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.

/S/

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

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/s/

Virginia Yoerg
3/18/03 03:56:28 PM
CSO

hard copy signed and faxed to applicant.

Steven Gitterman
3/19/03 03:41:48 PM
MEDICAL OFFICER

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

FACSIMILE TRANSMITTAL SHEET

DATE: March 21, 2003

To: Martine Kraus, Ph.D., Director, Regulatory Affairs	**From:** Virginia L. Yoerg, Regulatory Health Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Drug Products
Fax number: 650-522-5489	**Fax number:** 301-827-2523
Phone number: 650-522-5722	**Phone number:** 301-827-2335

Subject: NDA 21-500
Request for pharmacokinetics information

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES | Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: March 21, 2003

To: Martine Kraus
333 Lakeside Drive
Foster City, CA 94404

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

Through: Steven Gitterman, M.D., Ph.D., Medical Team Leader, HFD-530
Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader, HFD-530
Jennifer DiGiacinto, Pharm.D., Pharmacokinetics Reviewer, HFD-530

NDA: 21-500, emtricitabine capsules

Subject: Request for pharmacokinetics information

After reviewing Study FTC-107 results, there are some issues regarding how emtricitabine would be dosed in patients with varying degrees of renal impairment using the 200-mg capsule. Please respond to the questions below by April 3, 2003.

1. Please provide your rationale for selecting 50 mL/min as your cutoff point for emtricitabine dose reduction from 200-mg daily to 100-mg daily.

2. Please provide your plans for emtricitabine dose adjustments due to decreased renal function, using the 200-mg capsule.

3. Please provide predicted exposure data (AUC, C_{max}, and concentration vs. time profiles) for the recommended dose adjustments due to renal impairment, including data for patients on dialysis.

4. Please provide an explanation for the unusual individual pharmacokinetic data for subjects 103 (221.4 mg excreted) and 104 (unusually low AUC).

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

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/s/

Virginia Yoerg
3/21/03 12:50:05 PM
CSO

hard copy signed and sent to applicant.

Steven Gitterman
3/22/03 09:06:58 AM
MEDICAL OFFICER

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

FACSIMILE TRANSMITTAL SHEET

DATE: March 31, 2003

To: Martine Kraus, Ph.D., Director, Regulatory Affairs	From: Virginia L. Yoerg, Regulatory Health Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Drug Products
Fax number: 650-522-5489	Fax number: 301-827-2523
Phone number: 650-522-5722	Phone number: 301-827-2335
Subject: NDA 21-500 Request for pharmacokinetics information	
Total no. of pages including cover: 2	

Comments:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: March 31, 2003

To: Martine Kraus
333 Lakeside Drive
Foster City, CA 94404

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

Through: Steven Gitterman, M.D., Ph.D., Medical Team Leader, HFD-530
Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader, HFD-530
Jennifer DiGiacinto, Pharm.D., Pharmacokinetics Reviewer, HFD-530

NDA: 21-500, emtricitabine capsules

Subject: Request for pharmacokinetics information

The following comments are provided on behalf of Jennifer DiGiacinto, Pharm.D., regarding your NDA 21-500.

After reviewing the submitted dissolution data for emtricitabine, additional data is needed. Please respond to our request by April 11, 2003.

- Please provide dissolution data (individual run data and dissolution profiles) for all three media (0.1 N HCl, pH 4.5 Acetate Buffer, and pH 6.8 Phosphate Buffer) using the intended to-be marketed emtricitabine formulation.

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

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/s/

Destry Sillivan
3/31/03 04:54:14 PM
CSO

Dr. Gitterman, this is the dissolution data request for ftc

Steven Gitterman
3/31/03 05:03:00 PM
MEDICAL OFFICER

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

FACSIMILE TRANSMITTAL SHEET

DATE: April 14, 2003

To: Peter Karlton, Global Regulatory Affairs, CMC	**From:** Virginia L. Yoerg, Regulatory Health Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Drug Products
Fax number: 650-522-5489	**Fax number:** 301-827-2523
Phone number: 650-522-5722	**Phone number:** 301-827-2335
Subject: NDA 21-500 Request for chemistry information	
Total no. of pages including cover: 3	

Comments:

Document to be mailed: ☐ YES ☑ NO

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Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: April 14, 2003

To: Peter Karlton
333 Lakeside Drive
Foster City, CA 94404

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

Through: Stephen P. Miller, Ph.D., Chemistry Team Leader, HFD-530
George Lunn, Ph.D., Chemistry Reviewer, HFD-530

NDA: 21-500 emtricitabine (aka FTC) capsules

Subject: Request for chemistry information

The following chemistry, manufacturing, and controls (CMC) comments and recommendations are being conveyed on behalf of George Lunn, Ph.D., regarding your NDA 21-500 for emtricitabine capsules.

1. describes (Amendment of 2/26/03, Appendix 2, p. 49) but . (Amendment of 2/26/03, Appendix 2, p. 63). Please verify which description is correct.

2. In your Amendment of 2/26/03 on page 7 you describe the addition of pig liver esterase. The activity of the pig liver esterase is apparently measured in FTC butyrate units. Please describe how FTC butyrate units are defined and measured. How long a period of time may elapse between when the activity of the enzyme is measured and when it is used in the manufacturing process? Please summarize the data that supports this time interval, if appropriate.

3. The out of specification results for the assay of batch and that this stability study has now been terminated. An investigation is included in Appendix 8 to the Amendment of 2/26/03. You ascribe the problem to the This "leaves little room for any assay variability" (p. 199). To address this issue you have reduced the acceptance criterion for (Amendment of 2/26/03, page 13) while the assay acceptance criterion remains at However, even this change leaves little margin for error. You may wish to change the way that you calculate the emtricitabine drug substance assay value by omitting the factor (Vol. 3.3, p. 63). Thus the assay value would include both (+)-FTC and (-)-FTC. However, the of the batch would still be evident from the determination. None of the acceptance criteria would be changed. If you adopt the

approach please indicate on the drug substance specification sheet that the assay includes both enantiomers.

4. We remind you that you have not yet submitted the artwork for the final bottle and carton labels.

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/S/

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

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/s/

Virginia Yoerg
4/14/03 04:07:06 PM
CSO

hard copy signed and faxed to applicant

Stephen Paul Miller
5/6/03 04:44:08 PM
CHEMIST

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

FACSIMILE TRANSMITTAL SHEET

DATE: May 9, 2003

To: Martine Kraus, Ph.D., Director, Regulatory Affairs	**From:** Virginia L. Yoerg, Regulatory Health Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Drug Products
Fax number: 650-522-5489	**Fax number:** 301-827-2523
Phone number: 650-522-5722	**Phone number:** 301-827-2335

Subject: NDA 21-500
Request for pharmacokinetics and clinical information

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: May 9, 2003

To: Martine Kraus
333 Lakeside Drive
Foster City, CA 94404

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

Through: Russ Fleischer, PA-C, M.P.H., Acting Medical Team Leader, HFD-530
Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader, HFD-530
Jennifer DiGiacinto, Pharm.D., Pharmacokinetics Reviewer, HFD-530

NDA: 21-500, emtricitabine capsules

Subject: Request for clinical and pharmacokinetics information

The following comments are provided on behalf of the Division of Antiviral Drug Products regarding your NDA 21-500.

Clinical

Please respond by **May 20, 2003**

1. Please provide the number of patients, by treatment group, in studies FTC-301A and FTC-303 who were co-infected with hepatitis B or C, and their identification numbers.

2. The case report forms (CRFs) for patients 055-008, 066-055, and 121-001 in the ALIZE study are in French. Please have the CRFs translated into English.

3. Please attempt to obtain any additional data on the death of patient 013651 in study ACTG-5015.

4. Please provide the outcomes of pregnancy for all patients with an ongoing pregnancy as of September 2002.

5. Please describe the adverse event: skin discoloration.

Pharmacometrics

Please respond by **May 15, 2003**

6. It is generally believed that decreased renal function affects the pharmacokinetics of the drug by decreasing the CL. However, in your model, the effect of CLcr was modeled as the effect on K10, K12 and K21. Please provide your rationale for CLcr being modeled as the effect on K10, K12, and K21.

7. Please repeat the simulation, with the effect of CLcr modeled as an effect on CL.

8. Please provide the documentation for the goodness of fit of the model.

9. Please provide the code for the [redacted]

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.

/S/

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

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/s/

Virginia Yoerg
5/9/03 10:42:03 AM
CSO

FTC fax signed and faxed to Gilead

Russell Fleischer
5/12/03 02:03:44 PM
MEDICAL OFFICER

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

FACSIMILE TRANSMITTAL SHEET

DATE: May 15, 2003

To: Peter Karlton, Global Regulatory Affairs, CMC	From: Virginia L. Yoerg, Regulatory Health Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Drug Products
Fax number: 650-522-5489	Fax number: 301-827-2523
Phone number: 650-522-5722	Phone number: 301-827-2335

Subject: NDA 21-500
Request for chemistry information

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: May 15, 2003

To: Peter Karlton
333 Lakeside Drive
Foster City, CA 94404

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

Through: Stephen P. Miller, Ph.D., Chemistry Team Leader, HFD-530
George Lunn, Ph.D., Chemistry Reviewer, HFD-530

NDA: 21-500 emtricitabine (aka FTC) capsules

Subject: Request for chemistry information

The following chemistry, manufacturing, and controls (CMC) comments and recommendations are being conveyed on behalf of George Lunn, Ph.D., regarding your May 9, 2003 amendment to NDA 21-500.

