ＦＡＸ ０３-３３４０-５４４８ 厚生労働省エイズ治療薬研究班 班長 へFAXでお送り下さい。
原本は施設長承諾書とともに事務局へ郵送してください。

（2）班員登録書

年　月　日

厚生労働省エイズ治療薬研究班　班長　福武　勝幸　殿

私は厚生労働省エイズ治療薬研究班に研究協力者（班員）として参加することを承諾します。

フリガナ 氏　名	印
所属病院名 住　所	
診療科名	
職　責	
緊急連絡先 自宅住所　電話　FAX E-mail 等	

厚生労働省エイズ治療薬研究班の薬剤による治療研究を実施する医師は、当研究班の規定により研究協力者（班員）となっていただかなければなりません。厚生労働省エイズ治療薬研究班はヒューマンサイエンス振興財団のエイズ医薬品等開発推進事業からの研究費により運営されています。

班長連絡先　東京医科大学病院　臨床検査医学科　主任教授　福武　勝幸
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事務局連絡先　パレクセル・インターナショナル株式会社
エイズ治療薬研究班事務局担当者
〒101-0054 東京都千代田区神田錦町 3-20　錦町安田ビル
TEL 03-3518-6022　FAX 03-3518-6014

（3）施設長承諾書の原本は（2）班員登録書とともに、厚生労働省エイズ治療薬研究班事務局へ郵便にて提出してください。

（3）施設長承諾書

年　月　日

厚生労働省エイズ治療薬研究班　班長　福武　勝幸　殿

フリガナ 氏　名	
診療科名	
職　責	

上記の者が厚生労働省エイズ治療薬研究班に研究協力者（班員）として参加することを承諾します。

施　設　長　氏　名	印
職　　責	
施　設　名 住所	

厚生労働省エイズ治療薬研究班の薬剤による治療研究を実施する医師は、当研究班の規定により研究協力者（班員）となっていただかなければなりません。厚生労働省エイズ治療薬研究班はヒューマンサイエンス振興財団のエイズ医薬品等開発推進事業からの研究費により運営されています。

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本文書は３通作成し、１通は厚生労働省エイズ治療薬研究班事務局へ書留郵便で提出し、他は患者、主治医がそれぞれ保管してください。（同一薬剤の継続時は初回のみ必要です。）

（4）患者同意書

年　月　日

厚生労働省エイズ治療薬研究班　班長　福武　勝幸　殿

フリガナ 申請者（主治医）氏名		病院名・〒住所	
診療科名			
職　責			
患者氏名（イニシャル）　姓 [　　]. 名 [　　].		男　・　女	
カルテ番号 [　　]	生年月日	年　月　日	

上記の患者さんに対して、以下の内容について十分に説明したうえ同意を得ました。

同意書

私は私の病気（　　）の治療のために、厚生労働省エイズ治療薬研究班から治療薬（　　）の提供を受けることに関して、上記の担当医師から下記の内容について説明を受け、また質問する機会も得て理解いたしましたので、この治療を受けることに同意いたします。

説明内容

1.この治療の目的と意義
2.予期される効果と副作用
3.他の治療法の有無とその内容
4.同意しない場合でも今後の治療に不利益を受けないこと。
5.同意した場合でも随時これを撤回でき今後の治療に不利益を受けないこと。
6.わからない点は、いつでも質問し説明を受けられること。
7.プライバシーは厳重に守られること。

同意取得日	年　月　日			
フリガナ 患者氏名 （自署）	印	フリガナ 代諾者氏名 （自署）	印	続柄
生年月日	年　月　日			
住所		代諾者住所		

本文書は薬剤を受け取り次第、念書とともに厚生労働省エイズ治療薬研究班事務局へ郵便で提出してください。

（5）薬剤受領書

年　月　日

厚生労働省エイズ治療薬研究班　班長　福武　勝幸　殿

薬剤名	数量

上記の薬剤を確かに受領いたしました。

フリガナ 受領者（主治医） 氏名	印
診療科名	
職責	
病院名・〒住所	

班長連絡先　東京医科大学病院　臨床検査医学科　主任教授　福武　勝幸
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(6) 臨床研究使用成績調査票 (1)

臨床経過と検査値の推移を各ポイント記載する毎に本表のコピーも事務局へお送り下さい

主治医氏名	印	病院名・〒住所
診療科名		
職　責		
電話番号	(　)	FAX番号 (　)
E－Mail		

患者氏名（イニシャル）　姓 [　]. 名 [　].	男・女	身長　cm
カルテ番号 [　]	生年月日	年　月　日
合併症 1. 無し 2. 慢性肝炎 3. 肝硬変 4. 腎障害 5. 糖尿病 6. 高脂血症 7. 血友病 8. その他（　）		

