Other Discussion Item: THE LAUNCH OF T-20

Prior to the meeting, the Sponsor informed the Division that a restricted launch of T-20 might be necessary based on drug availability. The Sponsor assured the Division that the first priority is to patients who are already receiving T-20.

Summary/Action Items

1. The Division agrees to work closely together on reviewing the patient education materials. Once the Division receives actual patient education materials, an industry meeting will be planned for further discussion.

2. The Sponsor and Division agree to continue discussions regarding the potential for a limited T-20 launch.

3. The Sponsor will submit data from Study 204 to the NDA.

4. If the Safety Update is not available within three months of the official User Fee clock start date then the review clock may need to be extended.

5. [ ]

Minutes Preparer: _____ Date: _____

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tony DeCicco
8/21/02 12:28:19 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

IND [redacted]

Hoffman-La Roche
Attention: Katrin Rupalla, Ph.D.
Senior Program Manager. Drug Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110

Dear Dr. Rupalla:

Please refer to the meeting between representatives of your firm, Trimeris, and FDA on September 4, 2002. The purpose of this meeting was to review your current draft of the Fuzeon® (enfurtide, T-20) patient education program, including the patient education materials and patient mock-ups. Additional objectives of this meeting were for the Division to review the patient education program and materials and to obtain our feedback on your plans to educate patients, caregivers, and health care providers on the appropriate administration of T-20.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Ms. Virginia Yoerg, Regulatory Health Project Manager, at (301) 827-2335.

Sincerely yours,

Anthony W. DeCicco, R.Ph.
Supervisory Consumer Safety Officer
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Attachment

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

RECORD OF INDUSTRY MEETING

Date of Meeting: September 4, 2002

IND: [redacted] (NDA 21-481)

Drug: Fuzeon® (enfurtide, T-20)

Indication: Treatment of HIV-1 infection

Sponsor: Hoffmann-La Roche and Trimeris Inc.

Type of Meeting: Fuzeon® Patient Education Program

FDA: Attendees
Debra B. Birnkrant, M.D., Division Director, DAVDP
Jeffrey S. Murray, M.D., M.P.H., Deputy Director, DAVDP
Steven Gitterman, M.D., Medical Team Leader, DAVDP
Melisse S. Baylor, M.D., Medical Officer, DAVDP
Rao V. Kambhampati, Ph.D., Chemist, DAVDP
William H. Taylor, Ph.D., Pharmacologist, DAVDP
Julian J. O'Rear, Ph.D., Microbiology Team Leader, DAVDP
Narayana Battula, Ph.D., Microbiologist, DAVDP
Lisa Nager, Ph.D., Microbiologist, DAVDP
Greg Soon, Ph.D., Biometrics Team Leader, DAVDP
Thomas Hammerstrom, Ph.D., Mathematical Statistician, DAVDP
Richard Klein, HIV/AIDS Program Director, OSHI
Laura Pincock, Pharm.D., Senior Regulatory Review Officer for HIV Drugs, DDMAC
Jeanine A. Best, Regulatory Project Manager, Patient Materials Reviewer, DSRCS
Jeff O'Neill, RN, ACRN, Regulatory Project Manager, DAVDP
Karen A. Young, RN, BSN, Regulatory Project Manager, DAVDP

Hoffman-La Roche Attendees
Robin Conrad, Group Director, Drug Regulatory Affairs
Katrin Rupalla, Ph.D., Drug Regulatory Affairs, Senior Program Manager
Cynthia Aronson, Brand Director
Tosca Kinchelow, Clinical Scientist, T-20

Maggie Hermoso, Clinical Specialist
Toby Hirsch, Project Manager

Trimeric Inc. Attendees
Alex Dusek, Director of Marketing
Marma Doucette, Director of Regulatory Affairs and Compliance

Background
The Sponsor submitted the following three patient education documents: July 3, 2002 (SN 356), July 25, 2002 (SN 370), and August 1, 2002 (SN 376).

The July 3, 2002 submission included draft outlines of the wording for the Patient Starter Kit, Welcome Letter, Injection Placement, Injection Rotation Calendar, Health Care Provider Demo Kit, Flip Chart, Injection Devices, Patient Education Brochure, and Patient Education Video.

The July 25, 2002 (SN 370) submission included sketches and rough layouts of the above listed materials.

The August 1, 2002 (SN 376) submission included individual patient mock-ups and photo/sketches of the above listed materials, for use in the early, access program.

On August 28, 2002 the Sponsor electronically sent a revised draft of the T-20 injection instructions for patient education (see Attachment #1) and the patient package insert (PPI).

Discussion
The Sponsor explained the following patient educational materials would be included in a patient kit: package insert (PI), PPI, Health Care Provider Kit, Patient Starter Kit, and discussed the plans for the Web/Hotline Site. After reviewing the materials, the Sponsor briefly explained the developmental process in designing these materials.

Division of Drug Marketing, Advertising, and Communications (DDMAC)
Dr. Laura Pincock suggested the following comments:

1. In all materials for T-20, the complete indication in the final approved product labeling should be communicated, including important limitations to the indication that convey the accelerated approval status of T-20. For patient materials, this indication should be communicated in patient-friendly language.

2. All claims (e.g., statements pertaining to the mode of action, indication, safety, tolerability, side effects, decreases in death and illness) must be in accordance with the PI.

3. All claims require fair balance with presentation of information relating to side effects and contradictions with a prominence and readability reasonably comparable with the presentation of information relating to effectiveness of the drug product T-20,

4. For all direct-to-consumer (DTC) materials and activities for human immunodeficiency virus (HIV) medications, DDMAC requests that manufacturers prominently convey the following important limitations of HIV drugs, including T-20:

   - T-20 does not cure HIV infection
   - T-20 does not reduce the transmission of HIV
   - T-20 should only be taken in combination with other drugs in HIV

5. Under CRF 314.550, all promotional materials (including patient education materials) for accelerated approval products are required to be submitted to DDMAC for prospective review 30 days prior to the intended approval date.

The Sponsor reports that they do not plan to include any branding on the Travel Pak.

Division of Surveillance, Risk, Communication and Safety (DSRCS)
Jeanine Best, N.P., Regulatory Project Manager, Patient Materials Reviewer suggested the following comments:

1. The reading comprehension of all patient education materials should be approximately at grade level 6.

2. The recommendation was made as to the importance in providing a balance of information so that patients receive adequate information without being overwhelmed.

3. DSRCS has a social scientist on staff who is available to review patient education materials to determine whether patients comprehend materials. If the Sponsor desires this testing and feedback, the testing questions should be submitted as soon as possible.

4. DSRCS encourages the Sponsor to submit the PPI for review at least 30 days prior to drug approval. In order to provide comments and facilitate suggestions and recommendations, please send the PPI electronically in Word format.

The Division distributed a list of questions and recommendations for the following patient education component: Patient Travel Pak, Welcome Letter, A Basic Guide to Subcutaneous Injection of Enfuvirtide, Patient Education Video, Patient Injection Practice Device, Certificate of Medical Need, Enfuvirtide Preparation Mat, and Flip Chart. (Please refer to Attachment #3.)

Summary/Action Items

1. The Sponsor verbalizes the importance that all patient education materials are at a reading level comprehension near grade 6 (approximately).

2. The Sponsor will supply the PPI electronically in Word format.

3. The Sponsor agrees to stress the importance of site rotation and to remind patients of inappropriate injection sites (moles, injection site reactions, scars, bruises, navel, etc.).

4. The Sponsor confirmed that the reconstitution instructions will inform patients to store the reconstituted vial in the refrigerator up to 24 hours. The Sponsor will ascertain whether studies have been conducted on storing reconstituted material in syringes. At this time, it is unknown if Fuzeon precipitates with other substances.

Minutes Preparer: _____ Date: _____

Attachment #1 (Fuzeon Instruction Sheet)

APPEARS THIS WAY
ON ORIGINAL

Attachment #3

Below are the Division's questions and recommendations. (Please note the Sponsor's responses are ***italicized*** and in **bold** font.)

Patient Travel Pak

1. How will distribution be handled, i.e., will patients receive the Travel Pak from their pharmacy or from their physician? Will there be a 1-800 number for requesting Travel Paks?

   The physicians will provide patients with the Patient Starter Kit (Travel Pak) when they begin Fuzeon treatment.

   In addition to English, the Sponsor plans to provide the patient education materials in Spanish.

2. Will the Travel Pak include Fuzeon when dispensed, or will Fuzeon be obtained separately?

   The starter kit will not include Fuzeon. Fuzeon will be obtained separately and will be supplied as a convenience kit containing a 30-day supply of drug, water, syringes, and alcohol swabs.

3. When traveling, should the Travel Pak include an ice pack for the storage of Fuzeon?

   The following are Fuzeon storage recommendation:
   Ship Fuzeon at a controlled room temperature;
   Store lyophilized powder at room temperature; and
   Once Fuzeon is reconstituted, refrigerate up to 24 hours.

   Patients will be instructed to keep their medication with them when traveling and not to store their Travel Pak with their checked luggage). As long as the vials are not reconstituted an ice pack should not be required. Further consideration will be given to instructions for traveling with reconstituted material.

Welcome Letter

4. The first sentence of second paragraph states, "Like treatments for other medical conditions, enfuvirtide is an injectable medication." Please add that enfuvirtide is injected subcutaneously.

   The Sponsor will make this change.

5. Please consider adding a sentence to the **Welcome Letter** stating that enfuvirtide does not cure or prevent the transmission of HIV, that patients need to continue to practice safer sex, and that patients should never share needles.

   This change is currently under consideration since a balance of the amount of information provided in the letter was also requested by DSRCS.