1. Please confirm that the specifications and analytical methods for emtricitabine, — — manufactured at — are unchanged from those previously described in the NDA.

2. Please confirm that the immobilized pig liver esterase may be sourced from either — (cf. Vol. 3.2, p. 134).

3. Please supply Certificates of Analysis and Origin, similar to those found in Vol. 3.2, pages 135-139, for the immobilized pig liver esterase. If the information is available, please describe the resin support used for the immobilized pig liver esterase.

4. Please amend the narrative description by adding a footnote (p. 13) to indicate that — will not be used at the — site.

5. Is immobilized enzyme routinely re-used (p. 14)? Please describe the criteria for deciding when re-use is or is not appropriate.

6. Batches of emtricitabine are identified with Triangle batch numbers (p. 16) but in the original NDA they are identified with — batch numbers (Vol. 3.3). Please provide a correspondence table for the Triangle and — drug substance batch numbers.

7. In the batch analysis data for — the — content for batches manufactured at — is indicated as n/a. However, the specification for — (Vol. 3.2, p. 101) does not indicate that the measurement of — is optional. We recommend that the specification be modified

to indicate that — does not need to be measured if — was not used in the manufacturing process.

8. Please supply release data for batch 01-109-C5 of 200 mg capsules manufactured from emtricitabine made at — (p. 32). Please supply dissolution data obtained in the same media for a similar lot manufactured from — drug substance and calculate the f2 values for each medium.

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/S/

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

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/s/

Virginia Yoerg
5/15/03 03:59:15 PM
CSO

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Stephen Paul Miller
5/21/03 05:07:59 PM
CHEMIST

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

FACSIMILE TRANSMITTAL SHEET

DATE: May 19, 2003

To: Martine Kraus, Ph.D., Director, Regulatory Affairs	From: Virginia L. Yoerg, Regulatory Health Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Drug Products
Fax number: 650-522-5489	Fax number: 301-827-2523
Phone number: 650-522-5722	Phone number: 301-827-2335
Subject: NDA 21-500 Clinical request	
Total no. of pages including cover: 2	

Comments: Please respond by May 30, 2003

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES | Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: May 19, 2003

To: Martine Kraus
333 Lakeside Drive
Foster City, CA 94404

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

Through: Russ Fleischer, PA-C, M.P.H., Acting Medical Team Leader, HFD-530

NDA: 21-500, emtricitabine capsules

Subject: Request for clinical information

The following comments are provided on behalf of the Division of Antiviral Drug Products regarding your NDA 21-500.

Please respond by **May 30, 2003**

1. Please describe the methods used to evaluate patients with skin discoloration, including any biopsy results.

2. Please describe the mechanism of skin discoloration.

3. Please provide narratives for each patient in studies FTC-301A, FTC-302, FTC-303, and FTCB-301 with skin discoloration. Include the timing of onset, the duration, if the skin discoloration ever resolved, the work-up and its outcome, concomitant medications, and any pertinent medical history.

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/S/

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

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

FACSIMILE TRANSMITTAL SHEET

DATE: May 28, 2003, 2003

To: Martine Kraus, Ph.D., Director, Regulatory Affairs	**From:** Virginia L. Yoerg, Regulatory Health Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Drug Products
Fax number: 650-522-5489	**Fax number:** 301-827-2523
Phone number: 650-522-5722	**Phone number:** 301-827-2335

Subject: NDA 21-500
Request for pharmacokinetics/pharmacometrics information

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: May 28, 2003

To: Martine Kraus
333 Lakeside Drive
Foster City, CA 94404

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

Through: Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader, HFD-530
Jennifer DiGiacinto, Pharm.D., Pharmacokinetics Reviewer, HFD-530
Jenny J. Zheng, Ph.D., Pharmacometrics Reviewer, HFD-880

NDA: 21-500, emtricitabine capsules

Subject: Request for pharmacokinetics/pharmacometrics information

The following requests and comment are provided on behalf of Jenny J. Zheng, Ph.D., regarding your NDA 21-500.

Information requests:

1. Please provide detailed information on the simulation of emtricitabine concentrations in subjects on dialysis, including methodology and the code.

2. The estimated geometric mean absorption rate constants are 2.65, 2.56, 7.10, and 1.57 h^{-1} in subjects with CLcr >50 mL/min, 30-49 mL/min, 15-29 mL/min, and <15 mL/min, respectively. Yet in the simulation, a mean of 0.5851 h^{-1} was used according to the code. Please explain why this absorption rate constant was used.

3. The effect of renal function represented as CLcr was modeled on both total clearance (CL/F) and the distribution clearance (CLD2/F). Please clarify the physiological rationale for CLcr impacting CLD2/F.

Additional comment:

4. Your method of calculating the off-diagonal elements of the correlation matrix is questionable. In the FTC-107 analysis, the off-diagonal elements of the correlation matrix for these parameters were estimated by averaging the corresponding elements of the correlation matrices from pharmacokinetic model fits across all subjects. However, the correlation matrix for each individual fit reflects the correlation between the

parameters in the individual. Averaging the values across individuals does not reflect the correlation of the parameters between subjects.

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.

/S/

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

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/s/

Virginia Yoerg
5/29/03 05:21:25 PM
CSO

hard copy faxed to applicant. As acting TL, please sign off.

Jeffrey Murray
5/30/03 12:34:44 PM
MEDICAL OFFICER

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 2, 2003

To: Carla Fiankan, Global Regulatory Affairs, CMC	**From:** Virginia L. Yoerg, Regulatory Health Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Drug Products
Fax number: 650-522-5489	**Fax number:** 301-827-2523
Phone number: 650-522-5722	**Phone number:** 301-827-2335
Subject: NDA 21-500 Request for chemistry information	
Total no. of pages including cover: 2	

Comments:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: June 2, 2003

To: Carla Fiankan
333 Lakeside Drive
Foster City, CA 94404

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

Through: Stephen P. Miller, Ph.D., Chemistry Team Leader, HFD-530
George Lunn, Ph.D., Chemistry Reviewer, HFD-530

NDA: 21-500 emtricitabine capsules

Subject: Request for chemistry information

The following chemistry, manufacturing, and controls (CMC) comments are being conveyed on behalf of George Lunn, Ph.D., regarding your amendment dated May 20, 2003 to NDA 21-500.

Please identify the origin of the analytical report on page 7. Is the immobilized pig liver esterase sourced from an outside supplier or is it prepared at —. If the immobilized pig liver esterase is prepared at — please describe the procedure and the controls employed.

We would appreciate a response by June 9, 2003.

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.

/S/

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

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/s/

Virginia Yoerg
6/2/03 03:09:42 PM
CSO

hard copy signed and faxed to applicant.

Stephen Paul Miller
6/2/03 05:19:36 PM
CHEMIST

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 12, 2003

To: Martine Kraus, Ph.D., Director, Regulatory Affairs	**From:** Virginia L. Yoerg, Regulatory Health Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Drug Products
Fax number: 650-522-5489	**Fax number:** 301-827-2523
Phone number: 650-522-5722	**Phone number:** 301-827-2335
Subject: NDA 21-500 Request for clinical pharmacology information	
Total no. of pages including cover: 2	

Comments:

Document to be mailed: ☐ YES ☑ NO

Kirk Kraus

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: June 12, 2003

To: Martine Kraus
333 Lakeside Drive
Foster City, CA 94404

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

Through: Russ Fleischer, PA-C, M.P.H., Acting Medical Team Leader, HFD-530
Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader, HFD-530
Jennifer DiGiacinto, Pharm.D., Pharmacokinetics Reviewer, HFD-530

NDA: 21-500, emtricitabine capsules

Subject: Request for clinical pharmacology information

Reference is made to your April 4, 2003 response providing additional information about patients with renal insufficiency. In that submission you note 40 patients with CrCl 50-80 mL/min, and describe that there were no differences in adverse events between those patients and those with CrCl >80 mL/min.

For each of these 40 patients, please provide the following data: study number, identification number, sex, race, age, CrCl, and a listing of each individual's adverse events. Then please compare the frequency of the adverse events between these 40 patients and the 765 patients with normal renal function.

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.

/S/

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

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/s/

Virginia Yoerg
6/12/03 04:24:56 PM
CSO

hard copy signed and faxed to applicant.