今回使用した研究班の薬（研究班の薬剤を全てを記載して下さい。）

薬剤名	含有量・剤形	1日量と投与回数	投与期間（年/月/日）
		/日　回/日	/ /　－　/ /
		/日　回/日	/ /　－　/ /
		/日　回/日	/ /　－　/ /
		/日　回/日	/ /　－　/ /
		/日　回/日	/ /　－　/ /
		/日　回/日	/ /　－　/ /

研究班の薬剤を投与中に使用した併用薬を全て記載してください。

薬剤名	剤形	1日量と投与回数	投与期間（年/月/日）
		/日　回/日	/ /　－　/ /
		/日　回/日	/ /　－　/ /
		/日　回/日	/ /　－　/ /
		/日　回/日	/ /　－　/ /
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		/日　回/日	/ /　－　/ /
		/日　回/日	/ /　－　/ /

(7) 臨床研究使用成績調査票 (2)

臨床経過と臨床検査値の推移　　ポイント毎に記入し、記入毎に事務局へお送り下さい。

主治医氏名	印	病院名・〒住所	
診療科名			
職　責			
患者氏名（イニシャル）　姓 [　　]. 名 [　　].		男 ・ 女	
カルテ番号 [　　]		生年月日	年　月　日

検査ポイント	投与前	開始後　ヶ月	開始後　ヶ月	開始後　ヶ月
検査日	年 月 日	年 月 日	年 月 日	年 月 日
外来・入院	外来・入院	外来・入院	外来・入院	外来・入院
体重	Kg	Kg	Kg	Kg
体温	℃	℃	℃	℃
血圧	/ mmHg	/ mmHg	/ mmHg	/ mmHg
症状の程度	3+・2+・1+・−	3+・2+・1+・−	3+・2+・1+・−	3+・2+・1+・−
CD4細胞数	/μl	/μl	/μl	/μl
HIV-RNA量	×10　/ml	×10　/ml	×10　/ml	×10　/ml
白血球数 WBC	/μl	/μl	/μl	/μl
赤血球数 RBC	/μl	/μl	/μl	/μl
Hb	g/dl	g/dl	g/dl	g/dl
Htc	%	%	%	%
血小板数	/μl	/μl	/μl	/μl
好中球%	%	%	%	%
好酸球%	%	%	%	%
好塩基球%	%	%	%	%
リンパ球%	%	%	%	%
単球%	%	%	%	%
TP	g/dl	g/dl	g/dl	g/dl
T-Bil	mg/dl	mg/dl	mg/dl	mg/dl
GOT	IU/L	IU/L	IU/L	IU/L
GPT	IU/L	IU/L	IU/L	IU/L
γGTP	IU/L	IU/L	IU/L	IU/L
BUN	mg/dl	mg/dl	mg/dl	mg/dl
クレアチニン	mg/dl	mg/dl	mg/dl	mg/dl
尿酸	mg/dl	mg/dl	mg/dl	mg/dl
総コレステロール	mg/dl	mg/dl	mg/dl	mg/dl
中性脂肪	mg/dl	mg/dl	mg/dl	mg/dl
グルコース	mg/dl	mg/dl	mg/dl	mg/dl
尿蛋白	−・+−・+・++	−・+−・+・++	−・+−・+・++	−・+−・+・++
尿糖	−・+−・+・++	−・+−・+・++	−・+−・+・++	−・+−・+・++
尿潜血反応	−・+−・+・++	−・+−・+・++	−・+−・+・++	−・+−・+・++
尿沈さ異常と内容	無・(　　)	無・(　　)	無・(　　)	無・(　　)

(8) 臨床研究使用成績調査票 (3)

その他の重要な臨床検査成績

XP，CT，MRI，シンチグラム等

検査毎に記入し、記入毎に事務局へお送り下さい。

主治医氏名	印	病院名・〒住所	
診療科名			
職　　責			
患者氏名（イニシャル）　姓［　　］. 名［　　］.		男 ・ 女	
カルテ番号［　　］		生年月日	年　　月　　日

（9）有害事象発生報告書

年　月　日

有害事象が発生したら直ちに記入して、FAXで事務局03-3518-6014へお送り下さい。

主治医氏名	印	病院名・〒住所	
診療科名			
職　責			
患者氏名（イニシャル）．姓［　　］．名［　　］．		男・女	
カルテ番号［　　］		生年月日	年　月　日
有害事象の内容			
発生日時	年　月　日　午前・午後　時		
経過と処置			
程度（主治医判断）	軽症　・　中等度　・　重篤		
薬剤との因果関係	1.関連有り　2．関連が否定出来ない　3．関連無し　4．不明		
関連有ると思われる薬剤	薬剤名	理由	

