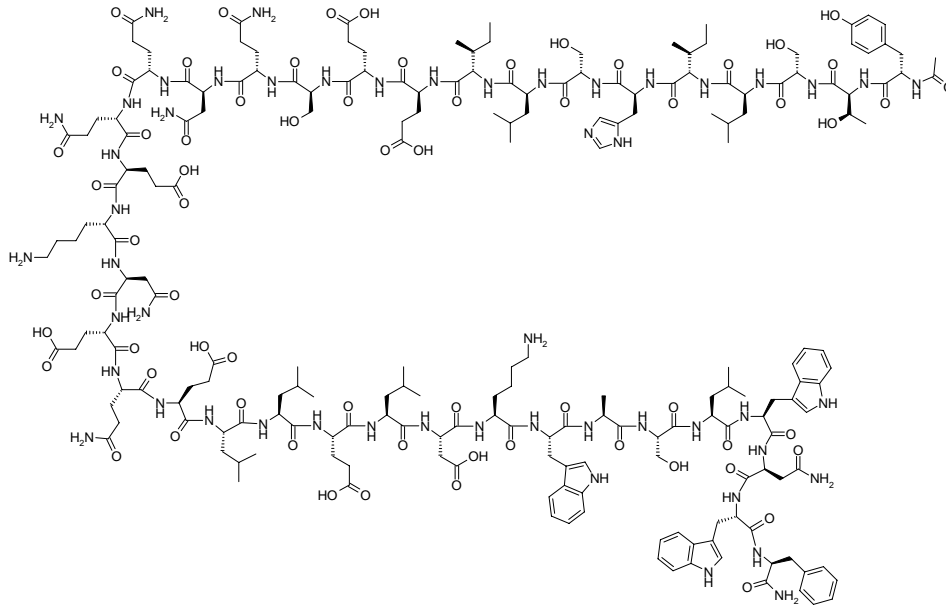
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DESCRIPTION

FUZEON (enfuvirtide) is an inhibitor of the fusion of HIV-1 with CD4⁺ 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 C₂₀₄H₃₀₁N₅₁O₆₄, and the molecular weight is 4492. It has the following primary amino acid sequence:

CH₃CO-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-NH₂ 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⁺ cell
35 types with laboratory and clinical isolates of HIV-1. The IC₅₀ 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_{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 $5.5 \pm 1.1 \text{ L}$.

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 α -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 $3.8 \pm 0.6 \text{ h}$ and the mean \pm SD apparent clearance
97 was $24.8 \pm 4.1 \text{ mL/h/kg}$. 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 $30.6 \pm 10.6 \text{ mL/h/kg}$.

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_{max} was $6.3 \pm 2.4 \mu\text{g/mL}$, C_{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 ^{†x} (90% CI)		
			C _{max}	AUC	C _{trough}
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 ^x 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**

	FUZEON+Background Regimen	Background Regimen
	N=663	N=334
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 ₁₀ copies/mL) (range)	5.2 (3.5-6.7)	5.1 (3.7-7.1)
Median Baseline CD4 ⁺ Cell Count (cells/mm ³) (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)**

Outcomes	FUZEON+Background Regimen 90 mg bid N=663	Background Regimen N=334	
Virological Responder (at least 1 log ₁₀ below baseline)	304 (46%)	61 (18%)	
Virological Non-responder:			
• Switch	0	220 (66%)	
• Completed 48 weeks randomized regimen*	191 (29%)	12 (4%)	
		Continued Background Regimen (N=112)	Switched to FUZEON (N=220)
Discontinued due to insufficient treatment response [#]	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 ^{##}	18 (3%)	NA	2 (1%)
Discontinued due to other reasons [†]	25 (4%)	14 (13%)	6 (3%)

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

184 [#]Includes study discontinuation for virological failure and insufficient response as per the
185 judgment of the investigator.

186 ^{##}Includes difficulties with injection, such as injection fatigue and inconvenience.

187 [†]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 log₁₀ below baseline.

195 The mean log change in HIV-1 RNA from baseline was -1.4 log₁₀ copies/mL in subjects
196 receiving FUZEON+background and -0.5 in those receiving background alone. The mean
197 change in CD4⁺ cell count from baseline to week 48 was +91 cells/mm³ in the
198 FUZEON+background arm and +45 cells/mm³ 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⁺ 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⁺ 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 **Information for Patients**

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

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

286 syringes, and be instructed in safe disposal procedures including the use of a
287 puncture-resistant container for disposal of used needles and syringes. Patients must
288 be instructed on the safe disposal of full containers as per local requirements.
289 Caregivers who experience an accidental needle stick after patient injection should
290 contact a healthcare provider immediately.