Russell Fleischer
6/16/03 07:37:31 AM
MEDICAL OFFICER

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 13, 2003

To: Martine Kraus, Ph.D., Director, Regulatory Affairs	**From:** Virginia L. Yoerg, Regulatory Health Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Drug Products
Fax number: 650-522-5489	**Fax number:** 301-827-2523
Phone number: 650-522-5722	**Phone number:** 301-827-2335
Subject: NDA 21-500 Postmarketing commitments	
Total no. of pages including cover: 3	

Comments:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: June 13, 2003

To: Martine Kraus
333 Lakeside Drive
Foster City, CA 94404

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

Through: Russ Fleischer, PA-C, M.P.H., Acting Medical Team Leader, HFD-530
Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader, HFD-530
Jennifer DiGiacinto, Pharm.D., Pharmacokinetics Reviewer, HFD-530
James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader, HFD-530
Pritam Verma, Ph.D., Pharmacology/Toxicology Reviewer, HFD-530

NDA: 21-500, emtricitabine capsules

Subject: emtricitabine postmarketing commitments

The Division of Antiviral Drug Products requests that you fulfill the following postmarketing commitments for NDA 21-500. When appropriate, please add the time estimates (Ideal Format) for each commitment. At minimum, propose a completion date for each commitment and submit your proposal by Monday, June 23, 2003.

Ideal Format:

Description of Commitment:
Protocol Submission: Within X months of the date of this letter
Study Start: Within Y months of the date of this letter
Final Report Submission: Within Z months of the date of this letter

If you have questions regarding these commitments, please contact me.

Clinical

1. Please propose a study to assess the mechanism of action and clinical significance of the skin discoloration observed in patients. Please include a protocol outline or concept sheet by Monday, June 23, 2003.

Clinical Pharmacology

2. Please identify the enzymes responsible for emtricitabine metabolism.

3. Please determine the potential for enzyme inducers to decrease emtricitabine plasma concentrations.

Pharmacology/Toxicology

4. Please submit the final study reports from your ongoing carcinogenicity studies.

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

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/s/

Virginia Yoerg
6/13/03 04:35:14 PM
CSO

hard copy faxed to applicant.

Russell Fleischer
6/16/03 07:49:32 AM
MEDICAL OFFICER

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 16, 2003

To: Carla Fiankan, Global Regulatory Affairs, CMC	**From:** Nitin Patel, R.Ph., Regulatory Project Manager, for Virginia L. Yoerg, Regulatory Health Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Drug Products
Fax number: 650-522-5489	**Fax number:** 301-827-2523
Phone number: 650-522-5722	**Phone number:** 301-827-2335

Subject: NDA 21-500
Request for chemistry information

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: June 16, 2003

To: Carla Fiankan
333 Lakeside Drive
Foster City, CA 94404

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

Through: Stephen P. Miller, Ph.D., Chemistry Team Leader, HFD-530
George Lunn, Ph.D., Chemistry Reviewer, HFD-530

NDA: 21-500 emtricitabine capsules

Subject: Request for chemistry information

The following chemistry, manufacturing, and controls (CMC) comment is being conveyed on behalf of George Lunn, Ph.D., and refers to Volume 3.3 of your NDA submission dated September 3, 2002:

The [redacted] are not specifically controlled in the drug substance specification. These compounds are controlled at NMT 0.1% under the "Individual Unspecified Impurities" specification of the drug substance specification (p. 27).

We note that levels of [redacted] were measured in 8 batches using a [redacted] method (p. 26), although this method will not be used for future batch release.

The trans-compound is also controlled [redacted] to NMT [redacted]% in the [redacted] Step 1 product

Please clarify whether either of the two release [redacted] methods would be expected to detect [redacted] in emtricitabine drug substance. [redacted] is not contained in the list of test compounds for the [redacted] method (p. 106). In the [redacted] method [redacted] and [redacted] are clearly resolved (p. 70) but the method is not validated for the determination of these compounds.

If you have any questions we would be happy to take part in a teleconference to resolve the matter.

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.

/S/

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

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/s/

Nitin Patel
6/17/03 11:42:47 AM
CSO
Chemistry comment for NDA 21-500
Chemistry comment for NDA 21-500. Hard copy sign-off by George Lunn for Stephen Miller - 6/16/03.

Stephen Paul Miller
6/27/03 05:02:52 PM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

RECORD OF INDUSTRY MEETING

Date of Meeting: January 12, 2000

IND: [redacted] (Serial No. 092)

Drug: Coviracil® (emtricitabine, FTC) Capsules

Indication: Treatment of HIV Infection

Sponsor: Triangle Pharmaceuticals

Type of Meeting: Clinical Development Meeting

FDA Attendees:
Sandy Kweder, M.D., Acting Director, Office of Drug Evaluation IV
Heidi Jolson, M.D., M.P.H., Director, Division of Antiviral Drug Products
Therese Cvetkovich, M.D., Medical Team Leader
Russell Fleischer, PA-C, M.P.H., Clinical Reviewer
Harry Haverkos, M.D., Clinical Reviewer
Ekopima Ibia, M.D., Clinical Reviewer
Kate Laessig, M.D., Clinical Reviewer
John Martin, M.D., Clinical Reviewer
Tom Hammerstrom, Ph.D., Statistical Reviewer
Narayana Battula, Ph.D., Microbiology Reviewer
Antoine El Hage, Division of Scientific Investigations
Carol Drew, Regulatory Policy Staff
Tony DeCicco, R.Ph., Chief Project Manager
Grace Carmouze, Regulatory Project Manager
Leslie Stephens, R.N., M.S.N., Regulatory Project Manager

External Constituents:
Jill Buckley, PharmD., Principal Clinical Scientist
Mike Dalton PharmD., Director of Regulatory Affairs
Claude Drobnes, M.D., Director of Drug Safety Surveillance
Anne McKay, Vice President of Regulatory Affairs
Diego Miralles, M.D., Senior Medical Advisor
Sandra Palleja, M.D., Director of Phase III/IV Clinical Development
Joseph Quinn, M.S.P.H., Director of Biometrics
Franck Rousseau, M.D., Vice President of Medical Affairs and Chief Medical Officer
Charles Wakeford, Ph.D., Associate Director of Biometrics

Background:

Triangle Pharmaceuticals is conducting clinical study FTC-302, "A Randomized, Double Blind Equivalence Trial Comparing Emtricitabine to Lamivudine within a Triple Combination in Antiretroviral-Drug Naïve HIV-1 Infected Patients." This study is designed to include 400 treatment naïve patients, randomized to FTC (emtricitabine) + d4T (stavudine) + NVP (nevirapine) vs. 3TC (lamivudine) + d4T + NVP.

In light of recent serious adverse events (SAEs) and deaths in study FTC-302 which is being conducted in South Africa, the sponsor was invited to meet with DAVDP to discuss issues related to the future plans for this study. Among these issues are the following: (1) What are the unique issues related to conducting a study in South Africa (for example; socioeconomic/medical infrastructure, monitoring issues, ethical issues); (2) What plans does the sponsor have for exploring the interaction of nevirapine with FTC/3TC and for the further investigation of hepatotoxicities in this study? (3) if the FTC-302 study continues, how will the sponsor insure safe management of patients?; (4) the sponsor's interpretation of the regulation related to SAE reporting and their failure to report SAEs in a timely fashion to the IND; and (5) concern regarding the absence of an independent oversight committee for this study.

Dr. Jolson stated that a regulatory letter to the sponsor would follow this meeting in which the regulation for reporting SAEs would be clarified for the sponsor, along with the Division's recommendations for managing a study outside the United States.

Discussion:

1. Clarification of regulatory status.

Dr. Jolson explained that FDA has no jurisdiction in countries outside the United States. However, if Triangle continues the FTC-302 study and intends to include it as part of an NDA submission, it must be conducted under good clinical practices. Further, she strongly recommended that the study, if continued, remain under the U.S. IND.

2. Given the serious toxicities and questionable patient management, concern about the manner in which the South African study is being conducted with regard to: (1) socioeconomic/medical infrastructure; (2) issues related to adequate monitoring study participants; and, (3) ethical considerations.

- The Division raised the concern that a number of patients with serious adverse events were not treated by study physicians, and that many of these patients appeared to have been mismanaged because the local physician did not know the patient was enrolled in a clinical trial.

- Triangle reported its actions to improve the monitoring and management of patients in FTC-302, as outlined in its December 29, 1999 correspondence. These actions include, but are not limited to: re-consenting of patients to inform them of the potential for hepatic toxicity; enrollment of no additional patients the nevirapine strata, weekly clinic visits with monitoring of liver function tests for patients on study less than 8 weeks; and instructing patients to discontinue study medications and contact their study site should they experience systemic symptoms (rash, with or without nausea, vomiting, or abdominal pain) following escalation of their nevirapine dose. The CRO [redacted] conducts site visits every four to six weeks; Triangle will ask the CRO to increase the frequency of site monitoring.

  Triangle reported that each site has its own ethics committee, and each site has been informed of the adverse events and deaths reported in study FTC-302. In addition, Triangle stated that the protocol was filed with the Medicines Control Council (MCC) and the MCC has been informed of the deaths.

- Because there are generally no alternative therapies available to patients who discontinue from clinical trials, there appears to be more pressure on patients and physicians to remain on study medications, even in the face of significant adverse events. Triangle stated that they believe that it is not in the patients' best interests to discontinue from the study and that appropriate revisions could be made to the protocol to ensure that the risk to patient safety are minimized. They proposed open label treatment with efavirenz to those who are unable to tolerate nevirapine.