転帰報告書

転帰を判定したら直ちに記入し事務局へお送り下さい。

判定日時	年　月　日　午前・午後　時
転　帰	回復　・　軽快　・　死亡　・　後遺症
死因・後遺症	
薬剤との因果関係	1．関連有り　2．関連が否定出来ない　3．関連無し　4．不明

［別紙第２号様式］

念　　書

平成　　年　　月　　日

厚生労働大臣　殿

輸入業者（受取人）氏名（法人にあっては名称及び代表者の氏名）

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿印

同住所（法人にあっては主たる事務所の所在地）

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

今般、別紙輸入報告書により報告いたしました下記 医薬品は（　医師個人用　）として使用するもので、他に販売、授与するものではありません。
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上述のとおり、後日のため念書差入れます。

記

品　　名	数　　量

（この様式の大きさは日本工業規格Ａ４とすること）

念書の取扱についてのお願い

厚生労働省エイズ治療薬研究班
主任研究者(班長)　福武　勝幸

この念書は医師個人輸入の手続きにおいて厚生労働省へ必ず提出しなければならないものです。研究班の存続のために最も重要な書類ですので、遅滞なく班長へご返送いただきますようお願いいたします。

当研究班においては、厚生労働省の特別な配慮により薬剤を班長名であらかじめ輸入し通関しておりますが、本念書をご提出いただくことにより、各主治医か個人輸入したのと同等に扱うこととなり、薬事法に抵触することなく各医師へ薬剤をお届けする形で研究班が機能できる仕組みになっております。(この念書は当研究班専用のもので、一般の個人輸入の書式とは異なります。)

記載上の注意

日付欄には薬剤をお受け取りになった日付をご記入ください。輸入業者（受取人）氏名（法人にあっては名称及び代表者の氏名）の欄には、薬剤を研究班へ申請された医師の所属施設と氏名をご記入ください。また、同住所（法人にあっては主たる事務所の所在地）の欄には、医師の所属する施設の住所を御記載ください。お受け取りになった薬剤の品名と数量をご記載ください。

念書返送先

班長連絡先　　東京医科大学病院　臨床検査医学科　主任教授　福武　勝幸
〒160-0023 東京都新宿区西新宿 6-7-1
TEL03-3342-6111 EXT5086　FAX 03-3340-5448

薬剤受領書返送先

事務局連絡先　パレクセル・インターナショナル株式会社
エイズ治療薬研究班事務局担当者
〒101-0054 東京都千代田区神田錦町 3-20　錦町安田ビル
TEL 03-3518-6022　FAX 03-3518-6014

Roche

FUZEON®

(enfuvirtide)

for Injection

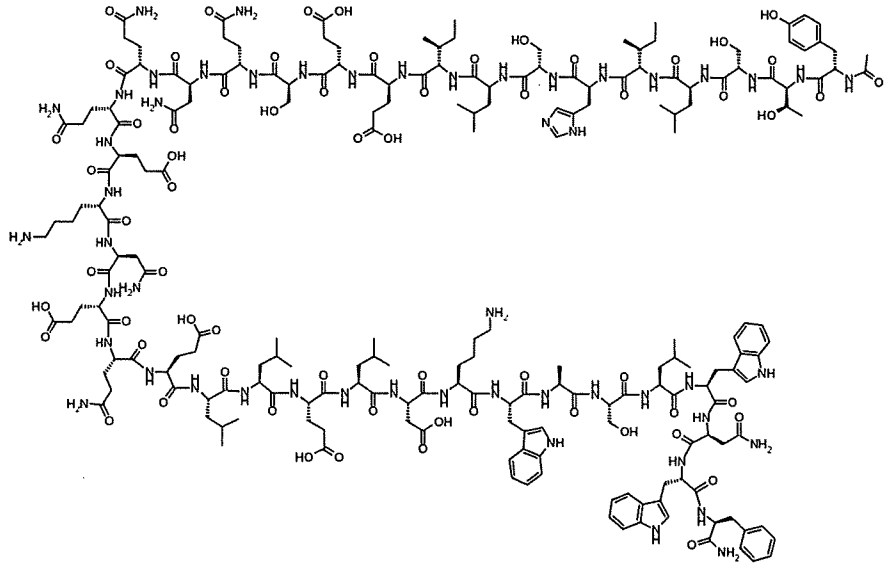
R_x only

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 $C_{204}H_{301}N_{51}O_{64}$, and the molecular weight is 4492. It has the following primary amino acid sequence:

