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*APPLICATION NUMBER:*

**021752Orig1s030**

**OTHER REVIEW(S)**

**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology Review (OSE)**  
**Office of Pharmacovigilance and Epidemiology (OPE)**

**Epidemiology: Review of Post-Marketing Commitment Requests**

Date: July 16th, 2012

Reviewer(s): James Phillip Trinidad, M.P.H., M.S., Regulatory Review Officer  
Division of Epidemiology II  
Grace Chai, Pharm.D., Drug Utilization Analysis Team Leader  
Division of Epidemiology II

Team Leader Elizabeth Maloney, M.S., Dr.P.H., Epidemiology Team Leader  
Division of Epidemiology II

Division Director Judy Staffa, Ph.D., R.Ph., Director  
Division of Epidemiology II

Drug Name(s): Emtricitabine / Tenofovir Disoproxil Fumarate (Truvada®)

Subject Review of Postmarketing Commitment Requests Regarding Drug Utilization of and Adherence to Truvada® for HIV Pre-Exposure Prophylaxis

Application Type/Number: NDA 21752

Submission Number: S-30

Applicant/sponsor: Gilead Sciences, Inc.

OSE RCM #: 2012-1468

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## **EXECUTIVE SUMMARY**

The Division of Antiviral Products (DAVP) has been evaluating Truvada®, a combination product (emtricitabine / tenofovir disoproxil fumarate) developed by Gilead Sciences, Inc., for pre-exposure prophylaxis against HIV infection, and has consulted the Division of Epidemiology II (DEPI II) for input on postmarketing studies. As such, DEPI II did the following:

1. reviewed an observational study of Truvada® proposed by Gilead Sciences, Inc., and provided feedback in the form of a general advice letter
2. developed the requirements for a postmarketing commitment requesting drug utilization information
3. developed two postmarketing commitments requesting an assessment of adherence to Truvada® and subsequent clinical outcomes

## **1 INTRODUCTION**

The Division of Antiviral Products (DAVP) and the Division of Epidemiology II (DEPI II) met on Jun 6, 2012, to discuss the need for postmarketing commitments and requirements for Truvada®. A subsequent meeting was held on Jun 14, 2012, for further discussion. It was determined that it was important to assess drug use and adherence in the postmarket “real world” setting, and both were deemed as postmarketing commitments (PMC). On Jun 18, 2012, Gilead Sciences, Inc. submitted a protocol for an observational study to measure the association between self-reported adherence based on questionnaire data and patients’ knowledge, attitudes and beliefs about Truvada®. Gilead Sciences, Inc. also proposed this study as a postmarketing commitment. DAVP requested that DEPI II develop separate PMCs to describe utilization of and adherence to Truvada®. Additionally, DAVP requested that DEPI II review the sponsor’s proposed observational study.

## **2 REVIEW METHODS AND MATERIALS**

### **2.1 DOCUMENTS REVIEWED**

The draft protocol reviewed for this consult was the following:

- Gilead Sciences, Inc. (2012). Observational Study Protocol: The Gilead Pre-Exposure Prophylaxis (PrEP) Registry of Uninfected Individuals Taking Truvada® as Part of a Comprehensive HIV Prevention Strategy. Response to FDA’s Request for Information of 18 June 2012. Submitted to DARRTS on Jun 26, 2012, for NDA #021752.