3. What role has FTC had in fatal and non-fatal hepatotoxicities in this population?

Three patients have died in the FTC-302 study, two due to hepatotoxicity (one treated with FTC; one treated with 3TC), and one due to meningitis (treated with FTC). In a separate study, (MKC-401), one patient receiving FTC in combination with Triangle's non-nucleoside, MKC-442, and d4T, died of hepatic failure. In addition, there have been a significant number of patients with elevation of LFTs with or without gastrointestinal complaints and with or without rash. All of these cases followed a similar pattern: elevation of LFTs (with or without nausea, vomiting and abdominal pain) that develops approximately two weeks after NVP escalation from 200 mg once per day to 200 mg twice per day.

The sponsor stated that they believe the hepatotoxicity to be solely due to nevirapine because it fits the pattern described in the NVP label. Further, in reviewing other combination and monotherapy studies involving FTC they have not seen similar LFT abnormalities. The sponsor also stated that they do not believe that the fluorine component of the emtricitabine molecule is responsible for the LFT abnormalities.

The sponsor reported that they had communicated with [redacted] regarding the hepatotoxicity observed in FTC-302. The sponsor stated that the gender ratio

in FTC-302 trials is 3:1, female to male, which represents a larger proportion of women than previously described[ ]has not disclosed whether gender might be a factor in the interaction with NVP. The sponsor has also asked[ ] for racial distributionof patients who experienced hepatotoxicity while receiving NVP. The sponsor will evaluate whether race and/or gender are factors in the FTC trials.

4. How will the sponsor ensure the safe management of these patients?

DAVDP asked how patients were managed when they had grade 3 or 4 elevation in liver function tests (LFTs). The sponsor stated that for a grade 4 elevation all treatment was discontinued. When a patient had grade 3 elevation, some patients stopped treatment then restarted study medications once the toxicity had resolved. On re-challenge, almost no patients had recurrence of LFT abnormalities. The Division requested that all grade 3 and 4 LFT abnormalities be reported as SAEs.

5. What plans does the sponsor have for an independent oversight committee for this study?

The Division was concerned that there is no independent Data Safety Management Board (DSMB) for study FTC-302. The Division suggested that an independent oversight committee with members from the U.S. and South African be included on this committee. Further, it was suggested that a hepatologist with expertise in drug induced hepatotoxicity be included on the committee.

6. What is the sponsor's understanding of the regulation on SAE reporting to the IND (21CFR §312.32)?

Drs. Jolson and Kweder both expressed serious concern about Triangle's failure to report SAEs to this IND in a timely fashion and in accordance with the regulations. The Division is quite concerned about the sponsor's delay in reporting Grade 3 and 4 toxicities, and in allowing patients with grade 4 toxicities to continue on study. The combination of the setting of the study and the sponsor's misinterpretation of the regulation for reporting SAEs to the IND make this a serious problem.

The sponsor responded with strong disagreement regarding the issue of non-compliance with the SAE reporting regulation. The sponsor interpreted the SAE reporting regulations to include only those events that were "associated with the drug," in this case, FTC. Since all the hepatotoxicities seen in FTC-302 followed a pattern consistent with NVP toxicities and were thus labeled as expected, Triangle's interpretation of the regulations was that these events did not need to be reported to the IND.

It was the Division's position that since all patients are receiving at least two other antiretroviral agents and, because the adverse event profile associated with FTC is not well described, all SAEs should be reported regardless of attribution (by either the reporter or your representatives). Further, reporting of an SAE should occur irrespective of whether

the event is an "expected" event associated with a concomitantly administered approved agent.

Recommendations and Agreements:

1. The sponsor should form an independent oversight committee to review the available data and to determine if study FTC-302 should continue. If the committee determines that the trial should continue, it should provide guidance on what changes to the trial design should be made to better ensure patient safety. Further, the committee should periodically review safety data from the study and make additional recommendations as needed. The committee should be composed of clinical trial specialists with representation from the Republic of South Africa.

2. The sponsor must demonstrate that the CRO in South Africa [redacted] is adequately ensuring that patients are receiving appropriate medical care, and that investigators and patients are being informed of the adverse events occurring in the study. The sponsor agreed to provide this information.

3. The Division recommended that the sponsor further investigate, either independently or with [redacted], the hepatotoxicity seen in FTC-302. This investigation should include, but not be limited to, possible pharmacokinetic interactions between FTC and NVP. A scientific rationale/explanation for the hepatotoxicity will be required should FTC-302 be included in an NDA for FTC. The sponsor agreed to carry out such investigations.

4. The sponsor should consider what, if any, changes to study medications might be made in study FTC-302 to protect patient safety. Proposals discussed included stopping the study, continuing the study as currently designed, or changing NVP to efavirenz in all or some patients. The sponsor agreed to provide the Division with plans for FTC-302 as soon as possible.

5. The Division requested that the sponsor report all SAEs to the IRBs and the MCC, and provide the Division with any communications regarding the study from these organizations. The sponsor agreed to this request.

6.The sponsor agreed to report all SAEs, regardless of causality, to the IND within the requirements set forth in 21 CFR §312.32.

Minutes preparer: /S/ **Date:** _____

Conference Chair: /S/ **Date:** _____

Concurrence:
HFD-530/MO/Fleischer /S/ 3/27/00
HFD-530/MTL/Cvetkovich /S/ 3/22/00
HFD-530/DivisionDir/Jolson /S/ 3/29/00
HFD-530/ActingOfficeDir/Kweder

Distribution:
Original IND [redacted]
Division file
HFD-530/MTL/Cvetkovich
HFD-530/MO/Fleischer
HFD-530/DivDir/Jolson
HFD-530/ActingOfficeDir/Kweder
HFD-530/Chem/Lunn
HFD-530/PT/Verma
HFD-530/Stat/Hammerstrom
HFD-530/BP/Rajagopalan

Location: V:\DAVDP\CSO\Stephens\IND [redacted] Minutes\000112mm.doc

IND [redacted] Serial No. 092

Meeting Minutes

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

RECORD OF TELECONFERENCE

Date of Meeting: **February 14, 2001**

IND: [redacted] **(Serial No. 294)**

Drug: **Coviracil® (emtricitabine, FTC) Capsules**

Indication: **Treatment of HIV Infection**

Sponsor: **Triangle Pharmaceuticals**

Type of Meeting: **Continuation of Clinical Hold**

FDA Attendees:

Debra Birnkrant, M.D., Acting Division Director
Therese Cvetkovich, M.D., Medical Team Leader
Russell Fleischer, PA-C, M.P.H., Senior Clinical Reviewer
Leslie Stephens, R.N., M.S.N., Regulatory Project Manager

External Constituents:

Anne McKay, Vice President of Regulatory Affairs
Mike Dalton PharmD., Director of Regulatory Affairs
Joseph Quinn, M.S.P.H., Director of Biometrics

Background:
Triangle Pharmaceuticals' submission dated January 15, 2001 (SN 294) was a complete response to the partial clinical hold placed on IND [redacted] on February 6, 2000, due to medical risks identified in Study FTC-302, "A Randomized, Double Blind Equivalence Trial Comparing Emtricitabine to Lamivudine with Triple Combination in Antiretroviral-Drug Naïve HIV-1 Infected Patients". The requirements which were needed to resolve this hold were communicated to the sponsor in a letter dated April 12, 2000; they are as follows:

1. **Documentation of all findings and deliberations of the MCC's review of this trial**
2. **Documentation of an MCC decision to allow the study to continue**
3. **Satisfactory inspection of clinical trial sites audited by the MCC and FDA, along with resolution of any unacceptable findings; and**
4. **Establishment of an independent data safety monitoring board (DMSB).**

Comments to the Sponsor:

Dr. Birnkrant informed representatives of Triangle via teleconference on February 14, 2001, that a thorough review of the complete response to the partial hold had been conducted by the Division and that the partial hold would be maintained for the following reasons:

1. The Medicines Control Council of the Republic of South Africa terminated Study FTC-301. Therefore, the requirement outlined in the original partial hold letter, **"Documentation of an MCC decision to allow the study to continue"** had not been met.

2. The requirement of the partial clinical hold, **"Satisfactory inspection of the clinical trial sites audited by the MCC and the FDA, along with resolution of any unacceptable findings"**, was not met. [redacted] was contracted by Triangle to evaluate the study sites. [redacted] identified two sites that exhibited a number of significant deficiencies. Deviations from acceptable standards were identified in the following areas: documentation of Informed Consent; enrollment of study subjects; compliance and drug accountability; management and reporting of Serious Adverse Event's; and review of case report forms "to maintain currency with study data and developments." Documentation of the resolution of these deviations was not provided in this submission.

3. The requirement for resolution of the partial clinical hold was the **"Establishment of an independent data safety monitoring board"**. Because Triangle established a Clinical Steering Committee which included employees of Triangle Pharmaceuticals, as well as the principal investigator of the study, the committee's independence was called into question. Therefore, the Division determined that the requirement was not met.