CH_3CO-Tyr-Thr-Ser-Leu-Ile-His-Ser-Leu-Ile-Glu-Glu-Ser-Gln-Asn-Gln-Gln-Glu-Lys-Asn-Glu-Gln-Glu-Leu-Leu-Glu-Leu-Asp-Lys-Trp-Ala-Ser-Leu-Trp-Asn-Trp-Phe-NH_2 and the following structural formula:



The drug product, FUZEON (enfuvirtide) for Injection, is a white to off-white, sterile, lyophilized powder. Each single-use vial contains 108 mg of enfuvirtide for the delivery of 90 mg. Prior to subcutaneous administration, the contents of the vial are reconstituted with 1.1 mL of Sterile Water for Injection giving a volume of approximately 1.2 mL to provide the delivery of 1 mL of the solution. Each 1 mL of the reconstituted solution contains approximately 90 mg of enfuvirtide with approximate amounts of the following excipients: 22.55 mg of mannitol, 2.39 mg of sodium carbonate (anhydrous), and sodium hydroxide and hydrochloric acid for pH adjustment as needed. The reconstituted solution has an approximate pH of 9.0.

MICROBIOLOGY

Mechanism of Action

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

Antiviral Activity In Vitro

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

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

Drug Resistance

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

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

Cross-resistance

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

CLINICAL PHARMACOLOGY

Pharmacokinetics

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

Absorption

Following a 90-mg single subcutaneous injection of FUZEON into the abdomen in 12 HIV-1 infected subjects, the mean (±SD) C_{max} was 4.59 ± 1.5 μg/mL, AUC was 55.8 ± 12.1 μg•h/mL and the median T_{max} was 8 hours

(ranged from 3 to 12 h). The absolute bioavailability (using a 90-mg intravenous dose as a reference) was 84.3% ± 15.5%. Following 90-mg bid dosing of FUZEON subcutaneously in combination with other antiretroviral agents in 11 HIV-1 infected subjects, the mean (±SD) steady-state C_{max} was 5.0 ± 1.7 μg/mL, C_{trough} was 3.3 ± 1.6 μg/mL, AUC_{0-12h} was 48.7 ± 19.1 μg•h/mL, and the median T_{max} was 4 hours (ranged from 4 to 8 h).

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

Distribution

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

Enfuvirtide is approximately 92% bound to plasma proteins in HIV-infected plasma over a concentration range of 2 to 10 μg/mL. It is bound predominantly to albumin and to a lower extent to α-1 acid glycoprotein.

Metabolism/Elimination

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

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

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

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

Special Populations

Hepatic Insufficiency

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

Renal Insufficiency

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

Gender and Weight

Gender

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

Weight

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

No dose adjustment is recommended for weight or gender.

Race

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

Pediatric Patients

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

In the 23 pediatric subjects receiving the 2 mg/kg bid dose, the mean ±SD steady-state AUC was 56.3 ± 22.3 μg•h/mL, C_{max} was 6.3 ± 2.4 μg/mL, C_{trough} was 3.1 ± 1.5 μg/mL, and apparent clearance was 40 ± 17 mL/h/kg.

Geriatric Patients

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

Drug Interactions

Influence of FUZEON on the Metabolism of Concomitant Drugs

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

Influence of Concomitant Drugs on the Metabolism of Enfuvirtide

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

Table 1 Effect of Ritonavir, Saquinavir/Ritonavir, and Rifampin on the Steady-State Pharmacokinetics of Enfuvirtide (90 mg 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)

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

x No interactions were clinically significant.

INDICATIONS AND USAGE

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

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

Description of Clinical Studies

Studies in Antiretroviral Experienced Patients

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

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

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

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

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

	FUZEON+Background Regimen	Background Regimen
	N=663	N=334
Sex Male Female	 90% 10%	 90% 10%
Race White Black	 89% 8%	 89% 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)

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

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 • Completed 48 weeks randomized regimen*	 0 191 (29%)	 220 (66%) 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 adverse	46 (7%)	9 (8%)	13 (6%)

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

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

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

[##]Includes difficulties with injection, such as injection fatigue and inconvenience.

[†]Includes lost to follow-up, treatment refusal, and non-compliance.

At 48 weeks, 154 (23%) of subjects in the FUZEON+background regimen and 27 (8%) in the background regimen alone had HIV RNA. levels <50 copies/mL, and 225 (34%) of subjects receiving FUZEON+background regimen had HIV RNA levels <400 copies/mL compared to 44 (13%) in the background regimen alone. Subjects achieving HIV RNA levels <50 copies/mL were included in the <400 copies/mL category and both categories were incorporated in the overall virologic responder category of achieving HIV RNA at least 1 $\log_{10}$ below baseline.

The mean log change in HIV-1 RNA from baseline was -1.4 $\log_{10}$ copies/mL in subjects receiving FUZEON+background and -0.5 in those receiving background alone. The mean change in $CD4^+$ cell count from baseline to week 48 was +91 cells/mm^3 in the FUZEON+background arm and +45 cells/mm^3 in the background alone arm.

Subjects in the FUZEON+background arm achieved a better virologic and immunologic outcome than subjects in the background alone arm across all subgroups based on baseline $CD4^+$ cell count, baseline HIV-1 RNA, number of prior ARVs or number of active ARVs in the background regimen.

CONTRAINDICATIONS

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

WARNINGS

Local Injection Site Reactions (ISRs)

The majority of patients (98%) receiving FUZEON in the Phase 3 clinical trials had at least one local injection site reaction; ISRs occurred throughout treatment with FUZEON. Manifestations may include pain and discomfort, induration, erythema, nodules and cysts, pruritus, and ecchymosis (see **ADVERSE REACTIONS**).

Reactions are often present at more than one injection site. Patients must be familiar with the FUZEON *Injection Instructions* in order to know how to inject FUZEON appropriately and how to monitor carefully for signs or symptoms of cellulitis or local infection.

Pneumonia

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

Hypersensitivity Reactions

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

PRECAUTIONS

Non-HIV Infected Individuals

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

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including FUZEON. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP] or tuberculosis), which may necessitate further evaluation and treatment.

Information for Patients

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

- Patients should be informed that injection site reactions occur in almost all patients taking FUZEON. Patients must be familiar with the FUZEON *Injection Instructions* for instructions on how to appropriately inject FUZEON and how to carefully monitor for signs or symptoms of cellulitis or local infection. Patients should be instructed when to contact their healthcare provider about these reactions.
- Patients should be made aware that an increased rate of bacterial pneumonia was observed in subjects treated with FUZEON in Phase 3 clinical trials compared to the control arm. Patients should be advised to seek medical evaluation immediately if they develop signs or symptoms suggestive of pneumonia (cough with fever, rapid breathing, shortness of breath) (see **WARNINGS**).
- Patients should be advised of the possibility of a systemic hypersensitivity reaction to FUZEON. Patients should be advised to discontinue therapy and immediately seek medical evaluation if they develop signs/symptoms of systemic hypersensitivity such as combinations of rash, fever, nausea and vomiting, chills, rigors, and/or hypotension (see **WARNINGS**).
- FUZEON is not a cure for HIV-1 infection and patients may continue to contract illnesses associated with HIV-1 infection. The long-term effects of FUZEON are unknown at this time. FUZEON therapy has not been shown to reduce the risk of transmitting HIV-1 to others through sexual contact or blood contamination.
- FUZEON must be taken as part of a combination antiretroviral regimen. Use of FUZEON alone may lead to rapid development of virus resistant to FUZEON and possibly other agents of the same class.
- Patients and caregivers must be instructed in the use of aseptic technique when administering FUZEON in order to avoid injection site infections. Appropriate training for FUZEON reconstitution and self-injection must be given by a healthcare provider, including a careful review of the FUZEON Patient Package Insert and FUZEON *Injection Instructions*. The first injection should be performed under the supervision of an appropriately qualified healthcare provider. It is recommended that the patient and/or caregiver's understanding and use of aseptic injection techniques and procedures be periodically re-evaluated.
- Patients and caregivers should be instructed in the proper techniques for preparation, injection and disposal of needles and syringes (including not recapping needles) in order to avoid needle stick injuries. Patients should be told not to reuse needles or syringes, and be instructed in safe disposal procedures including the use of a puncture-resistant container for disposal of used needles and syringes. Patients must be instructed on the safe disposal of full containers as per local requirements. Caregivers who experience an accidental needle stick after patient injection should contact a healthcare provider immediately.
- Patients should contact their healthcare provider for any questions regarding the administration of FUZEON.
- Patients should inform their healthcare provider if they are pregnant, plan to become pregnant or become pregnant while taking this medication.
- Patients should inform their healthcare provider if they are breast-feeding.
- Patients should not change the dose or dosing schedule of FUZEON or any antiretroviral medication without consulting their healthcare provider.
- Patients should contact their healthcare provider immediately if they stop taking FUZEON or any other drug in their antiretroviral regimen.

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

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

Drug Interactions

CYP450 Metabolized Drugs

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

Antiretroviral Agents

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

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

Pregnancy

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

Antiretroviral Pregnancy Registry

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