The following document provided important background information on the biologic specimens used to assess levels of adherence and was used for the development of the PMC on adherence:

- The Review Team for NDA 21-752/S-30. (2012). Background Package for NDA 21-752/Supplement 30. Briefing information for the May 10, 2012, meeting of the Antiviral Drugs Advisory Committee.  
<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drug/AntiviralDrugsAdvisoryCommittee/UCM303213.pdf>

## **3 REVIEW RESULTS**

### **3.1 DRUG UTILIZATION STUDY POSTMARKETING COMMITMENT (PMC)**

To understand the real-world use of Truvada® for HIV pre-exposure prophylaxis, DEPI II drafted a communication for DAVP to request that Gilead Sciences, Inc. commit to a drug utilization PMC (Appendix A). A communication, revised by DAVP in conjunction with DEPI

II, was subsequently sent to Gilead Sciences, Inc. on Jun 13, 2012<sup>1</sup>. Gilead Sciences, Inc. responded on Jun 29, 2012, with minor edits to the draft PMC<sup>1</sup>. DEPI II, in turn, responded on Jul 6, 2012, with comments to the edited PMC (Appendix B). The intent of this response was to clarify and emphasize the importance of capturing use of the single-ingredient products emtricitabine and tenofovir disoproxil fumarate, as well as the combination product emtricitabine / tenofovir disoproxil fumarate, for the indication of HIV pre-exposure prophylaxis in all settings of care. Gilead Sciences, Inc. incorporated DEPI II's comments into the PMC<sup>2</sup>.

### **3.2 OBSERVATIONAL STUDY PROTOCOL AND POSTMARKETING REQUESTS TO ASSESS ADHERENCE**

Appendix C summarizes DEPI II's comments and recommendations upon review of the draft protocol submitted by Gilead Sciences, Inc. In brief, DEPI II found the study, as described in the draft protocol, to be inadequate in assessing adherence rate (and subsequent clinical outcomes) among individuals enrolled in the study who were prescribed Truvada® for HIV pre-exposure prophylaxis. On Jul 3, 2012, these comments and recommendations were sent in a memorandum of electronic correspondence to Gilead Sciences, Inc.<sup>3</sup>. This same memorandum contained two additional requests drafted by DEPI II. These requests outlined PMCs with the objectives to assess adherence (and subsequent clinical outcomes) among HIV-uninfected individuals prescribed Truvada® for pre-exposure prophylaxis (Appendix D). On Jul 12, 2012, Gilead Sciences, Inc. submitted revisions of the two additional requests for PMCs in lieu of conducting the study outlined in the draft protocol<sup>2</sup>. DEPI II found these revisions to be acceptable.

## **4 DISCUSSION**

Upon providing comments and reviewing revisions to postmarketing requests and the observational study protocol, which was submitted by Gilead Sciences, Inc., DEPI II finds the postmarketing commitments, that were mutually agreed to, acceptable in addressing drug use and adherence of Truvada® for the indication of HIV pre-exposure prophylaxis in the postmarket “real world” setting.

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<sup>1</sup> Gilead Sciences, Inc. (2012). Response to FDA Request for Postmarketing Requirements and Study Commitments under NDA 21-752/S-030. Submitted to DARRTS on Jun 29, 2012, for NDA #021752.

<sup>2</sup> Gilead Sciences, Inc. (2012). Response to Proposed Revisions to Postmarketing Commitments. Submitted to DARRTS on Jul 12, 2012, for NDA #021752.

<sup>3</sup> Schumann, K. (2012). Memorandum of Electronic Correspondence. Submitted to DARRTS on Jul 3, 2012, for NDA #021752.

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/s/  
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JAMES TRINIDAD  
07/17/2012

GRACE CHAI  
07/17/2012

ELIZABETH M MALONEY  
07/17/2012

LAURA A GOVERNALE  
07/17/2012  
Signed for Judy Staffa.

PMR 1906-3

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA # 21-752  
Product Name: TRUVADA®