During the February 14, 2001 teleconference, Triangle representatives were informed that a letter would be sent via telephone facsimile as well as by certified mail, detailing the reasons for which this complete response to the partial clinical hold was found to be inadequate by the Division. The sponsor indicated they understood that the intent of today's teleconference was to communicate the decision to maintain the partial clinical hold of IND [redacted] on Study FTC-302.

The conversation was cordial throughout.

/S/

Leslie Stephens, M.S.N., R.N.
Regulatory Project Manager

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/s/

Leslie Stephens
4/25/01 05:28:26 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Date: February 22, 2001

To: IND [redacted] serial 294

From: Russell Fleischer, PA-C, MPH
Senior Clinical Analyst, DAVDP

Through: Therese Cvetkovich, MD
Medical Team Leader, DAVDP

Re: Continuation of partial clinical hold on study FTC-302

Study FTC-302 was terminated by the Medicines Control Council of the Republic of South Africa on April 6, 2000 due to numerous and serious protocol violations which compromised the scientific integrity of the study. In response to the MCC's actions, the Division placed study FTC-302 on clinical hold and IND [redacted] on partial hold. Triangle Pharmaceuticals submitted a response to requirements outlines in our hold letter sent April 12, 2000, for resolution of the clinical hold placed on study FTC-302. This study was conducted entirely in South Africa. However, it was conducted under Triangle's US IND and they planned to submit the data in support of an NDA for Emtricitabine (FTC).

Below are the requirements outlined in our clinical hold letter that the sponsor would need to completely and adequately address in order for use to consider lifting the clinical hold. The requirements are presented in **bold** followed by the Division's interpretation of the responses.

Documentation of an MCC decision to allow the study to continue.

This requirement for resolution of the partial clinical hold was not met. Since the MCC has not reversed their decision to terminate Study FTC-302, the stipulation to document the MCC's decision to allow Study FTC-302 to continue was not met. Further, the Division understands from the MCC that there is no longer an opportunity for this decision to be reversed.

Satisfactory inspection of the clinical trial sites audited by the MCC and the FDA, along with resolution of any unacceptable findings.

The requirement to adequately address this partial clinical hold was not met. Triangle contracted with an independent consulting group specializing in Good Clinical Practice

audits and evaluations, [redacted] identified two sites that exhibited a number of significant deficiencies. In addition, deviations from acceptable standards were identified in the following areas: documentation of Informed Consent; enrollment of study subjects; compliance and drug accountability; management and reporting of Serious Adverse Event's; and review of case report forms "to maintain currency with study data and developments." Documentation of the resolution of the aforementioned deviations was not provided in the submission.

Establishment of an independent data safety monitoring board.

This requirement for resolution of the partial clinical hold was not met. Triangle's establishment of a Clinical Steering Committee (CSC) did not address the partial clinical hold obligation to establish an independent DSMB. The CSC for Study FTC-302 included employees of Triangle Pharmaceuticals, as well as the principal investigator of the study. This practice called the committee's independence into question.

Assessment/Recommended Regulatory Action

The sponsor has failed to adequately address the requirements for resolution of the clinical hold. Therefore, the partial hold on the IND and the clinical hold on study FTC-302 should be maintained. The sponsor was notified of this decision during a teleconference on February 14, 2001 which was followed by a letter dated the same day.

/s/

Russell Fleischer
2/22/01 11:54:42 AM
MEDICAL OFFICER

Therese Cvetkovich
3/1/01 08:11:45 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Date: May 1, 2001

To: David LePay, MD, PhD

From: Russell Fleischer, PA-C, MPH
Senior Clinical Analyst, DAVDP

Therese Cvetkovich, MD
Medical Team Leader, DAVDP

Through: Debra Birnkrant, MD
Acting Director, DAVDP

Re: Summary of DAVDP's activities on study FTC-302

Background

This memorandum summarizes the interactions between DAVDP, the Medicines Control Council (MCC) of the Republic of South Africa, and Triangle Pharmaceuticals regarding the conduct of study FTC-302.

Study FTC-302 was designed as a double-blind comparison of FTC versus 3TC in combination with nevirapine (NVP) (for patients with baseline HIV RNA <100,000 c/mL) or efavirenz (for patients with baseline HIV RNA >100,000 c/mL) and d4T in treatment-naïve HIV-1 infected adults. Duration of treatment was to be for 48 weeks. The study was conducted under the US IND solely in South Africa.

The study was terminated by the MCC in April 2000 with a request that Triangle provide antiretroviral therapy to patients demonstrating virologic benefit under compassionate use provisions. It was Triangle's position that patients should continue to receive blinded therapy. Despite numerous correspondences between Triangle and the MCC, the trial was not terminated. In fact, Triangle was able to continue the trial until the last patient completed 48 weeks of blinded therapy. Triangle is now requesting that FDA consider this study in an NDA as a registration study.

Chronology

In January 2000, DAVDP contacted the MCC (Dr. Helen Rees, Chairperson) to inform them of three deaths due to hepatotoxicity and other serious adverse events that had occurred in FTC-302. On February 2, 2000, Dr. Rees of the MCC, Dr. Kweder (acting

ODE IV director) and this reviewer discussed the serious nature of the adverse events occurring in FTC-302 in a teleconference. We provided Dr. Rees with our response to these events as well as agreements made by Triangle to improve the safe management of patients in the study. Dr. Rees informed us that she would be meeting with the sponsor and the CRO ( ) responsible for oversight of the conduct of study FTC-302.

On March 8, 2000, DAVDP was informed that the MCC had met with the sponsor and that a number of protocol amendments had been effected. In addition, Triangle agreed to provide patients with a telephone card to facilitate contact with study sites; to arrange for home visits if a patient could not come to clinic; and to submit the CV's of all investigators. Finally, maximum allowable elevations in hepatic enzymes would be reduced (no specifics were provided).

Of note, at the meeting between the MCC and Triangle, Triangle was asked about progress in investigating the hepatotoxicity seen in FTC-302, as requested by FDA. The response provided from Triangle to investigators in a letter dated February 22, 2000 stated: "we have assured ourselves that the liver toxicity grade III and IV events were probably related to Nevirapine and remotely related to a drug interaction with the blinded study drugs FTC and lamivudine." No supporting data for this conclusion was provided to the MCC.

At the same time, DAVDP was made aware that Triangle granted 350 protocol exemptions. The main reasons included lower than allowed CD4 cell counts, prolonged time between screening and baseline visits, and various exceptions for out of range laboratory parameters.

On April 6, 2000, the MCC issued a letter to Triangle stating that because of numerous serious protocol violations that compromised the scientific integrity of study FTC-302, the study should be terminated. Triangle was asked to submit a plan to unwind the study within 7 days. Triangle responded that they would enroll no additional patients into the study, but that they preferred to continue the study in a controlled clinical research setting.

DAVDP placed the study on clinical hold because of questions about the appropriateness of medical management of subjects who experienced adverse events; the inadequacy of investigations and reporting of adverse events; the capacity of the medical infrastructure in South Africa to support the conduct of such a study; and the inadequacy of communication between Triangle and the MCC; and the lack of a DSMB or other oversight group to review safety data and make recommendations regarding human subject protection. In order to remove the hold, we requested that Triangle provide documentation of all findings and deliberations of the MCC's review of this trial; documentation of an MCC decision to allow the study to continue; satisfactory inspection of clinical trial sites audited by the MCC and the FDA, along with resolution of any unacceptable findings; and establishment of an independent data safety monitoring board (DMSB).

On April 14, 2000, the MCC again informed Triangle that the study was terminated, pointing out that there had been "poor adherence to GCP" and "protocol violations regarding patient recruitment." Further, the MCC requested that patients who had virologic response defined as HIV RNA <2,000 c/mL continue their present regimen on compassionate grounds. Again it was Triangle's position that the safest and most appropriate course of action would be to maintain the blinded therapy.

There were apparently no communications between the MCC and Triangle until June 29, 2000, when Triangle met with the MCC and again requested that the trial continue in a blinded manner.

On August 7, 2000 Triangle was informed by the MCC that the trial had been terminated and the data generated by FTC-302 could not be utilized to support a future registration application, and that the compassionate use recommended by the MCC implied that the study be unblinded.

On September 8, 2000, Triangle submitted a compassionate use protocol. According to Triangle, they did not receive a response from the MCC, and, in early December 2000, completed the original study in a blinded manner.

On January 15, 2001, Triangle submitted a response to the clinical hold letter. The clinical hold was maintained because the MCC had not reversed their decision to terminate FTC-302. Therefore, the stipulation to document the MCC's decision to allow FTC-302 to continue was not met. In addition, Triangle had contracted with [redacted] an independent consulting group specializing in Good Clinical Practice audits and evaluations to audit FTC-302. This audit identified two sites that exhibited a number of significant deficiencies. Further, deviations from acceptable standards were identified in the following areas: the process and documentation of Informed Consent; enrollment of several unsuitable subjects; discrepancies in compliance and drug accountability; unacceptable management and reporting of Serious Adverse Events in several instances; and backlogs of CRF reviews that were "insufficient to maintain currency with study data and developments."