   A Basic Guide to Subcutaneous Injection of Fuzeon.

6. On the first page, please consider adding a sentence such as, "This guide reinforces what you learned at your doctor's office."

   This change will be made.

7. Under the **Gather Supplies** section, if syringes are referred to as the [redacted] or [redacted] please be aware the manufacturer may change the color of the syringes or patients may receive syringes from another source (i.e. doctor's office, clinic). These situations could be potentially confusing to patients. Will patients receive additional syringes to allow for contamination or other procedural errors?

   The references to [redacted] syringes have been removed from the educational materials. Syringes are now described as "larger" and "smaller".

   Further consideration will be given to including additional syringes in the convenience kit to allow for contamination and procedural errors. In addition, as discussed during the meeting language will be included in this guide instructing patients in proper procedures should their needle become contaminated or they make a procedural error.

8. Under **Select Injection Site** section, please include the following areas to avoid:
   - Scar tissue
   - Bruises (in addition to the nodules)
   - Moles
   - Any injection site reactions
   - Navel

   Please stress the importance of injection site rotation.

   The current instructions include language advising patients to avoid the site of any injection site reaction and to avoid the area around the navel. Additional language will be added to instruct patients to avoid scar tissue, bruises, and moles.

   We will stress the importance of injection site rotation in the educational pieces.

9. In the section, **Mixing Enfuvirtide** under **Step 4**, the Sponsor should encourage patients to pull past the 1.1 mL (sterile water) mark so that they can just tap the syringe and press the plunger to 1.1 mL. This makes it much easier to eliminate air bubbles.

   This change will be made.

10. In the section, **Mixing Enfuvirtide** under **Step 6**, it says to make sure you never touch the needle with your fingers or any other object. Please instruct patients on handling of contaminated needles.

    Further consideration will be given to including additional syringes in the convenience kit to allow for containment and procedural errors. In addition, as discussed during the meeting language will be included in this guide instructing patients what to do should their needle become contaminated or they make a procedural error.

[redacted]

[redacted]

14. In "**A Basic Guide to Subcutaneous Injection of Enfuvirtide**", please clarify where patients will obtain sharps containers, how they will be labeled, and how they will be discarded.

    The Sponsor will provide sharps containers to physicians and pharmacies for distribution to patients as needed. There will be multiple avenues for replenishment of Sharps containers (field force delivery, fulfillment hourse, web site, etc.). The Sharps containers will contain no additional labeling besides the required statements. Regulations pertaining to the disposal of Sharps containers vary by State/county. Patients are instructed to speak with their doctor regarding proper disposal of Sharps containers per local regulations.

15. In the section, **Safety Tips**, we have the following comments:

    - You state, "Never mix enfuvirtide with tap water." In addition, please add the following statement, "Use only the sterile water provided to mix enfuvirtide."

      This change will be made.

    - Please include specific criteria for calling a health care provider about injection site reactions (ISRs).

      The Sponsor will include language in the materials that indicate under what circumstances a patient should call his/her health care provider regarding injection site reactions. As suggested by the Agency special attention will be paid to signs of cellulitis. The Sponsor will consider including pictures or reactions that would be considered "normal" and types of reactions that should be reported to the physician.

16. In "**A Basic Guide to Subcutaneous Injection of Enfuvirtide**" please describe the color of enfuvirtide powder and the solution. Please also consider including a photograph of how the solution looks when properly prepared. The Sponsor should also describe common problems and instructions on how to handle these problems (particulate matter, color change, etc).

    The current instructions include a picture of the properly reconstituted solution, a picture of an improperly reconstituted via, and instructions regarding inspecting the solution to make sure it is clear and free of particulate matter.

17. We suggest having, **"A Basic Guide to Subcutaneous Injection of Enfuvirtide"** laminated. Patients will be referring to this guide frequently.

With every prescription, these injection instructions will be provided to patients. The convenience kit will include the physician insert, patient package insert and injection instruction sheet. In addition, these instructions will be included in the patient starter kit (Travel Pak). The Sponsor will evaluate printing these instructions on material that will be longer lasting yet allow the instructions to be folded for inclusion in the convenience kit and starter kit.

Patient Education Video

18. What about those patients who do not own a VCR? Or, those who only have a DVD? Is it possible to include the video on the Fuzeon web site?

The video will be included on the Fuzeon web site.

Patient Injection Practice Device
No recommendations noted.

Certificate of Medical Need
No recommendations noted.

Enfuvirtide Preparation Mat

19. We are concerned about the potential for contamination of a reusable mat.

The mat will be laminated and patients will be instructed to clean the mat. Other injectable products use similar place mats.

Enfuvirtide Planner

20. The numbering system used suggests that there are only six possible injection sites. However, there are multiple potential sites within each area. Please explain how you choose this numbering system.

The Sponsor will indicate that there are multiple injection sites within an area.

21. The Planner should include wording to encourage patients to rotate among all sites.

Language encouraging patients to rotate among all sites will be included in the planner.

22. The Planner should have wording to remind patients those injection sites, which they should avoid, i.e., injection site reactions, moles, scars, bruises, navel, etc.

This change will be made.

Flip Chart

23. The Flip Chart refers to the **"A Basic Guide to Subcutaneous Injection of Enfuvirtide"** as **"Your Guide to Taking Enfuvirtide."** Please use terms consistently.

Final materials will be reviewed for consistency.

24. In the introduction, we would suggest that a statement be made that enfuvirtide is not a cure for HIV and it does not prevent the transmission of HIV. However, this statement is included under the section **"Enfuvirtide Q&A."**

This information will be moved to the introduction.

Other Comments:

25. You encourage the assistance of a caregiver. We recommend a pamphlet be developed for the caregiver that includes information on the importance of using gloves, what to do if they receive a needle stick, proper disposal of syringes, what will an injection site reaction look like, and when should you call a health care provider.

    The Sponsor will develop a separate guide for caregivers that covers the information listed above. These instructions will not be included in the convenience kit but will be provided to health care providers for further distribution. The Flip Chart will be updated accordingly.

26. We would suggest a "Health Care Provider Checklist" to ensure all teaching points are covered. This would facilitate teaching and also serve as documentation of teaching.

    The Sponsor will create a Health Care Provider Checklist.

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Debra Birnkrant
11/18/02 01:46:17 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELECONFERENCE

Date July 10, 2001

IND [redacted]

Sponsor Hoffmann-LaRoche, Inc.

Drug T-20 (RO 29-9800)

Indication Treatment of HIV-1 Infection

Subject Pre-clinical Reproductive Toxicity Studies

FDA Attendees
Joseph Toerner, M.D., Medical Officer, DAVDP
James Farrelly, Ph.D., Pharmacology Team Leader, DAVDP
Karen Young, RN, BSN, Regulatory Project Manager, DAVDP

Sponsor Attendees
Melanie Bishop, Program Director, Drug Regulatory Affairs
Robin L. Conrad, Program Director, Drug Regulatory Affairs
Dr. Thomas Steele, NonClinical Drug Safety, Hoffmann- La Roche
Dr. John Delehanty, Clinical Development, Trimeris

Background
On June 6, 2001, the Division provided the Sponsor a telephone facsimile expressing concern that in a series of nonclinical reproductive toxicology studies, there was no unequivocal toxicity demonstrated in parent animals in the high dose groups. The Sponsor responded to the question of the appropriateness of the studies for demonstrating the safety of T-20 for reproductive outcomes in a submission dated June 29, 2001. In the submission, the Sponsor indicated it is completing a placental transfer and milk secretion study and suggested that it might conduct one further Segment II study at higher doses. A brief teleconference was held to discuss the Sponsor's intended plans for future studies to demonstrate the safety of T-20 on reproductive and development parameters.

Discussion
The Division acknowledged the Sponsor's thorough response to the Division's concerns.

The Sponsor had indicated in its submission that higher animal doses were generally not feasible because of saturation of absorption of the drug via the subcutaneous injection route of administration. Dr. Farrelly indicated that the toxicokinetic data did not clearly show saturation and that some increase (albeit, small amounts) in drug substance was seen in plasma at the higher doses administered.

The Sponsor agreed to conduct the additional Segment II reproductive study of T-20 in rats at 250 mg/kg b.i.d. (500mg/kg/d). The Division said that if the Sponsor would submit the placental transfer and milk secretion study and the Segment II study using the higher T-20 doses, that further nonclinical reproductive studies will not be required.

Action
Hoffman-La Roche will complete the ongoing placental transfer and milk secretion study in rats with [3H]-T-20. The Sponsor agrees to conduct an additional Segment II rat study at doses up to 500 mg/kg/day. If the Sponsor completes the above studies in a good faith effort, the Division agrees to forego additional reproductive toxicity studies.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Young
7/31/01 09:36:40 AM
CSO

T-20 telecon meeting minutes, repro tox studies

James Farrelly
8/2/01 01:22:11 PM
PHARMACOLOGIST

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

RECORD OF DAVDP/INDUSTRY TELECON

Date of Teleconference: **January 22, 2003**

NDA: **21-481**

Drug: **Fuzeon (enfuvirtide) for injection; T-20**

Sponsor: **Hoffman-LaRoche, Inc.**

DAVDP Participants:

Steven Gitterman, M.D., Ph.D., Medical Team Leader, DAVDP
Melisse Baylor, M.D., Medical Reviewer, DAVDP
Andrea James, M.D., Medical Officer, DAVDP
Thomas Hammerstrom, Ph.D., Statistics Reviewer, DAVDP
Virginia L. Yoerg, Regulatory Project Manager, DAVDP

External Participants:

Hoffman-LaRoche
Silvia Bader-Weder, M.D., Drug Safety
Jain Chung, Ph.D., Statistics
Ms. Robin Conrad, Regulatory Affairs
David Reddy, M.D., Lifecycle/Project Leader
Katrin Rupalla, Ph.D., Regulatory Affairs
Miklos Salgo, M.D., Ph.D., Clinical Science

Trimeris:
Ms. Marna Doucette, Regulatory Affairs
Claude Drobnes, M.D., Drug Safety

Subject: Increased risk of pneumonia and sepsis in subjects receiving enfuvirtide

Background:

This teleconference was held to discuss the ongoing review of NDA 21-481, Fuzeon (enfuvirtide) for injection, particularly DAVDP's concern about the apparent increase of bacterial infections (primarily pneumonia and sepsis) in patients treated with enfuvirtide in studies T20-301 and T20-302. DAVDP alerted the applicant about this concern via telephone facsimile correspondence dated December 23, 2002. Please refer to the applicant responses dated January 14, 2003 and January 21, 2003 (2).

