

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-752

CHEMISTRY REVIEW(S)

NDA 21-752

**TruvadaTM (tenofovir disoproxil fumarate/emtricitabine)
Tablets**

Gilead Sciences, Inc.

**George Lunn, Ph.D.
Division of Anti-Viral Drug Products**

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Chemistry Review Data Sheet

1. NDA or ANDA 21-752
2. REVIEW #: 2
3. REVIEW DATE: 2-AUG-2004
4. REVIEWER: George Lunn, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Chemistry Review 1	22-Jun-2004

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	11-Mar-2004
Amendment (BZ)	5-Apr-2004
Amendment	23-May-2004
Amendment	3-Jun-2004
Amendment	10-Jun-2004
Amendment	18-Jun-2004
Amendment	17-Jul-2004
Amendment	26-Jul-2004
Amendment	28-Jul-2004

7. NAME & ADDRESS OF APPLICANT:

**CHEMISTRY REVIEW**

Chemistry Review Data Sheet

Name: Gilead Sciences, Inc.
Address: 333 Lakeside Drive
Representative: Foster City, CA 94404
Telephone: 650 754 3000

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Truvada™
- b) Non-Proprietary Name (USAN): Tenofovir disoproxil/emtricitabine
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 4
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Anti-viral

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 300 mg/200 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

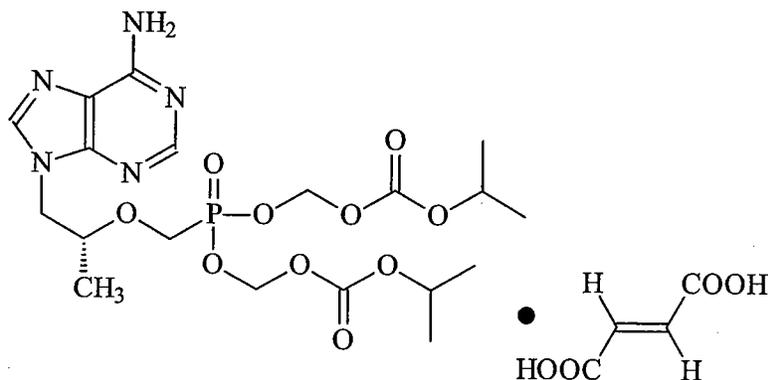
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Tenofovir disoproxil fumarate

9-[(R)-2-[[Bis[[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1)

Molecular formula: $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$

Molecular weight: 635.51



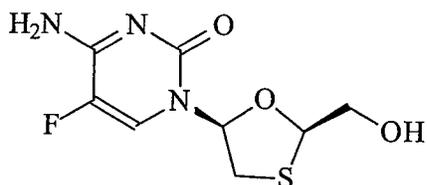
Emtricitabine

5-Fluoro-1-(2R,5S)-[2-hydroxymethyl]-1,3-oxathiolan-5-yl]cytosine

FTC

Molecular formula: $C_8H_{10}FN_3O_3S$

Molecular weight: 247.24



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: None

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS

CHEMISTRY REVIEW

Chemistry Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	01-Jun-2004	S. Adams
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Pending		
OPDRA	N/A		
EA	N/A		
Microbiology	N/A		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER

Chemistry Review Data Sheet

Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-752

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from the CMC perspective. All CMC issues have been satisfactorily resolved and an overall recommendation of Acceptable has been made by the Office of Compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

A batch of the export tablets in the light blue alternative trade dress will be placed on stability at 30°C/65% RH and 40°C/75% RH and the data will be submitted

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The chemistry, manufacturing, and controls for tenofovir disoproxil fumarate drug substance are described in approved NDA 21-356 for Viread (tenofovir disoproxil fumarate) Tablets.

The drug substance specification is essentially identical to that in the approved NDA 21-500 with the addition of specifications for a new impurity, _____ l. The new impurity is toxicologically qualified.

CHEMISTRY REVIEW

Executive Summary Section

Emtricitabine will be manufactured using the _____ process. Testing will take place at another _____ facility, Gilead Sciences, San Dimas CA, & _____
— All facilities were found to be acceptable based on profile or file review except for the _____ manufacturing facility. An inspection of this facility was conducted and it was found to be satisfactory. An overall recommendation of Acceptable was made by the Office of Compliance.