Finally, DAVDP did not agree that the Clinical Steering Committee (CSC) that Triangle had formed was an adequate response to the request that an independent DSMB be established. Specifically, the CSC included both Triangle employees and the principal investigator of the study, which called into question the independence of this committee.

DAVDP also recommended that Triangle withdraw study FTC-302 from their US IND.

DAVDP met with Triangle on April 17, 2001. Triangle maintained they did not interpret "terminated" to mean that the study had to be completely stopped and unblinded until the August 7, 2000 communication from the MCC. Regardless of their interpretation of the communications from the MCC, it was Triangle's position that their study qualifies as an adequate and well-controlled study that would support a marketing application for FTC. DAVDP stated it would be difficult to accept the study as adequate and well-controlled to

support an NDA since regulatory authorities had terminated the study in the country in which it had been conducted.

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/s/

Russell Fleischer
5/10/01 07:11:53 AM
MEDICAL OFFICER

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-420)

DATE RECEIVED: May 5, 2003	**DUE DATE:** July 2, 2003	**ODS CONSULT #:** 03-0160

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

THROUGH: Virginia L. Yoerg
Project Manager
HFD-530

PRODUCT NAME: **Emtriva** (Emtricitabine Capsules) 200 mg **NDA #:** 21-500	**SPONSOR:** Gilead Sciences, Inc.

SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.

SUMMARY: In response to a consult from the Division of Antiviral Drug Products, the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Emtriva" to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS has no objection to the use of the proprietary name "Emtriva". In addition, DMETS recommends implementation of the labeling revisions as outlined in Section III of this review. DMETS considers this a final review. If the approval of the application is delayed beyond 90 days from the signature date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

2. DDMAC finds the name "Emtriva" acceptable from a promotional perspective.

/S/

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

/S/

Jerry Phillips, R.Ph.
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 Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 5, 2003

NDA NUMBER: 21-500

NAME OF DRUG: **Emtriva**
(Emtricitabine Capsules)
200 mg

NDA SPONSOR: Gilead Sciences, Inc.

NOTE: This review contains proprietary and confidential information that can not be released to the public.

I. INTRODUCTION

This consult was written in response to a request from the Division of Antiviral Drug Products, for an assessment of the proprietary name "Emtriva" regarding potential name confusion with other proprietary or established drug names. The draft container labels, carton and package insert labeling for Emtriva were reviewed for possible interventions in minimizing medication errors. Additionally, the sponsor has submitted additional information, including an independent analysis conducted by the [redacted] to DMETS for review and comment.

PRODUCT INFORMATION

Emtriva is the proposed proprietary name for emtricitabine capsules, a synthetic nucleoside analogue, indicated in combination with other antiretroviral agents, for the treatment of HIV-1 infection. The recommended dose of Emtriva is 200 mg once daily, taken orally with or without food. Emtriva will be packaged in bottles of 30 capsules. The sponsor has submitted additional information, including an independent analysis conducted by the [redacted] for review and comment.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[i,ii] as well as several FDA databases[iii] for existing drug names which sound alike or look alike to "Emtriva" 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

[i] 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.

[ii] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[iii] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

Trademark Office's Text and Image Database[iv] and the data provided by Thomson & Thomson's SAEGIS™ Online Service[v] were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Emtriva. Potential concerns 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 three medication names that have potential for confusion with Emtriva. These products are listed in Table 1 (see below), along with the dosage forms available and usual FDA-approved dosage.

2. DDMAC did not have any concerns with Emtriva in regard to promotional claims.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	**Dosage form(s), Established name**	**Usual adult dose***	**Other****
Emtriva	**Emtricitabine Capsules 200 mg**	**200 mg once daily.**	
Kariva (Rx)	Desogestrel & Ethinyl Estradiol Tablets 0.15 mg/20 micrograms	One tablet daily.	**S/A

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
NOTE: **This review contains proprietary and confidential information regarding names that are pending approval. Therefore, it can not be released to the public.**

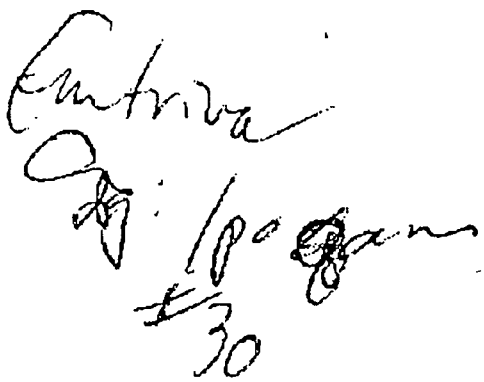
[iv] WWW location http://www.uspto.gov.

[v] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Emtriva 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 129 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Emtriva (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

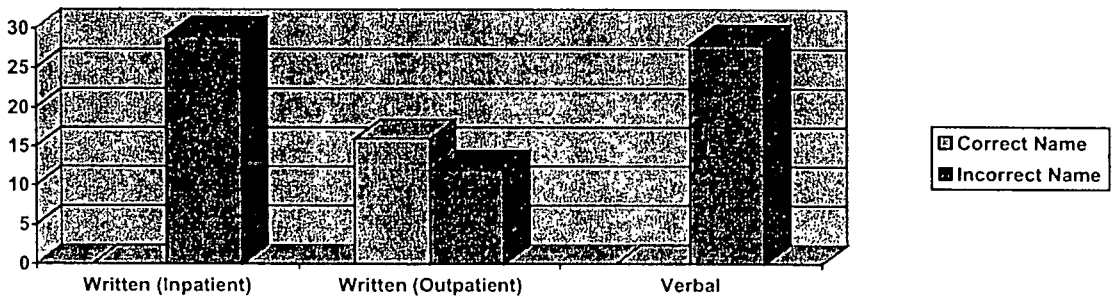
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: 	Emtriva, 1 by mouth every morning, disp. #30.
Inpatient RX:	

2. Results:

The results are summarized in Table 2.

Table 2

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	43	28 (65%)	0 (0%)	28 (100%)
Written Outpatient	43	28 (65%)	16 (57%)	12 (43%)
Verbal	43	28 (65%)	0 (0%)	28 (100%)
Total	129	84 (65%)	16 (19%)	68 (81%)



Among the verbal prescription study participants for Emtriva, 28 of 28 (100%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of "Emtriva". The incorrect responses were *Amtreva (1), Antreva (1), Antriva (1), Centreva (1), Entreava (1), Entreeva (3), Entreva (3), Entriva (9), Entrive (1), Intreva (2), Intriva (4), and Ventriva (1).* None of the interpretations are similar to a marketed drug product.

Among the written inpatient prescription study participants for Emtriva, 28 of 28 (100%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of "Emtriva". The incorrect responses were *Emtina (1), Emetona (1), Emetra (1), Emetrna (1), Emitina (2), Emitrina (1), Emitrna (1), Emotna (1), Emtina (3), Emtona (3), Emtora (1), Emtrana (1), Emtrina (2), Emtrna (4), Enatrna (1), Enctrona (1), Enitina (1), Enitona (1), and Enitrina (1).* None of the interpretations are similar to a marketed drug product.

Among the written outpatient prescription study participants for Emtriva, 12 of 28 (43%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of "Emtriva". The incorrect responses were *Centriva (1), Femtriva (1), Cutriva (1), Emtiva (1), Entiva (1), Entriva (3), Eurtriva (1), Eutriva (2), and Fentriva (1).* None of the interpretations are similar to a marketed drug product.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Emtriva", the primary concerns raised were related to three look-alike and/or sound-alike names. The products considered to have potential for name confusion with Emtriva were: Kariva[redacted]

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Emtriva and Kariva, Atriva, [redacted] The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name, Emtriva. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size.

Kariva was identified to have sound-alike potential with the proposed proprietary name, Emtriva. Kariva is the proprietary name for desogestrel and ethinyl estradiol, which is indicated for the prevention of pregnancy. Kariva and Emtriva have sound-alike similarities in that each name contains the same number of syllables (three) and identical letter combinations at the end of each name ("riva"). However, the beginning of each name is distinguishable when spoken ("Emt" vs. "Ka"). Kariva and Emtriva also share an overlapping route of administration (oral) and dosing regimen (once daily). Because each product comes in only one strength, it is possible for a prescription order for either medicine to be verbally communicated without indicating a strength. Despite these similarities, however, DMETS believes that the risk of confusion between Kariva and Emtriva is minimal due to the lack of convincing sound-alike characteristics.

[redacted]

*** NOTE: This review contains proprietary and confidential information regarding names that are pending approval. Therefore, it can be released to the public.***

differences, DMETS believes that there is minimal risk for confusion and error between Intrinsa and Emtriva.

Emtriva

Emtriva

D.