Discussion:

DAVDP referred to the applicant correspondences and stated that additional information is necessary to more fully evaluate the apparent increased risk of pneumonia and sepsis in subjects receiving enfuvirtide. DAVDP requested the following information:

- additional data including the mortality rates, incidence of AIDS defining events, and incidence of bacterial infections, particularly pneumonia and sepsis, in studies T20-301 and T20-302 (that occurred after the data cutoff for the safety update report). DAVDP specified that this should include the 'snapshot' of available data from which these analyses would be generated. The snapshot data should be submitted as soon as possible, even if this precedes the analyses cited above.

- a more detailed analysis of the risk factors for infection including baseline CD4 count, change in CD4 count, change in viral load, virologic failure, and absolute neutrophil count.

- association of the risk of infection with gender, smoking, age, or alcohol use.

- analysis of concomitant medication use including antibiotic use overall, use of individual antibiotics and classes of antibiotics, use of antibiotics for prophylaxis, reason for prophylaxis, and use of other concomitant medications.

- a more detailed analysis of the risk of infection in switch subjects, including correction for exposure and the analyses described previously.

- narratives for all patients with bacterial infections from studies T20-301 and T20-302.

DAVDP also encouraged the applicant to submit any additional analyses that they consider relevant to this particular issue.

The applicant agreed to conduct the analyses and to submit the requested information.

Actions:

- The applicant will estimate the amount of time required to fulfil DAVDP's information request and will inform DAVDP of that anticipated timeframe by January 24, 2003.
- The regulatory implications of this issue will be discussed at a later date.
- DAVDP will email the details of the above-mentioned information request to the applicant.
- DAVDP agreed to send a copy of these teleconference minutes to the applicant.

Addendum: DAVDP emailed the above information request to the applicant on January 23, 2003.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Virginia Yoerg
1/31/03 11:52:12 AM
CSO

hard copy signed. Sent minutes to sponsor.

Steven Gitterman
2/5/03 05:14:07 PM
MEDICAL OFFICER

CONSULTATION RESPONSE

Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: August 21, 2001	**DUE DATE:** October 1, 2001	**OPDRA CONSULT #:** 00-0303

TO: Debbie Birnkrant, MD
Acting Director, Division of Anti-Viral Drug Products
HFD-530

THROUGH: Melissa Truffa, Project Manager
HFD-530

PRODUCT NAME:	**MANUFACTURER:** Hoffmann-La Roche Inc.
Fuzeon (enfuvirtide injection) **IND #:** [redacted]	

SAFETY EVALUATOR: Alina R. Mahmud, RPh.

SUMMARY: In response to a consult from the Division of Anti-Viral Drug Products (HFD-530), OPDRA conducted a review of the proposed proprietary name "Fuzeon" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA does not object to the use of the proprietary name "Fuzeon"
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document.

APPEARS THIS WAY
ON ORIGINAL

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 18, 2001

IND NUMBER: ———

NAME OF DRUG: Fuzeon
(enfuvirtide injection)

IND HOLDER: Hoffmann-La Roche Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division Anti-Viral Drug Products (HFD-530), for assessment of the tradename "Fuzeon", regarding potential name confusion with other proprietary/generic drug names.

PRODUCT INFORMATION
Fuzeon is the proposed proprietary name for enfuvirtide, a fusion inhibitor for the treatment of HIV infection. The recommended dosage is 90 mg subcutaneously twice daily.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound-alike or look-alike to "Fuzeon" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database and Thomson and Thomson was also conducted[5,6]. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, to simulate the prescription ordering process.

---

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).
[2] American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.
[3] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.
[4] COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.
[5] WWW location http://www.uspto.gov/tmdb/index.html.
[6] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com."

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name "Fuzeon". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Three product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with Fuzeon. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have any concerns with the name in regard to promotional claims.

TABLE 1

Product Name*	Dosage form(s), Generic name*	Usual adult dose*	Other**
Fuzeon	Enfuvirtide	90 mg twice daily	
Aceon	Perindopril erbumine tablets 2 mg, 4 mg, 8 mg	4 to 8 mg administered as a single daily dose	S/A, L/A per OPDRA
Fluzone	Influenza virus vaccine	Dose varies according to age group	S/A, L/A per OPDRA
Visudyne	Verteporfin for injection 15 mg (reconstituted to 2 mg/ml)	6 mg/m² BSA withdrawn from reconstituted vial and diluted with 5% Dextrose for injection; IV infusion followed by activation of Visudyne with light from a non-thermal diode laser.	S/A, L/A per OPDRA
		*Frequently used, not all-inclusive.	**L/A (look-alike), S/A (sound-alike)

B. STUDY CONDUCTED BY OPDRA

1. Methodology

A separate study was conducted within FDA for the proposed proprietary name to determine the degree of confusion of Fuzeon with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 88 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Fuzeon (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone

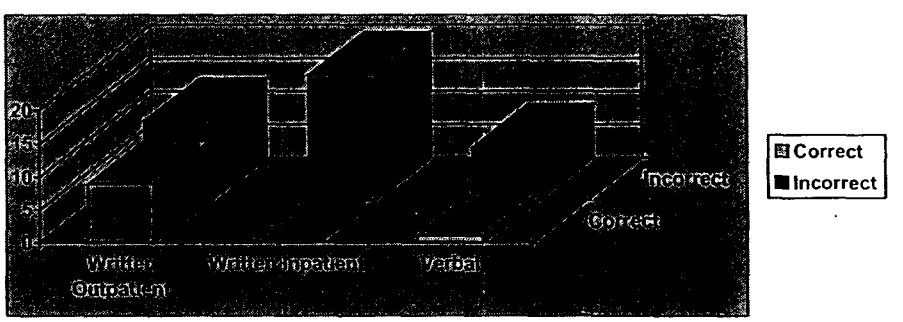
voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient: Fuzeon # Sig: 90 mg SQ twice daily	Fuzeon 90 mg subcutaneously twice daily Dispense #
Inpatient: Fuzeon 90 mg SQ twice daily	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Fuzeon" response	Other response
Written: Outpatient	30	21 (70%)	9 (43%)	12(57%)
Inpatient	29	19 (66%)	0 (0%)	19 (100%)
Verbal	29	9 (31%)	1 (11%)	8 (89%)
Total:	88	49 (56%)	10 (20%)	39 (80%)



Among participants in the two written prescription studies, 31 of 40 respondents (78%) interpreted the name incorrectly. The interpretations were misspelled variations of "Fuzeon" such as *Fuzian, Furjēon, Fuyeon,* and *Fugeon.* Other participants provided *Fuziar, Fuzcan, Furzan, Fuycon,* and *Fuzcar.*

Among verbal prescription study participants, 8 out of 9 study participants (89%) interpreted the name incorrectly. Most of the incorrect name interpretations were phonetic variations of "Fuzeon" such as *Fuseon, Fusion, Fuzione, Fuzuon, Fusium,* and *Fuseeon.*

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Fuzeon", the primary concerns raised were related to a sound-alike, look-alike name that already exists in the U.S. marketplace. One product, Visudyne, was believed to be the most problematic in terms of potential medication errors.

OPDRA conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Fuzeon could be confused with Visudyne. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The majority of the participants from the verbal and two written prescription studies provided phonetic/misspelled interpretations to the proposed drug name.

Visudyne for Injection contains verteporfin and is indicated for the treatment of age-related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularization. A course of Visudyne therapy is a two-step process requiring administration of both drug and light. The first step is the intravenous infusion of Visudyne. The second step is the activation of Visudyne. Each vial of Visudyne must be reconstituted with Water for Injection and then diluted in 5% Dextrose for Injection. Although Fuzeon and Visudyne do not look similar when scripted, the drug names sound similar. In addition, both drugs will be available as an injectable dosage form. However, the drug products differ in route of administration (subcutaneously vs. intravenously), indication, dosage, and dosing schedule. Furthermore, the distribution of Visudyne will primarily be limited to an ophthalmologist's office where qualified personnel in an appropriately equipped medical setting are required. Therefore, we believe that the potential for confusion between Fuzeon and Visudyne is low.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

Please provide for evaluation.

III. RECOMMENDATIONS

OPDRA does not object to the use of the proprietary name "Fuzeon".

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, R.Ph. at 301-827-3231.