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

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

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

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

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

300 • Patients should be told that they can obtain more information on the self-
301 administration of FUZEON at www.FUZEON.com or by calling 1-877-4-FUZEON
302 (1-877-438-9366).

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

307 **Drug Interactions**

308 CYP450 Metabolized Drugs

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

312 Antiretroviral Agents

313 No drug interactions with other antiretroviral medications have been identified that would
314 warrant alteration of either the enfuvirtide dose or the dose of the other antiretroviral
315 medication.

316 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

317 Carcinogenesis

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

319 Mutagenesis

320 Enfuvirtide was neither mutagenic nor clastogenic in a series of in vivo and in vitro
321 assays including the Ames bacterial reverse mutation assay, a mammalian cell forward

322 gene mutation assay in AS52 Chinese Hamster ovary cells or an in vivo mouse
323 micronucleus assay.

324 Impairment of Fertility

325 Enfuvirtide produced no adverse effects on fertility in male or female rats at doses up to
326 1.6 times the maximum recommended adult human daily dose on a m² basis.

327 Pregnancy

328 Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at
329 doses up to 27 times and 3.2 times the adult human dose on a m² basis. The animal
330 studies revealed no evidence of harm to the fetus from enfuvirtide. There are no adequate
331 and well-controlled studies in pregnant women. Because animal reproduction studies are
332 not always predictive of human response, this drug should be used during pregnancy only
333 if clearly needed.

334 Antiretroviral Pregnancy Registry

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

338 Nursing Mothers

339 **The Centers for Disease Control and Prevention recommends that HIV-infected**
340 **mothers not breast-feed their infants to avoid the risk of postnatal transmission of**
341 **HIV.** It is not known whether enfuvirtide is excreted in human milk. Because of both the
342 potential for HIV transmission and the potential for serious adverse reactions in nursing
343 infants, **mothers should be instructed not to breast-feed if they are receiving**
344 **FUZEON.**

345 Studies where radio-labeled ³H-enfuvirtide was administered to lactating rats indicated
346 that radioactivity was present in the milk. It is not known whether the radioactivity in the
347 milk was from radio-labeled enfuvirtide or from radio-labeled metabolites of enfuvirtide
348 (ie, amino acids and peptide fragments).

349 **Pediatric Use**

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

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

356 Study T20-204 was an open-label, multicenter trial that evaluated the safety and antiviral
357 activity of FUZEON in treatment-experienced pediatric subjects. Eleven subjects from 6
358 to 12 years were enrolled (median age of 9 years). Median baseline CD4⁺ cell count was
359 495 cells/μL and the median baseline HIV-1 RNA was 4.6 log₁₀ copies/mL.

360 Ten of the 11 study subjects completed 48 weeks of chronic therapy. At week 48, 6/11
361 (55%) subjects had $\geq 1 \log_{10}$ decline in HIV-1 RNA and 4/11 (36%) subjects were below
362 400 copies/mL of HIV-1 RNA. The median changes from baseline (for the As Treated
363 population) in HIV-1 RNA and CD4⁺ cell count were -1.48 \log_{10} copies/mL and +122
364 cells/ μ L, respectively.

365 Study T20-310 was an open-label, multicenter trial that evaluated the pharmacokinetics,
366 safety, and antiviral activity of FUZEON in treatment-experienced pediatric subjects and
367 adolescents. Fifty-two subjects from 5 through 16 years were enrolled (median age of 12
368 years). Median baseline CD4⁺ cell count was 117 cells/ μ L and the median baseline HIV-
369 1 RNA was 5.0 \log_{10} copies/mL.

370 Thirty-two of the 52 study subjects completed 48 weeks of chronic therapy. At week 48,
371 17/52 (33%) of subjects had $\geq 1 \log_{10}$ decline in HIV-1 RNA, 11/52 (21%) of subjects
372 were below 400 copies/mL of HIV-1 RNA and 5/52 (10%) were below 50 copies/mL.
373 The median changes from baseline (for the As Treated population) in HIV-1 RNA and
374 CD4⁺ cell count were -1.17 \log_{10} copies/mL and +106 cells/ μ L, respectively.

375 **Geriatric Use**

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

378 **ADVERSE REACTIONS**

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

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

384 **Local Injection Site Reactions**

385 Local injection site reactions were the most frequent adverse events associated with the
386 use of FUZEON. In Phase 3 clinical studies (T20-301 and T20-302), 98% of subjects had
387 at least one local injection site reaction (ISR). A total of 7% of subjects discontinued
388 treatment with FUZEON because of ISRs (4%) or difficulties with injecting FUZEON
389 (3%) such as injection fatigue and inconvenience. Eighty-five percent of subjects
390 experienced their first ISR during the initial week of treatment; ISRs continued to occur
391 throughout treatment with FUZEON. For most subjects the severity of signs and
392 symptoms associated with ISRs did not change during the 48 weeks of treatment. The
393 majority of ISRs were associated with erythema, induration, the presence of nodules or
394 cysts, and mild to moderate pain at the injection site (Table 4). In addition, the average
395 duration of individual ISRs was between three and seven days in 41% of subjects and
396 more than seven days in 24% of subjects. Also, the numbers of ISRs per subject at any
397 one time was between six to 14 ISRs in 26% of subjects and more than 14 ISRs in 1.3%
398 of subjects. Infection at the injection site (including abscess and cellulitis) was reported in
399 1.7% of adult subjects.