PMR Description: Conduct an analysis of data from ongoing and planned demonstration projects (trials) including at least 7000 uninfected individuals taking Truvada® for a pre-exposure prophylaxis (PrEP) indication with the objective of examining the association between levels of adherence to the once-daily dosing regimen and risk of seroconversion, resistance development, and renal and skeletal adverse events. Levels of adherence should measure a gradient of adherence levels rather than the simple dichotomy of ‘adherent’ versus ‘non-adherent’ using any available data on drug levels as the measure of adherence. Seroconversion will be assessed every three months, and, upon each seroconversion, resistance testing should be performed. Assessment for renal and skeletal adverse events will be performed every three months, including evaluation of available laboratory data. Analyses will be performed by geographic region, including the United States.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	11/2012
	Study/Trial Completion:	04/2016
	Final Report Submission:	12/2016
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The clinical trials submitted in support of this application strongly indicated that better adherence to Truvada was correlated with greater efficacy. Likewise, the safety of any intervention is related to compliance with its use. Because adherence to a bio-behavioral intervention may vary and because the levels of adherence to Truvada in the post-approval period cannot be wholly predicted by the clinical trials, an assessment of the relationship between levels of drug adherence to Truvada for pre-exposure prophylaxis of HIV-1 infection and the incidence of seroconversion, development of drug resistance, and development of the known serious risks of renal and bone toxicity associated with Truvada is appropriate for a PMR.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In the clinical trials submitted in support of this application, poor adherence to Truvada for pre-exposure prophylaxis was related to a greater risk of seroconversion. Conversely, poor drug adherence may have also contributed to the lack of drug-resistant variants observed among subjects who seroconverted during follow-up. The degree to which drug adherence affected the safety findings in these trials is not entirely clear. The risk is that while greater adherence to Truvada may result in lower risk of seroconversion and development of resistance, it may also result in greater risk of serious renal and bone toxicity. On the other hand, moderate adherence may result in less toxicity but greater risk of seroconversion and greater risk of drug resistance. Because adherence to Truvada for pre-exposure prophylaxis in the post-approval period may vary and cannot be wholly predicted by the clinical trials, and because different levels of adherence may affect the risk of seroconversion, drug resistance, and renal and bone toxicity in different and sometimes competing ways, the goal of the PMR clinical trial is to further assess the association between objective measures of adherence and the incidence of these events.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Safety trial to collect and analyze data from uninfected individuals enrolled in demonstration projects (trials) and taking Truvada for pre-exposure prophylaxis. The primary objective is to evaluate rates of seroconversion, development of drug resistance, and renal and skeletal adverse events in relation to levels of adherence as determined by objective measures of adherence.

Required

- Observational pharmacoepidemiologic study  
 Registry studies  
 Primary safety study or clinical trial  
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety  
 Thorough Q-T clinical trial  
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)  
 Pharmacokinetic studies or clinical trials  
 Drug interaction or bioavailability studies or clinical trials  
 Dosing trials  
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials  
 Immunogenicity as a marker of safety  
 Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)  
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)  
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E  
 Dose-response study or clinical trial performed for effectiveness  
 Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?  
 Are the objectives clear from the description of the PMR/PMC?  
 Has the applicant adequately justified the choice of schedule milestone dates?  
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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KATHERINE SCHUMANN  
07/16/2012

KENDALL A MARCUS  
07/16/2012

PMR 1906-2

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 21-752  
Product Name: TRUVADA®

PMR Description: Collect and analyze data from individuals who take Truvada® for pre-exposure prophylaxis (PrEP) of sexually acquired HIV-1 infection and who seroconvert during follow-up. The following data should be collected and the following analyses conducted on data collected from a minimum of 150 seroconverters over a time period not to exceed 3 years:

- Data regarding the presence or absence of signs and symptoms of acute HIV infection at the study visit or since the last study visit when seroconversion is identified.
- Frequency of screening and screening method(s) used for evaluation of the seroconverter, and in general, at that enrollment site.
- Analyses of baseline samples from early seroconverters to evaluate HIV-1 RNA and the presence or absence of resistance.
- Resistance analyses of viral isolates from seroconverters that include population nucleotide sequence analysis followed by ultrasensitive testing (such as ultra-deep sequencing of proviral DNA or allele-specific PCR) if no resistance is identified by population sequencing.