Satisfactory long term and accelerated stability data (up to 9 months) are provided for emtricitabine manufactured using the _____ process. The retest date remains _____ when stored below 30°C.

Truvada tablets contain tenofovir disoproxil fumarate and emtricitabine in a blue, capsule-shaped, film-coated tablet debossed with Gilead on one side and 701 on the other side. The inactive ingredients are croscarmellose sodium, NF, lactose monohydrate, NF, magnesium stearate, NF, microcrystalline cellulose, NF, pregelatinized starch, NF, and purified water, USP.

The formulation is very similar to that for Viread (tenofovir DF) tablets in the approved NDA 21-356 and not much formulation development work was carried out. To help combat re-importation problems an alternative trade dress for export only is also proposed. These tablets are light blue with Gilead debossed on one side and no marking on the other side. The change in color results from a change in the film coating material. The film coatings differ only in the ratio of the blue dye to titanium dioxide. There are no changes in the formulation, manufacturing, and controls of the core tablet. These tablets are approved for marketing in Climatic Zones I and II.

The inactive ingredients are all compendial except for the film coat. The film coat is, however, composed of compendial materials or materials that meet the requirements of 21 CFR (FD&C Blue#2 Aluminum Lake, hypromellose, USP, lactose monohydrate, NF, titanium dioxide, USP, and triacetin, USP).

The manufacturing process, which uses a _____ is described in detail and the critical steps are well controlled. The critical steps have been identified as follows. Adequate controls are proposed for each step.

Step	Test

_____ are used to demonstrate the consistency of each processing step. The parameters listed above were measured during the manufacturing process and shown to meet the acceptance criteria. These batches also gave satisfactory batch analyses.

CHEMISTRY REVIEW

Executive Summary Section

Manufacturing and testing will take place at _____
_____ Gillead Sciences, San Dimas CA; and Gillead Sciences, Foster City CA. All facilities were found to be acceptable based on profile or file review.

The drug product specification is comprehensive and acceptable. The specification closely resembles that for Viread (tenofovir DF) tablets described in the approved NDA 21-356. However, some of the acceptance criteria are looser, particularly for the impurities. The sponsor was asked about this and justified it on the grounds that the storage statement is now "Store below 30°C" compared with "Store at 25°C" for the individual products. The acceptance criteria are reasonable and the impurities are well qualified by toxicology studies.

For the most part the impurities have been previously described in the approved NDAs for the individual products. Two new impurities are observed that are adducts of emtricitabine and tenofovir DF. These impurities are only observed at low levels and are considered to be toxicologically qualified. Also the _____ process produces the new impurity _____

The analytical methods are well described and validated. Minor points were resolved by discussion with the sponsor during the review process. A complete Methods Validation package is supplied. Validation is not expected before NDA approval.

The container-closure system is a white _____ HDPE bottle fitted with a child-resistant cap and induction seal and contains an _____ cylinder or _____ pouch containing 3 g of silica gel desiccant and 30 tablets. The container-closure system is similar to that used for the approved Viread (tenofovir DF) tablets. At the request of FDA "Keep container tightly closed" and "Dispense only in original container" were added to the bottle label and package insert in consideration of the moisture sensitivity of the product.

The primary drug product stability data consists 12, 9, 9, and 6 months of long term (obtained at 25°C/60% RH) and intermediate stability data (obtained at 30°C/65% RH), and 6 months accelerated stability data (obtained at 40°C/75% RH) for _____ batches manufactured at the commercial site at the lower end of the commercial scale (_____).

There are no out of specification results but there are numerous trends. There is a decrease in water with time although this seems to level off. There are decreases in assay with time and temperature. There are increases in degradants, particularly _____ and _____ and unspecified with time and temperature. There is a very slight increase in one of the tenofovir/emtricitabine adducts. Dissolution does not appear to change.

Statistical analyses performed on the data obtained for these four primary stability batches stored at 25°C/60% RH and 30°C/65% RH predict that the specifications for tenofovir DF assay, emtricitabine assay, and selected and total impurities would not be exceeded during 24 months, the proposed expiration dating period. The sponsor proposed an expiration dating period of 24 months for tablets stored below 30°C and, based on the data submitted, this is reasonable. The storage recommendation is "Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F)."