Market Research for Proposed Name Emtriva dated May 2, 2003

The — conducted a study to evaluate the potential for error between Emtriva and currently marketed brand/generic drug products. The — reported that 100 physicians and 100 pharmacists participated in the study. The specialties of the physicians and pharmacists were: HIV Physicians (80), Infectious Disease Specialists (20), retail pharmacists (50), and hospital pharmacists (50). Overall, the response rate was 37% for practitioner nomenclature review and 39% for handwritten and verbal analysis. The medical professionals participated in various aspects of the three phases of the — study. The four sections of the study as well as study findings are discussed below.

1. Section A – Practitioner Nomenclature Review: Physicians

— asked 100 physicians to view the test name, Emtriva, and identify any existing brand or generic names that they considered similar to the test name based on sound and/or appearance. They also determined whether Emtriva had sound-alike or look-alike properties to any medical terms or devices. The participants evaluated the proposed name for any relationship to "hyperbole or false claims." Verbal and handwritten prescriptions of the proposed proprietary name were collected from these physicians to be used in Section B of the study. The physicians provided oral and handwritten interpretations of the following Emtriva prescription:

Emtriva 200 mg
1 capsule po qd

DMETS Response:

Although — indicates that 270 physicians were asked to participate in this phase of the study, the response rate was only 37% (100 physicians). — notes that this is a "typical" response rate for a survey of this type. However, there are limitations in the predicative value of these studies, primarily due to the sample size. It is not indicative as to what will occur once the drug is widely prescribed.

Physicians were requested to identify any hyperbole or false claims implied by Emtriva. Of the physicians polled, 1% of physicians thought that the name suggests it is an HIV medication, which correctly identified the indication of the test product. Physicians were also requested to identify medical terms or devices that had sound-alike or look-alike properties to Emtriva, and to identify any existing names they considered to be similar to Emtriva based on sound, appearance, or both. DMETS concurs with the —assessment that the nine proprietary names identified by the

physicians (*Abreva, Arava, Evista, Imitrex, Optivar, Sustiva, Emetrol, Enbrel, Evista, and Frova)* have a low potential for confusion with Emtriva. — did not identify any medical terms that were considered similar to the proposed proprietary name.

2. Section B – Handwritten and Verbal Analysis: Pharmacists

— provided fifty actively practicing pharmacists with a verbal prescription for Emtriva, and another group of fifty pharmacists with a written prescription for Emtriva. The objective of this phase is to determine if any of the sample Emtriva prescriptions would be interpreted as a currently marketed brand or established name product. Additionally, — asked 100 pharmacists to view the test name, Emtriva, and identify any existing brand or generic names that they considered similar to the test name based on sound and/or appearance. They also determined if Emtriva had sound-alike or look-alike properties to any medical terms or devices. The participants evaluated the proposed name for any relationship to "hyperbole or false claims."

DMETS Response:

reports that 50 (100%) of the pharmacists interpreted the verbal prescription correctly, and 50 (100%) of the pharmacists interpreted the handwritten prescription correctly. However, — states that two hundred sample prescriptions were collected from the physicians (i.e., 100 verbal and 100 written). Therefore, it appears that each of the one hundred pharmacists would have received two sample prescriptions to review, one written and one verbal. This methodology introduces bias because the participating pharmacists would have been exposed to the drug name before evaluation of the second sample. Pharmacists were requested to identify any hyperbole or false claims implied by Emtriva. Of the pharmacists polled, 1% of pharmacists thought that the name implied nausea relief, and 1 % thought that the name suggested that the product is an antiviral medication. Pharmacists were also requested to identify medical terms or devices that had sound-alike or look-alike properties to Emtriva, and to identify any existing names they considered to be similar to Emtriva based on sound, appearance, or both. Three medical terms were indicated as having similarity to the proposed name. There were empyesis, EMT (Emergency Medical Technician), and enzyme. There were eight proprietary names that were identified as being similar to the proposed name Emtriva *(Emla, Revia, Trizivir, Sustiva, Ultiva, Emetrol, Epivir, and Evista).* DMETS concurs with the — assessment that the eight proprietary names identified by the pharmacists have a low potential for confusion with Emtriva.

3. Section C – Computer-Assisted Analysis

— conducted a "comprehensive search of medical references" to identify brand and established name products that may sound-alike or look-alike to the proposed name Emtriva. Seventeen names were compared to Emtriva using [redacted] " database and using a "Phonological and Orthographical Similarity Analysis." The "Phonological and Orthographical Similarity Analysis" identifies a threshold of similarity between Emtriva and the products identified during the search of the medical references. The objective of this analysis is to identify the 'similarity between the proposed proprietary name and any sound-alike or look-alike product'. The proprietary name Emivan exceeded the threshold value for the Phonologic Similarity

Ratio, a measure of sound-alike similarity, when compared to Emtriva. Emivan is a respiratory stimulant, which is no longer actively marketed. Both Triaz and Trivora-28 exceeded the similarity thresholds in the bigram and trigram measurements, respectively. Additionally, — conducted a search of medical reference materials for medical terms, acronyms, and abbreviations similar to Emtriva, including medical terms mentioned by physicians in Section A of the study.

DMETS Response:

DMETS agrees with — that although Emivan, Triaz and Trivora-28 exceeded the threshold value for Phonologic Similarity Radio, Bigram and Trigram measurements, overall, these products have minimal common features when compared with the profile of Emtriva. — identified 14 medical terms, abbreviations, and acronyms that were similar to the proposed name. These were: *Embarc™ bone repair material, EmboGold™ microspheres, Embol-X™ liquid embolic system, Embosphere® microspheres, Embryon® GIFT transfer catheter set, Embryon™ HSG, Emcee™ introducer set, Emit® 2000, Empyesis, EMT (Emergency Medical Technician), Enzyme, MCA (Mean Corpuscular Volume), Trizma, Vitalab ViVa™ clinical chemistry analyzer, EM (Emmetropia), EM (Emotional Disorder), EM (Erythema Multiforme), IVA (Isovaleric Acid), and IVA (Isovaleric Acidemia).* DMETS concurs with — assessment that these medical terms, acronyms, and abbreviations pose no apparent safety issue for prescribing and dispensing of Emtriva.

4. —

Five actively practicing retail and hospital pharmacists provided an independent analysis of the proposed proprietary name, Emtriva, by considering its potential for error and potential for patient harm in the event of an error. The pharmacists were provided with the product concept and profile information for Emtriva, as well as research data from all sections of the study, and were asked to evaluate this information. The pharmacists evaluated all of the data obtained during this study. The — also considered postmarketing surveillance information, including errors and adverse events as reported in the National Coordinating Council for Medication Error Reporting and Prevention website, MedWatch website, U.S. Pharmacopoeia website, the U.S. Pharmacopoeia Quality Review – Stop, Look, and Listen! list, and the American Drug Index Monograph "Drug Names That Look Alike and Sound Alike". The — also stated that the study findings regarding the evaluation of hyperbole or fanciful claims indicated nothing misleading or inappropriate about the proposed proprietary name. Therefore, Emtriva should be considered an appropriate proprietary name.

DMETS Response:

DMETS agrees with the — conclusion that overall, the proposed proprietary name Emtriva is acceptable from a safety perspective.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In review of the container labels, carton and package insert labeling for Emtriva, DMETS has focused on safety issues relating to possible medication errors, and has identified areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

1. Please include the dosage form with the established name. For example:

   Emtriva
   (Emtricitabine Capsules)
   200 mg

2. Relocate the net quantity away from the product strength.

3. Ensure the established name is at least half the size of the proprietary name.

4. Include an "Each capsule contains....." statement.

B. CARTON LABELING

See comments under container label.

C. PACKAGE INSERT LABELING

In the DOSAGE AND ADMINISTRATION section please add the appropriate dose for each dosing interval provided in Table 8. For example, revise "every 24 hours" to read "200 mg every 24 hours".

IV. RECOMMENDATIONS

A. DMETS has no objection to the use of the proprietary name "Emtriva". In addition, DMETS recommends implementation of the labeling revisions as outlined in Section III of this review. DMETS considers this a final review. If the approval of the application is delayed beyond 90 days from the signature date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

B. DDMAC finds the name Emtriva acceptable from a promotional perspective.

DMETS 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 at 301-827-3242.

/S/

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

/S/

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Tia Harper-Velazquez
6/24/03 04:08:04 PM
PHARMACIST

Alina Mahmud
6/25/03 07:39:04 AM
PHARMACIST

Carol Holquist
6/25/03 01:20:14 PM
PHARMACIST

Jerry Phillips
6/27/03 10:54:50 AM
DIRECTOR

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

REQUEST FOR CONSULTATION

TO (Division/Office):
:y Jean Kozma-Fornaro
HFD-550

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
May 27, 2003		21-500	NDA amendment	May 16, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
emtricitabine capsules	Standard Review	Treatment of HIV	June 20, 2003

NAME OF FIRM: Gilead Sciences

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
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

We are concerned with the adverse reaction reported as "skin discoloration." Our faxed request for additional information from the applicant are included with this consult. We will forward their response (not submitted yet) to you by June 4, 2003. Please advise on the clinical significance or potential sequelae of drug assoicated hyperpigmentation based on your experience with other drug products. Also, please advise our division regarding the most effective way to manage this finding (e.g. language in the labeling).