Alina R. Mahmud, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Alina Mahmud
9/25/01 04:10:26 PM
PHARMACIST

Jerry Phillips
9/26/01 02:03:11 PM
DIRECTOR

Martin Himmel
9/28/01 10:54:34 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM(*Division/Office*)
Division of Dermatologic and Dental Drug Products, HFD-540 [redacted] J. Kozma-Fornaro, CPMS	Karen Young, Project Manager (X7-2376) Division of Antiviral Drug Products, HFD-530

DATE: 5/31/02	IND NO.	NDA NO.	TYPE OF DOCUMENT:	DATE OF DOCUMENT:
			New Protocol	May 23, 2002

NAME OF DRUGS:	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE
T-20 (Ro 29-9800) SC Injections (bid)	Standard	Fusion Inhibitor, tx of HIV Infection	July 31, 2002

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ■ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
SUMMARY OF ADVERSE EXPERIENCE
☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

♦ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please evaluate the protocol T-20 306 entitled: "A Clinical, Histological and Histochemical Examination of Injection Site Reactions after SQ Injections of T-20 during Treatment of HIV-1 Infection." for the appropriateness of planned assessments in order to characterize the dermatopathologic responses to T-20 subcutaneous injections. Should you have any questions about this protocol or T-20, please contact Dr. Melisse Baylor (X7-2482). A paper copy of this protocol will be sent to you. Please note that the sponsor (Roche) is planning to submit the NDA on 8/30/02.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ E-MAIL ■ HAND
ATURE OF RECEIVER	SIGNATURE OF DELIVERER

hand delivered 5/31/02
dfs 6/6/02

HFD-540 Trac No:0210534
Document ID: Consult 340

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 25, 2002

FROM: Phyllis A. Huene, M.D.
Medical Officer
Division of Dermatologic and Dental Drug Products
(HFD-540)

THROUGH: Markham Luke, M.D.
Team leader, Dermatology
Division of Dermatologic and Dental Drug Products
(HFD-540)

THROUGH: Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
(HFD-540)

TO: Karen Young, Project Manager
Division of Anti-Viral Drug Products
(HFD-530)

SUBJECT: IND ———

Date of request: 5/31/02

This consult is in regard to IND ——— for the drug T-20, which is to be used for the treatment of HIV infection by subcutaneous injection. The Division of Anti-Viral Drug Products has requested that we evaluate Protocol T-20-306, entitled 'A Clinical, Histological and Histochemical Examination of Injection Site Reactions after SQ Injections of T-20 during Treatment of HIV-1 Infection' for the appropriateness of the planned assessments in order to characterize the dermatopathologic responses to T-20 subcutaneous injections.

Background

During the Phase 2 and 3 trials on T-20, the most common adverse event has been injection site reactions (ISRs), which include pain/discomfort, induration, erythema, and pruritus. Most are mild to moderate in severity, and only 5% or fewer of patients have discontinued therapy because of these reactions.

The sponsor's statement of the rationale for the study is as follows: Before accurate recommendations can be given to treat or avoid ISRs, a better understanding of how they develop is necessary, and without this more detailed information, it is difficult to recommend accurate palliative or therapeutic measures to treat ISRs and maximize the compliance of T-20 administration. Protocol T-20-306 is designed to evaluate various aspects of T-20 ISRs by assessments in up to 20 patients on T-20. Clinical signs and symptoms of ISRs are to be closely monitored and photographed, and punch biopsies will be taken during the ISR clinical course for routine H/E staining and immunohistochemical identification of inflammatory cells, immunomodulators, and cytokines.

Protocol T-20-306

In Phase 2 and 3 trials, T-20 has been administered as a 100 mg/ml formulation at a dose of 90 mg, subcutaneously twice daily. This study is to determine whether the ISRs observed with the current formulation are related to the vehicle or to the total volume of each injection. In one part of the protocol patients will receive vehicle injections as well as the standard dose of T-20 twice daily. Another group of patients will receive two 45 mg doses of a 50 mg/mL formulation and another 90 mg dose, for the same overall daily dose.

On specific study days the patients will come to the clinic and self inject T-20 in the abdomen, and be followed for the appearance of an ISR. An ISR will be defined initially as the presence of erythema and possibly other signs, which persist for at least 30 minutes after injection. A clinical description will be recorded and photographs will be taken at specified times during the course of the ISR. Pain/discomfort, pruritus, the average size of nodules and cysts, and of areas of erythema, induration and ecchymoses, and the duration of individual lesions will be graded on scales of from 0 to 4. Punch biopsies will be taken for histological and immunohistochemical evaluation. This will include H & E, Giemsa and Lieder stains, and immunohistochemistry markers for inflammatory cells and immunomodulators.

Reviewer's evaluation: The clinical assessments appear to be appropriate to evaluate the clinical features and severity of injection site reactions, and their relationship to the vehicle formulation and to dosage per injection. Questions in regard to the dermatopathological assessments would need to be referred to a specialist in dermatopathological research.

Phyllis A. Huene, M.D.

Cc: HFD-540/Wilkin
HFD-540/Luke
HFD-540/Huene
HFD-540/Kozmafornaro

consult.340

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Phyllis Huene
7/1/02 01:14:48 PM
MEDICAL OFFICER

Markham Luke
7/1/02 05:15:55 PM
MEDICAL OFFICER

Jonathan Wilkin
7/7/02 05:53:47 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):
Jammie Beam, DMETS
HFD-420, (Rm. 6-34, PKLN Bldg.)

FROM: Virginia L. Yoerg, Regulatory Health Project Manager
Division of Antiviral Drug Products, HFD-530

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
October 21, 2002	—	21-481	Volume 214 Desk copy of proposed labeling	September 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Fuzeon™ (enfuvirtide) for injection	Priority Review	Treatment of HIV	January 15, 2003

NAME OF FIRM: Hoffman- La Roche, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

This tradename was reviewed by Alina Mahmud, RPh., finalized September 28, 2001 (OPDRA consult # 00-0303). OPDRA did not object to the tradename, Fuzeon, at that time. The NDA was submitted September 16, 2002, and DAVDP would appreciate a tradename re-evaluation by January 15, 2003.

PDUFA DATE: March 16, 2003, Internal Action Date: February 5, 2003.
ATTACHMENTS: Draft Package Insert, Container and Carton Labels (one volume desk copy).

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ■ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Virginia Yoerg
10/21/02 05:06:12 PM

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: October 4, 2002	**DUE DATE:** February 14, 2003	**ODS CONSULT #:** 02-0303-1

TO: Debra B. Birnkrant, MD
Director, Division of Anti-Viral Drug Products
HFD-530

THROUGH: Virginia Yoerg
Project Manager
HFD-530

PRODUCT NAME:	**NDA SPONSOR:**
Fuzeon (Enfuvirtide) for Injection 108 mg/vial **NDA: 21-481**	Hoffmann-La Roche Inc.

SAFETY EVALUATOR: Kevin Dermanoski, RPh

SUMMARY:
n response to a consult from the Division of Anti-Viral Drug Products (HFD-530), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name Fuzeon, to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:
DMETS has no objection to the use of the proprietary name Fuzeon.

DMETS recommends the label and labeling revisions outlined in Section III.

DDMAC finds the proprietary name acceptable from a promotional perspective.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: 301-827-3242 Fax: 301-443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Room 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 5, 2003

NDA: 21-481

NAME OF DRUG: Fuzeon
(Enfuvirtide) for Injection
108 mg/vial

NDA HOLDER: Hoffmann-La Roche Inc.

I. INTRODUCTION:

This review is in response to a request from the Division of Anti-Viral Drug Products (HFD-530), to review the proprietary name Fuzeon, regarding potential name confusion with other proprietary and established drug names. Fuzeon was found acceptable by DMETS in consult 00-0303, dated September 18, 2001. Since that review, DMETS identified two additional names with potential to cause sound-alike or look-alike confusion with Fuzeon. In addition, the container labels, carton and insert labeling, including the information packet for patients, were reviewed for possible interventions to minimize medication errors.

PRODUCT INFORMATION

Fuzeon is the proposed proprietary name for Enfuvirtide, Subcutaneous Injection. Fuzeon, in combination with other antiviral drugs, is used to treat HIV infected patients. Fuzeon is pharmacologically different from currently marketed HIV antiviral drugs. Current HIV anti-viral drugs begin to act after the HIV virus particle binds with and enters its target host cell. Fuzeon is the first drug under NDA review that acts by blocking the virus from binding (fusing) with its host cell. Drugs with this pharmacologic mechanism are called "fusion inhibitors."

Fuzeon will be available for patient self-injection in home settings. Fuzeon will be packaged in a "Monthly Convenience Kit" that contains a 30-day supply of the drug and items needed for drug administration. Specifically, the kit will contain 60 vials of Fuzeon (108 mg/vial), 60 vials of Sterile Water for Injection (1.1 mL as diluent), 60 syringes (3 mL for drug reconstitution), 60 syringes (1 mL for drug administration), and 200 alcohol swabs.

RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to "Fuzeon" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

The standard DMETS prescription analysis studies were not repeated for this review cycle.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Fuzeon. Potential concern regarding drug marketing and promotion related to the proposed name was also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified two proprietary names with look-alike and/or sound-alike similarities to Fuzeon that were not identified in the first DMETS' review. The primary concerns raised were related to one look-alike name, Serzone, and one sound-alike name, Vumon. These products are listed in Table I (see page 4) along with the dosage forms available and usual dosage.

2. DDMAC did not have concerns about the name "Fuzeon" with regard to promotional claims.

[1] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.
[4] WWW location http://www.uspto.gov/main/trademarks.htm
[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table I: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual dosage	Other
Fuzeon	(Enfuvirtide) for Injection, 90 mg/mL	90 mg twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen.	
Serzone	(Nefazodone Hydrochloride) Tablets 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg	Starting dose: 100 mg twice daily. Maintenance dose: 150 mg to 300 mg twice daily.	L/A
Vumon	(Teniposide) for Injection, 5 mg/mL	165 mg/m^2 given intravenously over at least 30 to 60 minutes once or twice weekly.	S/A

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Fuzeon, the primary concerns raised were related to one look-alike name, Serzone, and one sound-alike name, Vumon.