Executive Summary Section

For the export tablet the storage recommendation is "Store at up to 30°C (86°F)". Either statement is supported by the stability data.

To obtain approval of the alternate trade dress (light blue) tablets for marketing in Climatic Zones III and IV countries, in addition to the usual stability studies under long-term (30°C/65% RH) and accelerated conditions (40°C/75% RH), the sponsor has agreed to conduct a stress stability study on one batch of tablets that are stored for three months at 50°C/ambient humidity and at 25°C/80% RH conditions as recommended in the FDA Guidance for Industry document entitled *Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV (June 2004)*. The results of this study will be submitted as a Prior Approval Supplement.

A categorical exclusion from the requirement to file an Environmental Assessment is requested. This is reasonable.

This review was based upon a review of the data in Module 3. Module 2 contained almost all of the data found in Module 3 but in a compressed format with little effort expended on summaries or generalizations. The Quality Overall Summary in Module 2 comprised 139 pages. Module 3.2, omitting the executed batch records and the Methods Validation Package, is about 800 pages. For this product not much pharmaceutical development work was required so Section P2 was correspondingly brief.

B. Description of How the Drug Product is Intended to be Used

Truvada tablets are combination tablets containing tenofovir disoproxil fumarate and emtricitabine, both nucleoside reverse transcriptase antagonists. Truvada is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. The tablets contain 300 mg tenofovir disoproxil fumarate, equivalent to 245 mg tenofovir disoproxil, and 200 mg emtricitabine. The recommended dose is one tablet once daily taken orally with or without food. The tablets are supplied in HDPE bottles containing 30 tablets and a silica gel desiccant. The storage recommendation is "Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F)." For the export tablet the storage recommendation is "Store at up to 30°C (86°F)". The expiration dating period is 24 months.

C. Basis for Approvability or Not-Approval Recommendation

The chemistry, manufacturing, and controls for tenofovir disoproxil fumarate drug substance are described in approved NDA 21-356 for Viread (tenofovir disoproxil fumarate) Tablets. The chemistry, manufacturing, and controls for emtricitabine drug substance manufactured using the process are described in approved NDA 21-500 for Emtriva (emtricitabine) capsules. The process for the manufacture of emtricitabine drug substance is well controlled and described in detail in this application. The composition, manufacturing process, and specifications for the tablets are appropriate and the expiration dating period of 24 months is supported by adequate data. The container-closure system and

Executive Summary Section

labeling are appropriate. All manufacturing sites have been found to be acceptable. This NDA is therefore recommended for approval from a CMC perspective.

III. Administrative

A. Reviewer's Signature

George Lunn, Ph.D. {Signed Electronically in DFS}

B. Endorsement Block

Stephen P. Miller, Ph.D. {Signed Electronically in DFS}

C. CC Block

David Lin, Ph.D.

72 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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/s/

George Lunn
8/2/04 11:26:24 AM
CHEMIST

CMC Review 2 for FTC/TDF fixed-dose combination

Stephen Paul Miller
8/2/04 11:55:03 AM
CHEMIST



MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-752

Drug: Tenofovir DF/Emtricitabine Tablets

Date: July 14, 2004

To: Carla Fiankan, Associate Director, Global Regulatory Affairs, CMC

Sponsor: Gilead Sciences, Inc.

From: Jeff D. O'Neill, ACRN, Regulatory Health Project Manager, DAVDP

Concurrence: Jeffrey Murray, M.D., M.P.H., Deputy Division Director, DAVDP
Stephen P. Miller, Ph.D., Chemistry Team Leader, DAVDP

Through: Rao Kambhampati, Ph.D., Acting Chemistry Team Leader, DAVDP

Subject: Chemistry comments regarding NDA 21-752, amendment dated June 18, 2004.