This data may be collected from individuals participating in demonstration projects (trials).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>10/2012</u>
	Study/Trial Completion:	<u>03/2016</u>
	Final Report Submission:	<u>09/2016</u>
	Other: Interim Report Submissions:	<u>09/2013</u>
		<u>09/2014</u>
	<u>09/2015</u>	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

While development of drug resistance-associated substitutions were identified in the clinical trials submitted in support of this application, they were limited to the few individuals who were enrolled and initiated Truvada for pre-exposure prophylaxis in the presence of unrecognized acute or early HIV infection. No drug-resistant variants were identified among subjects who seroconverted during follow-up, bearing in mind that adherence issues and frequent (monthly) HIV monitoring may have been factors in this finding. Since adherence to Truvada for a pre-exposure prophylaxis indication may be different out of a clinical trial setting following approval, and since it is impractical for prescribers of Truvada to conduct monthly HIV screening, the assessment of drug resistance as a PMR is appropriate.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The development of resistance-associated substitutions was observed in viral isolates obtained from individuals with unrecognized HIV-1 infection who enrolled in the pivotal trials submitted in support of this sNDA application. Therefore, there is a serious risk that individuals taking Truvada for pre-exposure prophylaxis of sexually acquired HIV-1 infection may develop drug-resistant variants if they initiate Truvada for prophylaxis in the presence of unrecognized HIV infection (as was observed in the trials) or if they seroconvert while taking Truvada and continue taking drug while infected. Development of drug-resistant HIV variants may limit treatment options for the HIV-infected individual as well as increase the risk of transmitting drug-resistant virus to others.

The goal of the PMR clinical trial is to identify means of minimizing the risk of developing drug-resistant variants. To that end, the trial will characterize the signs and symptoms associated with acute HIV infection in individuals who seroconvert while using Truvada for pre-exposure prophylaxis and the screening methods used to identify these individuals, including the types of HIV tests used and the frequency of testing. In addition, the trial will analyze viral isolates from these individuals to characterize the incidence and nature of any resistance-associated substitutions that may develop and determine whether resistance was present at baseline among early seroconverters, who may have initiated Truvada in the presence of unrecognized HIV infection.

3. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk*

- Analysis using pharmacovigilance system?  
**Do not select the above study/clinical trial type if:** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
**Do not select the above study type if:** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Safety trial to be conducted through collection of data from a subgroup of HIV seroconverters taking Truvada for pre-exposure prophylaxis drawn from various PrEP implementation demonstration projects (trials) in different clinical settings.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)

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  - Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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PMR 1906-1

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA # 21-752  
Product Name: TRUVADA®

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PMR Description: Through collaboration with the Antiretroviral Pregnancy Registry, conduct a prospective observational study in order to collect and analyze data on maternal and fetal outcomes in 200 women who become pregnant while taking Truvada® for pre-exposure prophylaxis (PrEP) and choose to continue Truvada® during their pregnancies and in 200 women who become pregnant while taking Truvada® for PrEP and choose to discontinue it. Collect and analyze data from at least a similarly sized comparator group of pregnant HIV-infected women taking antivirals other than emtricitabine/tenofovir disoproxil fumarate. Data collected on pregnancy outcomes should include but not be limited to: timing of initiation and duration of Truvada® or other antiretrovirals, HIV seroconversions in mothers and infants, spontaneous and elective abortions, spontaneous and scheduled pre-term deliveries, stillbirths, infant weight (normal or low) and infant outcomes, including the presence or absence of congenital malformations.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	10/2012
	Study/Trial Completion:	09/2016
	Final Report Submission:	03/2017
	Other: Interim Report Submissions:	09/2013
		09/2014
		09/2015
		09/2016