Serzone and Fuzeon may share look-alike similarities. Serzone (Nefazodone) is an antidepressant for oral administration. Each name is of similar length (6 and 7 letters). Both names end in letters ("zone" and "zeon") that look similar when scripted (see below). Serzone and Fuzeon also share the same dosing interval (twice daily). However, multiple product differences reduce the potential for medication errors due to name confusion. Serzone is available in five strengths (50 mg, 100 mg, 150 mg, 200 mg, and 250 mg) none of which overlap with the single available Fuzeon strength and recommended dosage of 90 mg, thus reducing the potential for name confusion. Additionally, the products differ in dosage form and route of administration (oral tablet vs. subcutaneous injection), and in available packaging (bottles vs. "Monthly Convenience Kit."). These product differences reduce the potential for medication errors due to name confusion between Serzone and Fuzeon.

Serzone

Fuzeon

Vumon and Fuzeon share potential sound-alike similarities. Vumon (Teniposide) is an orphan-drug used as induction therapy, in combination with other anticancer agents, in patients with refractory childhood acute lymphoblastic leukemia. The names' initial sounds ("Vu" and "Fu") may sound-alike depending on pronunciation, and both names end with the letters "on". However, Vumon and Fuzeon differ in number of syllables (2 vs. 3) and the "ze" in Fuzeon has a distinct phonetic sound that distinguishes the two names. Vumon and Fuzeon have different dosing intervals (1-2 times weekly vs. 2 times daily). Additionally, Vumon is used in a limited pediatric population. Overall, the product differences and differences in the pronunciation of the two names, particularly the 2nd syllables, minimize the potential for medication errors due to name confusion.

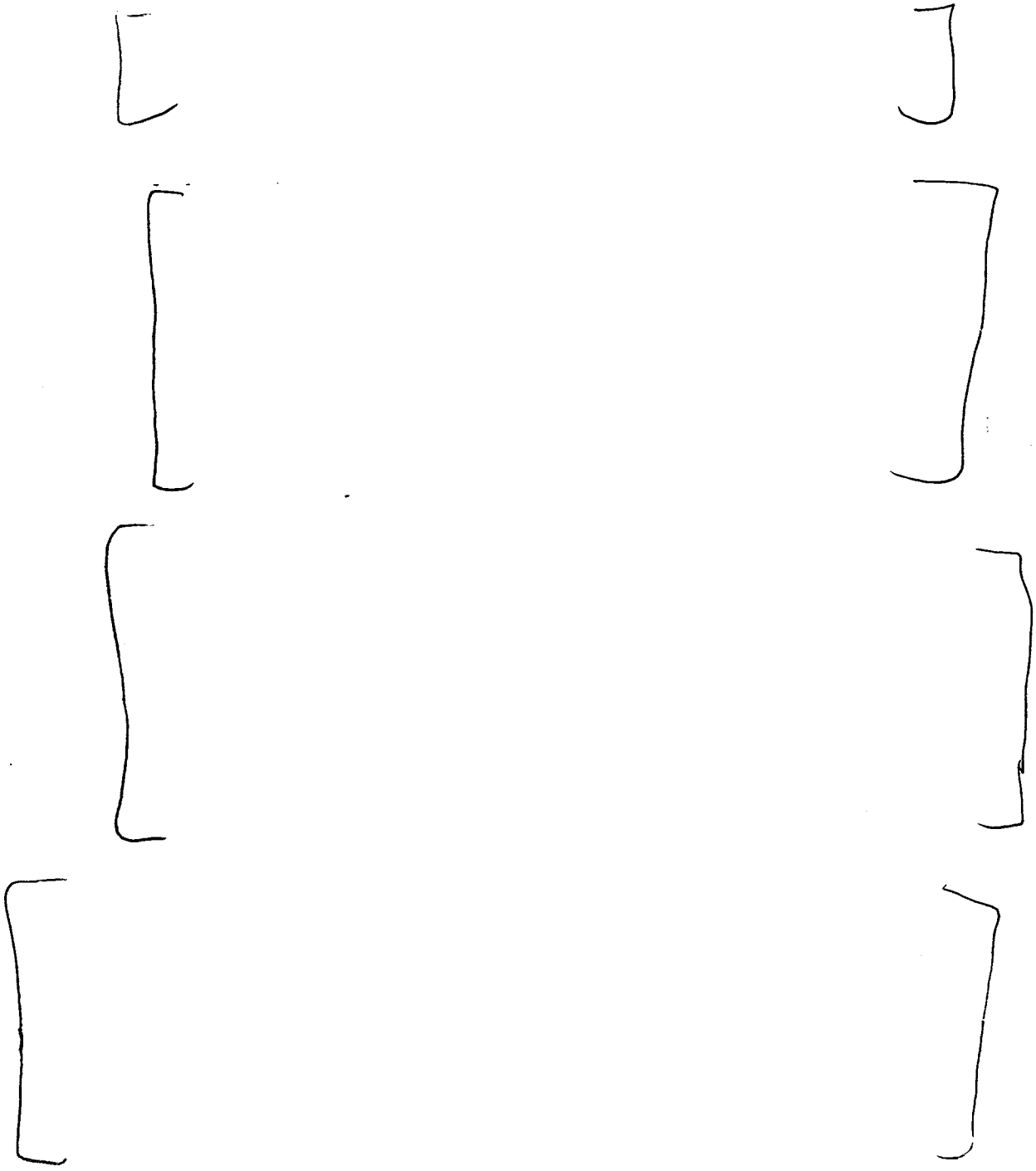
II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the Fuzeon container labels, carton and insert labeling, Fuzeon Injection Instructions, Your Guide to Taking Fuzeon flipchart, Fuzeon Preparation Mat, and the Fuzeon Planner, DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

[redacted]

[redacted]



APPEARS THIS WAY
ON ORIGINAL

V. RECOMMENDATIONS:

A. DMETS has no objections to the use of the name Fuzeon.

B. DMETS recommends the label and labeling revisions outlined in Section III.

C. DDMAC finds the proprietary name acceptable from a promotional perspective.

DMETS' comments on the patient information materials will be forwarded in a joint review from the Division of Surveillance, Research, and Communication Support.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Kevin Dermanoski, RPh Date
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Denise P. Toyer, PharmD Date
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kevin Dermanoski
2/14/03 03:23:16 PM
PHARMACIST

Denise Toyer
2/14/03 03:29:54 PM
PHARMACIST

Carol Holquist
2/14/03 03:45:24 PM
PHARMACIST

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 24, 2003

TO: Debra Birnkrant, M.D., Director
Division of Antiviral Drug Products
HFD-530

VIA: Virginia Yoerg, Regulatory Health Project Manager
Division of Antiviral Drug Products
HFD-530

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
(DSRCS) HFD-410

Jerry Phillips, R.Ph., Director
Division of Medication Errors and Technical Support
(DMETS) HFD-420

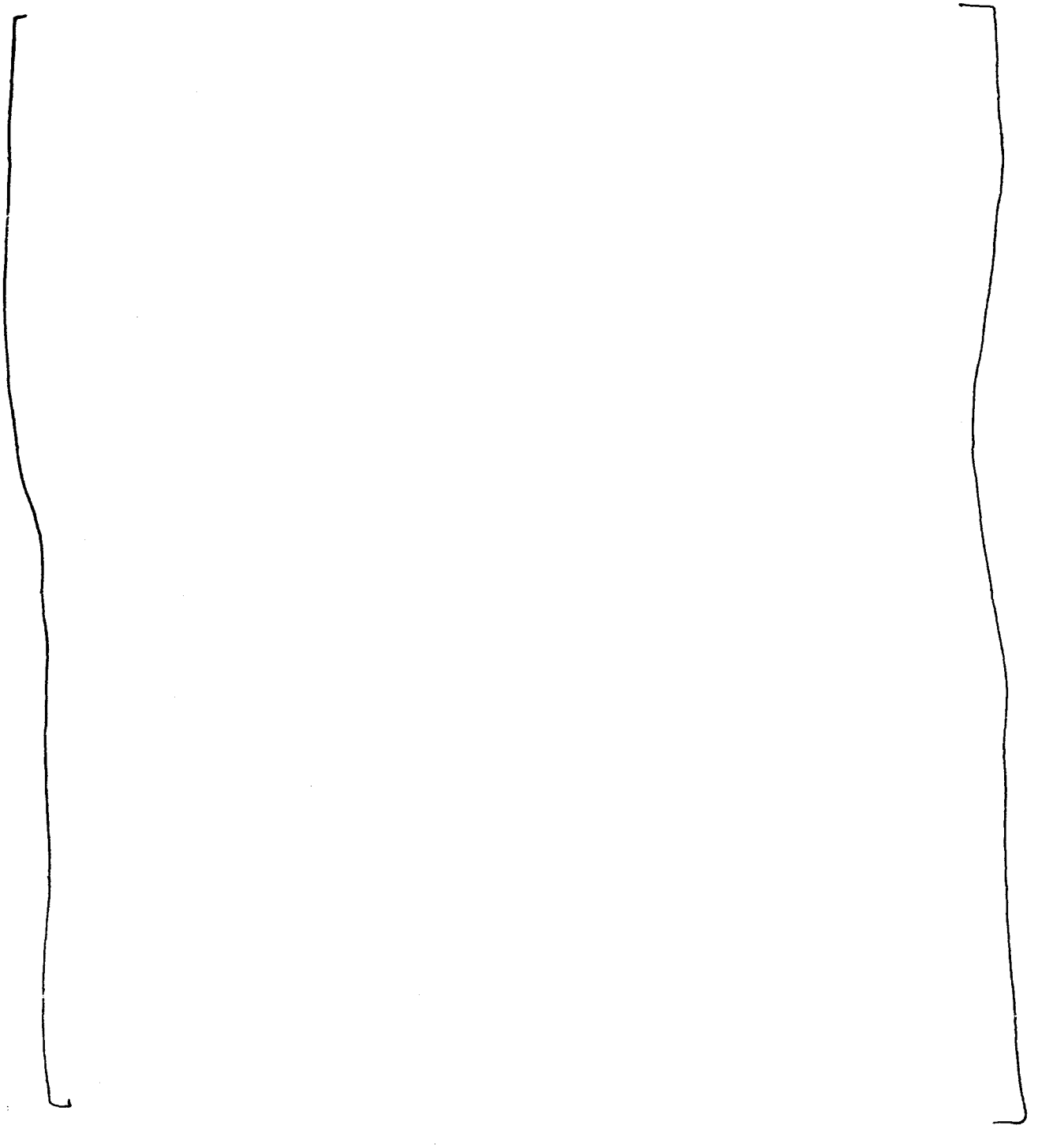
SUBJECT: ODS/DSRCS and DMETS Review of Patient Materials for
Fuzeon™ (enfuvirtide), NDA 21-481

The Office of Drug Safety (DSRCS and DMETS) conducted a review of the patient materials for Fuzeon™ (enfuvirtide), NDA 21-481, for the Division of Anti-Viral Drug Products (HFD-530). DSRCS reviews patient materials from a risk communication perspective and DMETS reviews patient materials from a medication error perspective.

Patient Information **(PPI)**

The attached patient labeling (clean copy) represents part of the revised risk communication materials for Fuzeon. It has been reviewed by our Office and by DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are

recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. Comments to the review division are bolded, underlined and italicized. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.



WITHHOLD 14 PAGE (S)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jeanine Best
2/24/03 09:16:35 AM
CSO

Jerry Phillips
2/24/03 10:05:01 AM
DIRECTOR

Toni Piazza Hepp
2/24/03 03:21:35 PM
PHARMACIST
for Anne Trontell

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION	OFFICE OF DRUG SAFETY DIVISION OF DRUG RISK EVALUATION (DDRE)	
TO: Melissa Baylor, MD **HFD-530**	**FROM: Allen Brinker, MD, MS** **HFD-430**	**ODS PID#** **D030130**
DATE OF CONSULT: Feb 28, 2003	**REQUESTOR: Melissa Baylor, MD**	
DATE COMPLETED: March 4, 2003		
DRUG (Gen): enfuviritide	**NDA # 21-481 (Hoffman-La Roche [HLR])**	
DRUG NAME (Trade): Fuzeon	**INDICATION: treatment of HIV infection**	
ISSUE / EVENT: Review of an observational cohort study outline		

SUMMARY OF FINDINGS: A one (1) page study outline entitled "Proposed postmarketing observational cohort study" submitted by HLR was reviewed. The objective of the study is to estimate the incidence of bacterial pneumonia in HIV-infected patients treated with Fuzeon in comparison with HIV-infected individuals receiving standard therapy. The study outline states that 3 Fuzeon patients will be selected from each participating practice setting, along with 4 control patients matched on CD4 cell count and previous history of pulmonary conditions. Additional information to be collected and used in modeling includes smoking status and IV drug use. The study outline includes a sample size of 684 Fuzeon patients and 2,736 control patients. The diagnostic criteria for "pneumonia," a primary study endpoint, is not included in the outline except that it is to be "defined more specifically in the study protocol."

COMMENT: The data supplied with the study outline indicate that the relative risk for pneumonia for HIV-infected patients on Fuzeon in comparison to a control group of HIV-infected patients on "optimized background" therapy was 7.7, based on a comparison of 30 Fuzeon patients with the event (4.7 per 100 pt-yrs) to 1 control patient (0.6 patients per 100 pt-yrs). Based on these rates, an alpha of 0.05, power of 0.8, and a 1:4 exposed:unexposed ratio, we calculate a required sample size of 400 to 600 Fuzeon-exposed patients and ~2,400 control patients to evaluate a relative risk of ~7. This is consistent with the sample size outlined by the sponsor. However, as approved labeling will no doubt highlight the risk for pneumonia in association with Fuzeon, clinicians may consciously (or unconsciously) channel only selected patients for Fuzeon therapy, based on perceived risk for pneumonia. This "channeling" of low risk patients to Fuzeon will decrease any observed relative risk estimate for pneumonia. As it is very difficult to fully adjust for "channeling" or "selection" biases, the point estimate derived from this study should not be looked upon as superior to that reported in clinical trials. It is further noted that pneumonia, the primary endpoint of interest, is yet to be defined. As pneumonia can be a very difficult clinical entity to diagnosis or to exclude, especially in individuals with concurrent lung pathology, we strongly recommend predefined and very specific criteria for diagnosis. Misclassification of endpoint / outcome between study arms also decreases the magnitude of any potential differences between arms, thus permitting another opportunity to degrade the relative risk estimate derived from the clinical trials.

I. BEITZ SIGNATURE / DATE:	A. BRINKER SIGNATURE / DATE:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Allen Brinker
3/6/03 03:21:06 PM
MEDICAL OFFICER

Julie Beitz
3/7/03 04:09:49 PM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

IND ——

Trimeris
Attention: Sam Hopkins, Ph.D.
Vice President of Medical Affairs
4727 University Drive
Durham, NC 27707

Dear Dr. Hopkins:

Reference is made to your Investigational New Drug application for T-20, and to your November 19, 1998, request for Fast Track designation for use of T-20 for the treatment of HIV infection submitted under Section 506 of the Federal Food, Drug, and Cosmetic Act.

We have reviewed your request and concluded that the data provided in the November 19, 1998, submission supports Fast Track designation. Therefore, we are designating T-20 for the treatment of HIV infection as a Fast Track product.

Please be advised that if you pursue a clinical development program that does not support use of T-20 for the treatment of HIV infection, the application will not be reviewed under the Fast Track program.

If you have any questions, please contact Ms. Christine Kelly, M.S., MBA, RN, Regulatory Health Manager, at (301) 827-2335.

Sincerely yours,

Heidi M. Jolson, M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Concurrence:

HFD-530/MO/Toerner
HFD-530/MTL/Murray
HFD-530/SCSO/DeCicco
HFD-530/DD/Birnkrant

cc:
IND
Division file
HFD-530/Jolson
HFD-530/Murray
HFD-530/Toerner
HFD-530/Kelly

Letter Granting Fast Track Designation

Drive: v\Kelly\IND\ ———fasttrack

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND ———

Hoffmann-La Roche Inc.
Attention: Robin Conrad
340 Kingsland Street
Nutley, New Jersey 07110

Dear Ms Conrad:

Reference is made to your investigational new drug application for T-20 (Ro 29-9800) for the treatment of HIV infection. We also refer to your proposed pediatric study request dated December 6, 2000, received December 7, 2000.

Please note that this Written Request supercedes the Written Request dated January 9, 2001.

To obtain needed pediatric information on T-20, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

Type of studies:
Multiple-dose pharmacokinetic, safety, and activity study of T-20 in combination with other antiretroviral agents in HIV-infected pediatric patients.

Multiple-dose pharmacokinetics and safety study of T-20 in HIV-exposed neonates (born to HIV-infected mothers).

Indication(s) to be studied:
Treatment of HIV infection

Age group in which studies will be performed:
HIV-infected pediatric patients from 1 month to adolescence and HIV-exposed neonates (born to HIV-infected mothers).

Drug information:
Dosage form: injectable
Route of administration: subcutaneous
Regimen: to be determined by development program

Drug specific safety concerns:
Injection site reactions and hypersensitivity reactions.

Statistical information, including power of study and statistical assessments:
Descriptive analyses of multiple-dose pharmacokinetic, safety, and activity data in HIV-infected pediatric patients.

Descriptive analyses of multiple-dose pharmacokinetic and safety data in HIV-exposed neonates (born to HIV-infected mothers).

Studies should include an adequate number of patients to characterize pharmacokinetics over the age range studied, taking into account inter-subject and intra-subject variability. The number of patients should be uniformly distributed across the age range studied.

Study Endpoints:
Pharmacokinetics
Parameters such as C_{max}, C_{min}, T_{max}, $t_{1/2}$, AUC.

Safety and tolerability
HIV-infected pediatric patients should be followed for safety for a minimum of six months at the recommended dose. HIV-exposed neonates (born to HIV-infected mothers) should have safety assessments, on or off treatment (as appropriate), for a minimum of six months from the initiation of therapy. In addition, please submit plans for long-term safety monitoring in HIV-exposed neonates (born to HIV-infected mothers) and HIV-infected pediatric patients who have received T-20.

Activity
Assessment of changes in plasma HIV RNA levels and CD4 cell counts.

Labeling that may result from the study (ies):
Information regarding dosing and safety in HIV-infected pediatric patients and information regarding dosing and safety in HIV-exposed neonates (born to HIV-infected mothers).

Format of reports to be submitted:
Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. Please include other information as appropriate.

Timeframe for submitting reports of the studies:
Reports of the above studies must be submitted to the Agency on or before December 31, 2004. Please remember that pediatric exclusivity extends only existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission

"**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as **a new drug application or as a supplement to an approved NDA** with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, contact Ms. Melissa M. Truffa, R.Ph., Regulatory Project Manager, at 301-827-2335.

Sincerely yours,

M. Dianne Murphy, M.D.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

/s/

Dianne Murphy
1/19/01 11:49:15 AM

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: May 22, 2001

To: Robin Conrad	**From:** Melissa M. Truffa
Company: Hoffmann-La Roche	Division of Antiviral Drug Products
Fax number: 973-562-3700	**Fax number:** 301-827-2471
Phone number: 973-562-3676	**Phone number:** 301-827-2335

Subject: Carcinogenicity waiver

Total no. of pages including cover:

Comments: Please see the attached comments. If you have any questions, let me know. Thanks,

Melissa

Document to be mailed: ☐ YES ☑ NO

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: May 22, 2001

To: Robin Conrad
Hoffmann-La Roche Inc.

From: Melissa M. Truffa, R.Ph., DAVDP

Through: William Taylor, Ph.D., Pharmacology/Toxicology Reviewer 5-22-01
James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader 5-22-01

IND: [redacted]

Drug: T-20

Subject: Request for a waiver of carcinogenicity studies dated September 7, 2000 (SN081).

Comment:

- We agree to grant you a waiver from conducting carcinogenic studies with T-20.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Melissa Truffa
5/22/01 11:13:12 AM
CSO

Therese Cvetkovich
5/24/01 01:06:14 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

IND ——

Hoffmann-La Roche Inc.
Attention: Robin Conrad
340 Kingsland Street
Nutley, New Jersey 07110

Dear Ms. Conrad:

Please refer to the Written Request, issued on January 19, 2001, that you received from the Center for Drug Evaluation and Research. This Written Request was issued under Section 505A of the Federal Food, Drug, and Cosmetic Act to conduct pediatric studies using T-20 (Ro 29-9800). As you know, on January 4, 2002, the President signed into law the "Best Pharmaceuticals for Children Act," (BPCA) which both extended the pediatric exclusivity program established in the 1997 FDA Modernization Act (FDAMA) and provided new mechanisms for studying pediatric uses for drugs. The BPCA also contains new provisions of which you should be aware related to user fees, priority review, drug labeling, and disclosure of pediatric study results. FDA is revising its Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act to provide additional information on the pediatric drugs study provisions of the BPCA.

FDA has received questions about whether sponsors who were issued Written Requests to conduct pediatric studies prior to passage of the BPCA, but who had not as yet submitted the reports of the studies as of January 4, 2002, would be governed by the provisions of FDAMA or the BPCA. In order to maximize the benefit to be derived from the BPCA and to minimize uncertainty and delay in implementing the pediatric exclusivity program, FDA has decided to reissue those Written Requests originally issued prior to passage of the BPCA for which studies have not already been submitted.

This letter is your notification that the Written Request (and any subsequent amendments) described above is considered to be reissued as of the date of this letter. The terms of the Written Request are not otherwise altered by this letter. If you believe that the Written Request should be amended, please contact the division directly.

Please note that if the original Written Request was issued under Section 505A(a), it will now be considered to be issued under Section 505A(b), due to the reordering of the sections, as described in Section 19 of the BPCA. If the original Written Request was issued under Section 505A(c), it will still be considered to be issued under Section 505A(c).

An important change to note is that, if the drug for which FDA issued the Written Request under 505A(c) has listed patent or exclusivity protection, new section 505(d)(4)(A) states that within 180 days of receipt of this "reissued" Written Request, you must notify FDA when the pediatric studies will be initiated, or that you do not agree to conduct the requested studies. New provisions at Section 505(d)(4)(B)-(F) describe alternative methods for obtaining these pediatric studies.

If you have questions regarding the BPCA, please contact the Division of Pediatric Drug Development at (301) 594-7337. As noted above, requests to amend your Written Request should be directed to the review division.

Sincerely,

{See appended electronic signature page}

M. Dianne Murphy, M.D.
Director
Office of Counter-terrorism and Pediatric Drug Development
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dianne Murphy
7/3/02 12:03:01 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: August 14, 2002

To: Robin Conrad, Program Director
Drug Regulatory Affairs
Hoffman-La Roche, Inc.

From: Virginia L. Yoerg, Regulatory Health Project Manager, HFD-530

Through: Melisse Baylor, M.D., Medical Officer, HFD-530
Russell Fleischer, PA-C, M.P.H., Acting Medical Team Leader, HFD-530

IND: ———

Drug: T-20/Ro 29-9800 Subcutaneous Injection

Subject: Clinical comments regarding SN374

The following comments are being conveyed on behalf of Melisse Baylor, M.D., and are directed toward your July 30, 2002 submission, which included Protocol MV16812: *"Multicenter, Open-Label, Early Access Program of Enfuvirtide (T-20/Ro 29-9800, HIV-1 fusion inhibitor) in Combination with Free Choice Antiretroviral Regimen in Patients with Advanced HIV-Infection."* The submission also included a request for a waiver of the requirement for a local Institutional Review Board (IRB) for this protocol.

1. Please consider using the patient education materials currently under development to teach self-injection of T-20 to study subjects in the early access program and to obtain preliminary information about the usefulness of these teaching materials.

2. All adolescents who receive both T-20 and tenofovir should be at least Tanner Stage 5 and weigh at least 50 kg.

3. Please explain why the grading scales for individual signs and symptoms of injection site reactions will not be used in this study.

4. Please explain how the information collected in the patient and coordinator journals will be used in study analysis.

5. The section of the informed consent that deals with adverse events related to T-20 is too detailed and should be edited so that the most common adverse events related to the use of T-20 can be recognized by study subjects.

6. Based on review of 21 CFR parts 56.103 to 56.105, we have decided that your request for a waiver of the requirement for local IRB approval is not justified. Specifically, a central IRB should not supercede a local IRB and should provide primary oversight only when there is no local IRB; in this instance there should be multiple local IRBs available for protocol review.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Virginia L. Yoerg
Regulatory Health Project Manager
Division of Antiviral Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Virginia Yoerg
8/14/02 03:11:50 PM
CSO

Fax sent. Fleischer signed as Acting TL for Gitterman.

Steven Gitterman
8/22/02 08:52:06 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Yoerg, Virginia L

From:
Sent: Friday, September 06, 2002 9:40 AM
To: Robin Conrad {PDR~Nutley} (E-mail); Cynthia Dillon (E-mail)
Cc: Yoerg, Virginia L; Gitterman, Steven; Baylor, Melisse S
Subject: Fuzeon impurities limits acceptable

Robin,

As stated in our voicemail message regarding Fuzeon (enfuvirtide) for HIV, your proposed specified limits for impurities in the production batches for initial marketing are acceptable to the Division.

Regards,

Virginia L. Yoerg
Regulatory Health Project Manager
FDA/DAVDP

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

faxed 7/22 dfs

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: July 18, 2002

To: Cynthia Dillion, Program Director
Drug Regulatory Affairs
Hoffman-La Roche, Inc.

From: Karen Young, RN, BSN, Regulatory Project Manager

Through: Rao Kambhampati, Ph.D., Chemist [/S/] 7/18/02
Stephen P. Miller, Ph.D., Chemistry Team Leader [/S/] 7/18/02
Melisse S. Baylor, M.D., Medical Officer [/S/] 7/19/02
Steven Gitterman, M.D., Ph.D., Medical Team Leader [/S/] 7/19/02

NDA: 21-481

Drug: T-20/RO 29-9800 Subcutaneous Injection

Subject: Draft Labeling and Proposed Expiry: Sterile Water for Injection (SWFI)

The following comments are being conveyed on behalf of the chemistry review team and are in reference to your amendment dated June 26, 2002.

The proposed vial and carton labels for Sterile Water for Injection (SWFI) and a 36-month expiration period for SWFI are acceptable, however, the final determination will be made after a complete review of the chemistry, manufacturing, and controls (CMC) information in _____ DMF# _____. If you choose to produce labeled vials prior to approval of NDA 21-481, please understand that you do so at your own risk. While the division would work with you to resolve concerns which might arise, it is possible that concerns identified prior to approval could prevent marketing of the labeled vials of SWFI.

If you have any questions, please call Karen A. Young, Regulatory Project Manager at (301) 827-2376.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Young
7/22/02 03:49:35 PM
CSO

Stephen Paul Miller
7/23/02 10:32:35 AM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-481

Hoffman-La Roche, Inc.
Attention: Robin Conrad
Program Director, Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Conrad:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Fuzeon™ (enfuvirtide) for injection, 90 mg

Review Priority Classification: Priority (P)

Date of Application: September 13, 2002

Date of Receipt: September 16, 2002

Our Reference Number: NDA 21-481

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 30, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 16, 2003.

We have determined that this application will be reviewed under 21 CFR 314 Subpart H (accelerated approval). We remind you that as required under 21 CFR 314.550, unless otherwise informed by the Agency, you must submit for Agency review before approval of this application copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days after marketing approval.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). In this NDA, you requested a deferral of pediatric studies for ages birth to 6 months until June, 2006 and a deferral for infants from 6 to 36 months until June, 2004. You also stated that you did not request a deferral for ages through 16 because data on patients in this age

group was included in the NDA, and studies are ongoing in this patient group.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. Please note that a Written Request was issued on January 19, 2001, and your deadline to submit the reports of pediatric studies to the Agency is December 31, 2004.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room, N115
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room N115
9201 Corporate Boulevard
Rockville, Maryland 20850-3202

If you have any questions, call Virginia L. Yoerg, Regulatory Health Project Manager, at 301 827 2335.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Debra Birnkrant
10/8/02 01:51:06 PM
NDA 21-481

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 5, 2002

To: Robin Conrad, Program Director
Drug Regulatory Affairs
Hoffman-La Roche, Inc.