The following comments are being provided on behalf of Rao Kambhampati, Ph.D:

Please refer to your Amendment dated June 18, 2004 to your NDA 21-752 describing an alternate trade dress for export to developing world countries. In view of the minor changes we felt that the original stability data supported the alternate trade dress for use in Climatic Zones 1 and 2. However, in view of the drop in assay seen at 50 deg C (3.2.P.8.3, pp. 26-27) we feel that additional stability data may be appropriate if this product is to be marketed in Climatic Zones 3 and 4. Given the recommendations in ICH Q1F we would be interested, separately from the pending NDA 21-752, in exploring additional stability data, or packaging changes to address distribution and patient use in Climatic Zones 3 and 4. We also note that information about the facilities involved in manufacturing, packaging and testing of the alternate trade dress tablet should be submitted as recommended in the draft FDC guidance.

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.

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this page is the manifestation of the electronic signature.**

/s/

Jeff ONeill
7/14/04 11:21:00 AM
CSO

Chemistry comments regarding NDA 21752, amendment dated June 18,
2004, for an alternate trade dress for export
to developing world countries. Hard copy sign-off 7/14/04

Jeffrey Murray
7/19/04 05:22:54 PM
MEDICAL OFFICER



MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-752

Drug: Tenofovir DF/Emtricitabine Tablets

Date: May 14, 2004

To: Martine Kraus, Ph.D., Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc.

From: Jeff D. O'Neill, ACRN, Regulatory Project Manager, DAVDP

Through: George Lunn, Ph.D., Chemistry Reviewer, DAVDP

Subject: Chemistry comments regarding NDA 21-752 dated March 11, 2003.

-
- Please provide a rationale for the absence of an assay specification for the Product. Additionally, please reassess the total impurities limit of NMT for this compound. The total impurities values for the batches described ranged from . Please also supply data to show that product containing impurities close to their acceptance criteria (NMT and NMT respectively) will provide acceptable drug substance.
 - If available, please provide more data describing the polymorph form, particle sizes for more batches of emtricitabine drug substance produced by the processes (Section 3.2.S.3.1)
 - The listing of impurities/degradants in the drug product specification may be confusing. To avoid confusion please assign each compound to a separate line. It is not clear if a statement such as "NMT" means that each compound should be NMT (which would be similar to Viread) or that the total of all compounds should be NMT (a literal reading). If a particular acceptance criterion applies to the sum of a number of components then a listing similar to "NMT" should be used to avoid ambiguity.
 - Please identify each specified impurity by full name, structure, relative retention time, and a code name/number and provide such a listing as an appendix to the drug product specification. Terms such as are discouraged since there is

- In the validation for HPLC Procedure _____ please provide LOD, LOQ, and RRF values for all the specified impurities including _____
- HPLC Procedure _____ will probably not resolve all impurities from the active peak yet it is proposed as an acceptable method for determining the assay in the drug product specification. Please provide a justification for this practice. We agree that method _____ is acceptable for determining content uniformity and blend uniformity.
- Please provide a justification for the generally higher acceptance criteria for degradants in Truvada as compared to the acceptance criteria for the same compounds in Viread or Emtriva.
- In the description of the container-closure system two different cap liners/induction seals (from _____) are specified. Please provide the identity of the materials used in these liners and seals. We would expect that the liners and seals would not be changed without notifying FDA.
- In consideration of the moisture sensitivity of this product please consider adding "Keep container tightly closed" and "Dispense only in original container" or words to that effect to the container label and package insert.
- Please indicate when we may expect to receive a stability update.
- Since your storage statement is "Store below 30 deg C" we recommend that you provide statistical analyses on the stability data obtained at 30 deg C/65% RH for all primary stability batches.

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.

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this page is the manifestation of the electronic signature.**

/s/

Jeff ONeill
5/14/04 02:54:36 PM
CSO

Chemistry comments regarding NDA 21-752. Hard copy sign-off 5/14/04

George Lunn
5/14/04 03:12:59 PM
CHEMIST

DMF No:

ADA:

Responsibilities:

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-APR-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment :

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

DMF No:

AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 31-MAR-04
 Decision : ACCEPTABLE
 Reason : , BASED ON PROFILE

Establishment :

7

DMF No:

AADA:

Responsibilities:

Profile : CSN OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 31-MAR-04
 Decision : ACCEPTABLE
 Reason : BASED ON PROFILE

Establishment :

JMF No:

AADA:

Responsibilities:

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-JUL-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment

DMF No:

AADA:

Responsibilities:

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-APR-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION