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1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The clinical trial submitted in support of this application that enrolled women mandated that female subjects stop Truvada for pre-exposure prophylaxis when they became pregnant. Therefore, the potential for an unexpected serious risk of adverse maternal-fetal outcomes in uninfected women was not fully evaluated during the review. Nonclinical data and the limited postmarketing experience of Truvada use in pregnancy, however, do not indicate that there is a serious risk, so it remains a theoretical concern. Given that the risk of HIV seroconversion in women is considered to be greater during pregnancy (5 of 45 women who seroconverted in the submitted trial did so during treatment interruption for pregnancy), formal evaluation of Truvada use for pre-exposure prophylaxis in pregnancy is warranted and appropriate for a PMR.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The review did not note any particular safety risk related to pregnancy outcomes; however, the trial submitted in support of this application that enrolled women mandated that women stop study drug when they became pregnant. Therefore, the potential for an unexpected serious risk associated with use of Truvada in pregnancy was not fully assessed. The goal of the PMR clinical trial is to formally evaluate use of Truvada in pregnancy by comparing pregnancy outcomes and seroconversion rates between women who continue to use Truvada for pre-exposure prophylaxis after becoming pregnant and those who choose to stop, as well as women using other antiretroviral drugs during pregnancy.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study:** all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

**Do not select the above study type if:** a study will not be sufficient to identify or assess a serious risk

- Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Prospective registry comparing pregnancy outcomes and seroconversion rates among women taking Truvada for pre-exposure prophylaxis who continue to use Truvada during pregnancy and those who choose to discontinue its use. Pregnancy outcomes for these women will also be compared to women using other antiretrovirals during pregnancy.

Required

- Observational pharmacoepidemiologic study  
 Registry studies  
 Primary safety study or clinical trial  
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety  
 Thorough Q-T clinical trial  
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)  
 Pharmacokinetic studies or clinical trials  
 Drug interaction or bioavailability studies or clinical trials  
 Dosing trials  
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials  
 Immunogenicity as a marker of safety  
 Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)  
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)  
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E  
 Dose-response study or clinical trial performed for effectiveness  
 Nonclinical study, not safety-related (specify)

- 
- Other
-

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- Are the objectives clear from the description of the PMR/PMC?
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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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KATHERINE SCHUMANN  
07/16/2012

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07/16/2012

# REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

## Division of Antiviral Products

**Application Number:** 21752 S-030  
21752 S-031

**Name of Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate) tablets

**Applicant:** Gilead Sciences, Inc.  
333 Lakeside Dr.  
Foster City, CA 94404

### Materials Reviewed:

**Submission Date:** December 14, 2011 (S-030, initial submission)  
January 20, 2011 (S-031, initial submission)  
July 10, 2012 (S-030 and S-031)

**Receipt Date:** December 15, 2011 (S-030, initial submission)  
January 23, 2011(S-031, initial submission)  
July 11, 2012 (S-030 and S-031)

**Submission Date of Structured Product Labeling (SPL):** December 14, 2011 (S-030)  
January 20, 2011 (S-031)

**Type of Labeling Reviewed:** Word for content and SPL for format.

The final draft of the labeling (July 13, 2012, with agreed-upon changes made by FDA) compared to FDA's July 8, 2011, approved labeling for NDA 21752/S-027.

### Background and Summary:

Efficacy supplement S-030 was submitted on December 14, 2011 to provide a new indication for Truvada<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate), in combination with safer sex practices, for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.

Labeling supplement S-031 was submitted on January 20, 2011 to incorporate safety information pertaining to the risk of the autoimmune disorder as syndromes that can occur in the setting of immune reconstitution with the use of antiretroviral products.

On June 15, 2012, the Division asked the applicant to incorporate the safety information proposed in S-031 into the labeling undergoing revision as part of the review of S-030. Thereafter, the labeling for both supplements has been the same from that point forward. As such, my review below is applicable to both supplements.

The labeling for these supplements was compared to the most recent approved labeling dated July 8, 2011 (NDA 21752/S-027).

Of note, a new Risk Evaluation and Mitigation Strategy (REMS) is being established for Truvada<sup>®</sup> with the approval of S-030, including a Medication Guide. Therefore, the previous Patient Package Insert (PPI) has been supplanted by a new Medication Guide.