PDUFA DATE: July 3, 2003, Internal Action Date: July 2, 2003.
ATTACHMENTS: Most recent version of labeling, the May 16, 2003 amendment, and DAVDP's request (fax) for additional information.

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

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/s/

Virginia Yoerg
5/28/03 11:11:28 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

Tel 301-827-2020
FAX 301-827-2075

M E M O R A N D U M

Date: June 17, 2003

From: Markham C. Luke, M.D., Ph.D., Dermatology Team Leader

Through: Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540

Jonca Bull, M.D., Office Director, ODE V

To: Virginia L. Yoerg, Regulatory Health Project Manager, HFD-530
Russ Fleischer, PA-C, MPH, Acting Medical TL, HFD-530
Debra Birnkrant, M.D., Division Director, DAVDP, HFD-530

Cc: Mark Goldberger, M.D., Office Director, ODE IV
M.J. Kozma-Fornaro, R.N., Supervisory PM, HFD-540

Re: Consult 453 was received on May 29, 2003 and consisted of the following questions:
"We are concerned with the adverse reaction reported as "skin discoloration." Our faxed request for additional information from the applicant are included with this consult. We will forward their response (not submitted yet) to you by June 4, 2003. Please advise on the clinical significance or potential sequelae of drug associated hyperpigmentation based on your experience with other drug products. Also, please advise our division regarding the most effective way to manage this finding (e.g. language in the labeling). PDUFA Date July 3, 2003."

Material Reviewed: Most recent version of labeling, May 16, 2003 amendment, and DAVDP's request to Sponsor for additional information.

Review:

Skin discoloration adverse events noted during the conduct of trials supporting NDA 21-500 were discussed by the Sponsor in their May 16, 2003 submission. "The events of skin discoloration were typically reported as hyperpigmentation/skin

discoloration, usually affecting either the palm of the hands and/or the sole of the feet...All of the skin discoloration events were a-symptomatic and were generally assessed by the investigator as being mild in severity."

The skin discoloration in the pivotal long-term studies demonstrated a racial predilection for Blacks:

ETHNIC GROUP	STUDIES FTC-301A AND FTC-303 COMBINED (N=580)
Total	15/580 (2.6%)
Black	11/111 (9.9%)
Caucasian	1/329 (0.3%)
Hispanic	3/111 (2.7%)
Asian	0/6 (0%)
Other	0/23 (0%)

The photographs provided by the Sponsor appeared to show hyperpigmented macules on the sole of the foot or palmar surface of the hands (only 2 photographs were included). The utility of the photographs were limited by their resolution and size. It was not possible to determine the exact nature of the hyperpigmented macules.

The Sponsor stated that "The available data suggest that the event is cosmetic in nature and of limited clinical significance. This event appears to be akin to the reports of changes in skin and nail pigmentation in black patients treated with zidovudine."

The Division of Antiviral Drug Products sent a Request for Information dated May 19, 2003 to the Sponsor asking to further clarify the nature of the skin discolorations. The Sponsor submitted a response dated June 2, 2003 and received on June 5, 2003 where further discussion is provided. Further, the Sponsor provides a narrative from their expert dermatologist, Dr. Timothy Berger. This report acknowledges that the hyperpigmentation reported for patients treated with emtricitabine occurred on the palms and soles in many of the patients along with increased skin fold, nail, and mucosal pigmentation.

Hyperpigmentation has been noted in patients with HIV infection and is well documented in the literature. Many of the cases may be associated with anti-retroviral therapy. From this reviewer's clinical experience, many of the cases of hyperpigmentation in HIV infected patients may be due to concomitant medications such as Bactrim. This type of drug induced hyperpigmentation is especially common in African-American patients. The hyperpigmentation has been described as being more prominent in the sun-exposed areas of the skin (e.g. greater darkening of the face than the covered torso. Mucosal and non-sun-exposed surfaces have also been noted to be involved. Poliferation or accentuation of palmar/plantar hyperpigmented macules due to zidoviudine has been noted in one publication (Bendick, Rasokat, and Steigleder, Arch. Dermatol., 1989 – page 95 of June 2, 2003 submission). Accentuation of palmar/plantar

and non-palmar/plantar hyperpigmented macules can be seen in patients on various chemotherapeutic agents, such as doxorubicin, adriamycin, bleomycin.

The differential diagnosis of new onset palmar/plantar hyperpigmented macules includes secondary syphilis. This should be given high consideration due to the population being studied (HIV positive). Long-standing, single hyperpigmented macules on the palms and soles in African Americans that are changing (e.g., becoming more accentuated) should give rise to concern about acral lentiginous melanoma. However, this could be ruled out by examination of the lesions by a dermatologist and from history.

A post-marketing commitment to evaluate further the nature of these lesions should be obtained from the Sponsor. Subjects should have pigmented lesions further assessed. Additional work-up should include screening for RPR and evaluation of concomitant medications. Close-up photographs could help in the documentation and evaluation of these lesions. Biopsies should only be obtained when clinically indicated.

Labeling should be requested from the Sponsor that would adequately address this concern and direct evaluation for pigmented lesions to a trained healthcare professional.

A consultation to the Office of Drug Safety regarding reports of hyperpigmentation in patients on other anti-retroviral therapies may be helpful to discern the extent of a possible class effect. This is hinted in some of the literature and in Dr. Berger's statement sent on June 2, 2003.

Thank you for giving us the opportunity to assist you. Please do not hesitate to contact the Division of Dermatologic and Dental Drug Products with any additional questions or concerns.

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/s/

Markham Luke
6/17/03 12:02:08 PM
MEDICAL OFFICER
Consult #453 for Division of Antiviral Drug Products

Jonathan Wilkin
6/18/03 09:44:06 AM
MEDICAL OFFICER
Alopecia from cancer chemotherapy has led some patients to D/C potentially life-saving Tx. Sponsor should evaluate the impact of the hyperpigmentation on patient Tx decisions & possibility of photoaugmentation (& sun protection) post marketing.

Jonca Bull
6/20/03 05:17:48 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: June 2, 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 (DSRCS), HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support (DSRCS), HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for emtricitabine, NDA 21-500

The attached patient labeling (clean copy) represents part of the revised risk communication materials for emtricitabine, NDA 21-500. 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, not to provide detailed information about the condition), 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.

Please call us if you have any questions. 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.

6 pages redacted from this section of the approval package consisted of draft labeling

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/s/

Jeanine Best
6/2/03 09:49:01 AM
CSO

Toni Piazza Hepp
6/2/03 02:07:14 PM
DRUG SAFETY OFFICE REVIEWER

Redacted 4

pages of trade

secret and/or

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

FACSIMILE TRANSMITTAL SHEET

DATE: September 20, 2002

To: Anne McKay	**From:** Nitin Patel, R.Ph., Regulatory Project Manager
Company: Triangle Pharmaceuticals	Division of Antiviral Drug Products
Fax number: 919-493-5925	**Fax number:** 301-827-2471
Phone number: 919-493-5980	**Phone number:** 301-827-2442
Subject: NDA 21-500 Chemistry comments	
Total no. of pages including cover: 3	

Comments:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: September 20, 2002

To: Anne McKay
Vice President
Drug Regulatory Affairs
Triangle Pharmaceuticals, Inc.

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

Through: Stephen P. Miller, Ph.D., Chemistry Team Leader, HFD-530
George Lunn, Ph.D., Chemist, HFD-530

NDA: 21-500

Drug: Coviracil® (emtricitabine) Capsules

Subject: Chemistry comments

The following comments are being conveyed on behalf of Stephen P. Miller, Ph.D., Chemistry Team Leader, and George Lunn, Ph.D., Chemist:

Please confirm that the following facilities are the ONLY sites involved in the manufacturing, testing, and packaging of drug substance and drug product for your NDA 21-500 for Coviracil (emtricitabine) capsules. Please confirm that the address and the functions listed for each site are correct, and that all the facilities are ready for the GMP inspection:

Product:

Drug substance:

Drug product:

Additionally, please supply a more complete address for [redacted] and supply the site where drug substance stability testing is carried out.

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.

/S/

Nitin Patel, R.Ph.
Regulatory 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/

Nitin Patel
9/20/02 02:20:24 PM
CSO

Chemistry comments for Coviracil Capsules, NDA 21-500: Hard copy sign-off by Stephen Miller - 9/20/02.

Chemistry comments for Coviracil Capsules, NDA 21-500: Hard copy sign-off by Stephen Miller - 9/20/02.

Stephen Paul Miller
9/20/02 05:24:50 PM
CHEMIST

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

FACSIMILE TRANSMITTAL SHEET

DATE: September 30, 2002

To: Anne McKay	From: Nitin Patel, R.Ph., Regulatory Project Manager
Company: Triangle Pharmaceuticals	Division of Antiviral Drug Products
Fax number: 919-493-5925	Fax number: 301-827-2471
Phone number: 919-493-5980	Phone number: 301-827-2442

Subject: ~~——~~ NDA 21-500
Pharmacology comments/requests

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ☑ NO