400 **Table 4** **Summary of Individual Signs/Symptoms Characterizing**
 401 **Local Injection Site Reactions to Enfuvirtide in Studies T20-**
 402 **301 and T20-302 Combined (% of Subjects) Through 48**
 403 **Weeks**

	N=663		
Event Category	Any Severity Grade	% of Patients with Grade 3 Reactions	% of Patients with Grade 4 Reactions
Pain/Discomfort ^a	96%	11%	0%
Induration	90%	39% >25 but <50 mm	18% ≥50 mm
Erythema	91%	22% >50 but <85 mm	10% ≥85 mm
Nodules and Cysts	80%	23% >3 cm average diameter	0.2% draining
Pruritus ^b	65%	3%	NA
Ecchymosis	52%	5% >3 but ≤5 cm	2% >5 cm

404 ^aGrade 3 = severe pain requiring prescription non-topical analgesics or limiting usual
 405 activities.

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

409 ^bGrade 3 = refractory to topical treatment or requiring oral or parenteral treatment; Grade
 410 4 = not applicable.

411 **Other Adverse Events**

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

414 In the T20-301 and T20-302 studies, after study week 8, patients on background alone
 415 who met protocol defined criteria for virological failure were permitted to revise their
 416 background regimens and add FUZEON. Exposure on FUZEON+background was 557
 417 patient-years, and to background alone 162 patient-years. Due to this difference in
 418 exposure, safety results are expressed as the number of patients with an adverse event per
 419 100 patient-years of exposure. For FUZEON+background, adverse events are also
 420 displayed by percent of subjects.

421 The events most frequently reported in subjects receiving FUZEON+background
 422 regimen, excluding injection site reactions, were diarrhea (38 per 100 patient-years or
 423 31.7%), nausea (27 per 100 patient-years or 22.8%), and fatigue (24 per 100 patient-years
 424 or 20.2%). These events were also commonly observed in subjects that received
 425 background regimen alone: diarrhea (73 per 100 patient-years), nausea (50 per 100
 426 patient-years), and fatigue (38 per 100 patient-years).

427 Treatment-emergent adverse events, regardless of causality and excluding ISRs, from
 428 Phase 3 studies are summarized for adult subjects, in Table 5. Any Grade 2 or above
 429 events occurring at ≥ 2 percent of subjects and at a higher rate in subjects treated with
 430 FUZEON are summarized in Table 5; events that occurred at a higher rate in the control
 431 arms are not displayed.

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

434 **Table 5 Rates of Treatment-Emergent Adverse Events* (\geq Grade 2)**
 435 **Reported in ≥ 2 % of Patients Treated with FUZEON** (Pooled**
 436 **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
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

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
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

437 *Excludes Injection Site Reactions

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

440 The incidence of pneumonia was 2.7% or 3.2 events/100 patient-years in subjects
441 receiving FUZEON+background regimen. On analysis of all diagnoses of pneumonia
442 (pneumonia, bacterial pneumonia, bronchopneumonia, and related terms) in the Phase 3
443 clinical trials, an increased rate of bacterial pneumonia was observed in subjects treated
444 with FUZEON compared to the control arm (6.9%, 6.7 pneumonia events per 100
445 patient-years versus 0.6 events per 100 patient-years, respectively). Approximately half
446 of the study subjects with pneumonia required hospitalization. Three subject deaths in the
447 FUZEON arm were attributed to pneumonia; all three had serious concomitant AIDS-
448 related illnesses that contributed to their deaths. Risk factors for pneumonia included low
449 initial CD4⁺ lymphocyte count, high initial viral load, intravenous drug use, smoking, and
450 a prior history of lung disease. It is unclear if the increased incidence of pneumonia was
451 related to FUZEON use. However, because of this, finding patients with HIV infection
452 should be carefully monitored for signs and symptoms of pneumonia, especially if they
453 have underlying conditions which may predispose them to pneumonia (see
454 **WARNINGS**).