From: Nitin Patel, R.Ph., Regulatory Project Manager, HFD-530

Through: William H. Taylor, Ph.D., Pharmacologist, HFD-530 /S/ 11/5/02
James G. Farrelly, Ph.D., Pharmacology Team Leader, HFD-530 /S/ 11/5/02
Melisse Baylor, M.D., Medical Officer, HFD-530
Steven Gitterman, M.D., Medical Team Leader, HFD-530 /S/ 11/5/02

NDA: 21-481

Drug: Fuzeon (enfuvirtide) for Injection

Subject: Pharmacology/Toxicology requests concerning study TMS 005/002348/SS

The following Pharmacology/Toxicology requests concerning study TMS 005/002348/SS (NDA 21-481 Reference 3601, Volume 35) are being conveyed to you on behalf of the review team:

1. Please confirm or clarify that the doses given by injection to Groups 2 and 4 as depicted in Figure 1 on page 140 (study page 18) under

   "Test animals (Groups 2 and 4)
   (2) 0.1 ml of T-20, 100 mg/ml in sterile water"

   means that the test animals were administered nominally, 100 mg T-20 in sterile water AND buffer solution-carbonate or Tris-as depicted in the table, page 132 (study page 10).

2. The report (pages 134-135) never actually states that T-20 in the buffer solutions are administered to the animals. Please clarify what solutions are administered to the animals by injection and dermally at the induction and challenge phases.

We are providing this information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Nitin Patel, R.Ph. for Virginia L. Yoerg
Regulatory Health Project Manager
Division of Antiviral Drug Products

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Nitin Patel
11/6/02 09:40:27 AM
CSO
NDA 21-481 Pharmacology/Toxicology requests concerning study TMS 005/002348 copy sign-off by Steven Gitterman - 11/5/02.
NDA 21-481 Pharmacology/Toxicology requests concerning study TMS 005/002348 copy sign-off by Steven Gitterman - 11/5/02.

Steven Gitterman
11/7/02 01:16:40 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 8, 2002

To: Robin Conrad, Program Director
Drug Regulatory Affairs
Hoffman-La Roche, Inc.

From: Virginia L. Yoerg, Regulatory Health Project Manager, HFD-530

Through: Tom Hammerstom, Ph.D., Statistics Reviewer, HFD-530
Greg Soon, Ph.D., Statistics Team Leader, HFD-530
Melisse Baylor, M.D., Medical Officer, HFD-530
Steven Gitterman, M.D., Medical Team Leader, HFD-530

NDA: 21-481

Drug: Fuzeon (enfuvirtide) for Injection

Subject: Statistical comments regarding T20-301 and T20-302

The following comments are being conveyed on behalf of Tom Hammerstrom, Ph.D., regarding your statistical analyses for protocols T20-301/NV16504 and T20-302/BV16052.

- We have calculated the percent with sustained viral suppression on assigned therapy using the standard algorithm and note that the results that you submitted with this application are incorrect. We have attached the correct numbers representing the patients who sustained viral suppression (see accompanying pages).

We look forward to discussing this issue with you during our November 15, 2002 teleconference. Please contact us if you need to reschedule the teleconference.

We are providing this information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Virginia L. Yoerg
Regulatory Health Project Manager
Division of Antiviral Drug Products

The data in Figures 2 and 3 and accompanying tables and text are not correct. In trial 302, the percent with confirmed viral load below 50 copies/mL at week 24 are 15/170 on OB and 68/337 on T-20.

The subjects with confirmed viral suppression without new drugs are:

TRT=OB

1061, 1135, 1137, 2062, 3273, 3470, 4333, 4376, 5064, 5189, 6031, 7065, 7093, 7158, 7277

TRT=T-20

1032, 1035, 1091, 1092, 1093, 1152, 1153, 1183, 1184, 1188, 1190, 1235, 2064, 2155, 2236, 2281, 2283, 3062, 3275, 3276, 3281, 3282, 3477, 4031, 4065, 4080, 4085, 4093, 4098, 4185, 4274, 4331, 4332, 4335, 4377, 4432, 5063, 5065, 5066, 5095, 5122, 5136, 5152, 5181, 5182, 5186, 5211, 6033, 6064, 6092, 6093, 6121, 6123, 6127, 6138, 6159, 6213, 6365, 6431, 7017, 7032, 7151, 7154, 7161, 7181, 7183, 7212, 7273

In trial 302, the percent with confirmed viral load below 400 copies/mL at week 24 are 23/170 on OB and 113/337 on T-20.

The subjects with confirmed viral suppression without new drugs are:

TRT=OB

1061, 1135, 1137, 1234, 2062, 3273, 3470, 4071, 4272, 4273, 4333, 4376, 5034, 5064, 5189, 6031, 6135, 6162, 6331, 7065, 7093, 7158, 7277

TRT=T-20

1032, 1035, 1091, 1092, 1093, 1129, 1151, 1152, 1153, 1154, 1183, 1184, 1188, 1190, 1232, 1235, 2041, 2042, 2064, 2066, 2153, 2155, 2236, 2238, 2281, 2282, 2283, 3031, 3062, 3100, 3182, 3189, 3275, 3276, 3281, 3282, 3465, 3472, 3474, 3477, 4031, 4062, 4065, 4069, 4077, 4078, 4080, 4085, 4093, 4097, 4185, 4274, 4331, 4332, 4335, 4375, 4377, 4378, 4432, 4437, 4443, 5035, 5061, 5063, 5065, 5066, 5095, 5122, 5127, 5136, 5152, 5181, 5182, 5186, 5211, 5212, 6033, 6064, 6092, 6093, 6121, 6123, 6127, 6133, 6137, 6138, 6155, 6159, 6213, 6247, 6362, 6365, 6431, 6439, 7008, 7017, 7031, 7032, 7128, 7151, 7153, 7154, 7155, 7161, 7181, 7182, 7183, 7212, 7214, 7273, 7278, 7280, 8031

In trial 301, the percent with confirmed viral load below 50 copies/mL at week 24 are 20/167 on OB and 101/338 on T-20.

The subjects with confirmed viral suppression without new drugs are:

TRT=OB

1081, 1101, 1141, 1185, 1225, 1296, 1422, 1434, 1445, 1564, 1589, 1592, 1622, 1632, 1764, 1766, 1886, 1931, 1944, 1946

TRT=T-20

1003, 1006, 1007, 1044, 1045, 1046, 1063, 1064, 1084, 1089, 1090, 1091, 1092, 1110, 1123, 1129, 1131, 1135, 1142, 1144, 1145, 1166, 1168, 1170, 1172, 1175, 1180, 1181, 1182, 1183, 1208, 1209, 1220, 1228, 1242, 1248, 1260, 1261, 1266, 1281, 1286, 1289, 1290, 1295, 1303, 1327, 1330, 1341, 1347, 1361, 1368, 1380, 1391, 1403, 1424, 1427, 1439, 1442, 1443, 1483, 1505, 1507, 1515, 1523, 1580, 1582, 1584, 1588, 1591, 1593, 1594, 1600, 1605, 1623, 1627, 1630, 1634, 1641, 1643, 1644, 1684, 1685, 1700, 1703, 1706, 1723, 1741, 1744, 1748, 1756, 1765, 1780, 1782, 1809, 1825, 1830, 1843, 1870, 1881, 1883, 1920

In trial 301, the percent with confirmed viral load below 400 copies/mL at week 24 are 33/167 on OB and 140/338 on T-20.

The subjects with confirmed viral suppression without new drugs are:

TRT=OB

1048, 1081, 1095, 1101, 1141, 1185, 1210, 1225, 1294, 1296, 1320, 1422, 1434, 1445, 1564, 1581, 1589, 1592, 1622, 1632, 1726, 1764, 1766, 1808, 1823, 1846, 1871, 1886, 1900, 1931, 1942, 1944, 1946

TRT=T-20

1003, 1006, 1007, 1043, 1044, 1045, 1046, 1063, 1064, 1084, 1089, 1090, 1091, 1092, 1102, 1110, 1121, 1122, 1123, 1129, 1132, 1135, 1140, 1142, 1143, 1144, 1145, 1166, 1168, 1170, 1172, 1175, 1180, 1181, 1182, 1183, 1204, 1208, 1209, 1220, 1221, 1227, 1228, 1232, 1242, 1247, 1248, 1260, 1261, 1266, 1281, 1284, 1286, 1289, 1290, 1295, 1303, 1327, 1330, 1341, 1342, 1344, 1347, 1361, 1368, 1380, 1382, 1385, 1390, 1403, 1420, 1423, 1424, 1427, 1432, 1433, 1435, 1439, 1442, 1443, 1449, 1467, 1471, 1483, 1500, 1505, 1507, 1515, 1523, 1580, 1582, 1584, 1588, 1591, 1593, 1594, 1600, 1605, 1621, 1623, 1627, 1630, 1634, 1640, 1641, 1643, 1644, 1684, 1685, 1700, 1703, 1706, 1723, 1730, 1741, 1742, 1743, 1744, 1748, 1756, 1765, 1768, 1780, 1782, 1783, 1786, 1809, 1820, 1825, 1830, 1843, 1870, 1881, 1883, 1885, 1920, 1924, 1928, 1940, 1941

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Virginia Yoerg
11/8/02 01:40:15 PM
CSO

hard copy signed and faxed.

Steven Gitterman
11/16/02 04:28:44 PM
MEDICAL OFFICER