455 **Less Common Events**

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

- 458 *Immune System Disorders*: worsening abacavir hypersensitivity reaction
- 459 *Renal and Urinary Disorders*: glomerulonephritis; tubular necrosis; renal insufficiency;
460 renal failure (including fatal cases)
- 461 *Blood and Lymphatic Disorders*: thrombocytopenia; neutropenia; fever;
462 lymphadenopathy
- 463 *Endocrine and Metabolic*: hyperglycemia
- 464 *Infections*: sepsis; herpes simplex
- 465 *Nervous System Disorders*: taste disturbance; Guillain-Barre syndrome (fatal); sixth
466 nerve palsy; peripheral neuropathy
- 467 *Cardiac Disorders*: unstable angina pectoris
- 468 *Gastrointestinal Disorders*: constipation; abdominal pain upper
- 469 *General*: asthenia
- 470 *Hepatobiliary Disorders*: toxic hepatitis; hepatic steatosis
- 471 *Investigations*: increased amylase; increased lipase; increased AST; increased GGT;
472 increased triglycerides
- 473 *Psychiatric Disorders*: insomnia; depression; anxiety; suicide attempt
- 474 *Respiratory, Thoracic, and Mediastinal Disorders*: pneumopathy; respiratory distress;
475 cough
- 476 *Skin and Subcutaneous Tissue Disorders*: pruritus
- 477 **Laboratory Abnormalities**
- 478 Table 6 shows the treatment-emergent laboratory abnormalities that occurred in at least 2
479 subjects per 100 patient-years and more frequently in those receiving
480 FUZEON+background regimen than background regimen alone from studies T20-301
481 and T20-302.

482
483
484

Table 6 Treatment-Emergent Laboratory Abnormalities in ≥ 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

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

487 **Adverse Events in Pediatric Patients**

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

493 **OVERDOSAGE**

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

498 **DOSAGE AND ADMINISTRATION**

499 **Adults**

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

504 moles, scar tissue, bruises or the navel. Additional detailed information regarding the
505 administration of FUZEON is described in the FUZEON *Injection Instructions*.

506 **Pediatric Patients**

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

516 **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

517 **Directions for Use**

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

519 **Subcutaneous Administration**

520 FUZEON must only be reconstituted with 1.1 mL of Sterile Water for Injection. After
521 adding sterile water, the vial should be gently tapped for 10 seconds and then gently
522 rolled between the hands to avoid foaming and to ensure all particles of drug are in
523 contact with the liquid and no drug remains on the vial wall. The vial should then be
524 allowed to stand until the powder goes completely into solution, which could take up to
525 45 minutes. Reconstitution time can be reduced by gently rolling the vial between the
526 hands until the product is completely dissolved. Before the solution is withdrawn for
527 administration, the vial should be inspected visually to ensure that the contents are fully
528 dissolved in solution, and that the solution is clear, colorless and without bubbles or
529 particulate matter. If the FUZEON is foamy or jelled, allow more time for it to dissolve.
530 If there is evidence of particulate matter, the vial must not be used and should be returned
531 to the pharmacy.

532 FUZEON contains no preservatives. Once reconstituted, FUZEON should be injected
533 immediately or kept refrigerated in the original vial until use. Reconstituted FUZEON
534 must be used within 24 hours. The subsequent dose of FUZEON can be reconstituted in
535 advance and must be stored in the refrigerator in the original vial and used within 24
536 hours. Refrigerated reconstituted solution should be brought to room temperature before
537 injection and the vial should be inspected visually again to ensure that the contents are
538 fully dissolved in solution and that the solution is clear, colorless, and without bubbles or
539 particulate matter.

540 The reconstituted solution should be injected subcutaneously in the upper arm, abdomen
541 or anterior thigh. The injection should be given at a site different from the preceding
542 injection site and only where there is no current injection site reaction. Also, do not inject
543 into moles, scar tissue, bruises or the navel. A vial is suitable for single use only; unused
544 portions must be discarded (see FUZEON *Injection Instructions*).

545 Patients should contact their healthcare provider for any questions regarding the
546 administration of FUZEON. Information about the self-administration of FUZEON may
547 also be obtained by calling the toll-free number 1-877-4-FUZEON (1-877-438-9366) or
548 at the FUZEON website, www.FUZEON.com. Patients should be taught to recognize the
549 signs and symptoms of injection site reactions and instructed when to contact their
550 healthcare provider about these reactions.

551 **HOW SUPPLIED**

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

556 FUZEON is available in a Convenience Kit containing 60 single-use vials of FUZEON
557 (90 mg strength), 60 vials (2 cartons of 30 each) of Sterile Water for Injection (1.1 mL
558 per vial), 60 reconstitution syringes (3 cc), 60 administration syringes (1 cc), alcohol
559 wipes, Package Insert, Patient Package Insert, and Injection Instruction Guide (NDC
560 0004-0380-39).

561 **Storage Conditions**

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

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

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