### **Review of Package Insert:**

#### **General:**

Two new tables were added to the full prescribing information (Table 4 and Table 5). As a consequence, all subsequent table numbers were revised.

#### **Highlights Section:**

Following the name and dosage form, the following text regarding the route of administration was added (new text in blue).

TRUVADA<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate) tablets, **for oral use**

Boxed Warning, the following changes were made (new text in blue, deleted text in strikethrough):



Recent Major Changes section, the following lines were added:

23 pages of draft labeling have been withheld immediately following this page as b4 (CCI/TS)

**Review of Medication Guide:**

As a new Medication Guide was submitted with this supplement as part of the REMS, the Patient Package Insert for Truvada<sup>®</sup> was replaced by the Medication Guide. The new Medication Guide, reviewed by Patient Labeling and the Medical Officer, is appended.

**Conclusion:**

It will be conveyed to the applicant that labeling is acceptable, and an approval letter should be sent. See the clinical review for additional information.

*{See appended electronic signature page}*

Katherine Schumann  
Regulatory Project Manager

Supervisory Comment/Concurrence:

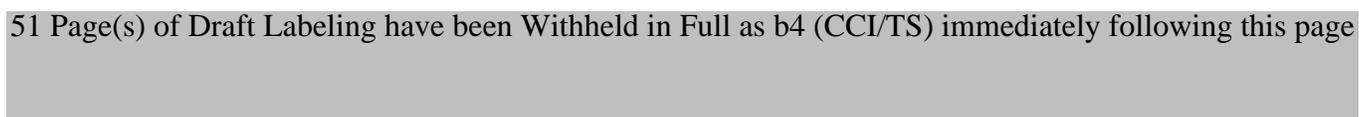
*{See appended electronic signature page}*

Karen Winestock  
Chief, Project Management Staff  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Attachments: PI and Medication Guide submitted by Gilead on December 14, 2011 (S-030) and January 20, 2012 (S-031), amended on July 10, 2012, with agreed-upon changes made by FDA on July 13, 2012, compared to the last approved label on July 8, 2011.

Drafted: RPM/Schumann/7-12-12  
Revised/Initialed: Winestock/  
Finalized: RPM/Schumann/7  
Filename:v: \\Cdsnas\oap\DAVDP\CSO\Schumann\NDA\021752\S-30\ NDA 21752 S-30 S-31 CSO Labeling Review.doc

51 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



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KATHERINE SCHUMANN  
07/13/2012

KAREN D WINESTOCK  
07/16/2012

## PMC 1906-5

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

---

NDA # 21-752  
Product Name: TRUVADA®

---

PMC Description: In the context of a U.S. Centers for Disease Control and Prevention (CDC) demonstration project (trial) for once-daily Truvada® for a pre-exposure prophylaxis (PrEP) indication, validate an adherence questionnaire over the period of the demonstration project (trial) using an objective quantitative measure such as drug levels. In addition, the demonstration project (trial) will utilize subject demographics and responses from a survey on knowledge, attitudes, and behaviors (sexual and non-sexual behaviors related to increased risk of HIV infection) in order to identify baseline characteristics associated with decreasing adherence, as measured via the adherence questionnaire and confirmed objectively by blood drug levels. The demonstration project (trial) will accrue 1200 individuals with an expected follow up of 12 months and use a national demographically representative sample that reflects the same target population described in 1906-4 above.

---

PMR/PMC Schedule Milestones:	Final Protocol Submission:	04/2013
	Study Completion:	07/2015
	Final Report Submissions:	02/2016

---

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The clinical trials submitted in support of this application indicated that the risk of HIV seroconversion was strongly correlated to drug adherence. Self-reported drug adherence, however, was poorly predictive of actual adherence as determined by objective measures such as blood drug levels. Because routine drug level monitoring is not practical in a real-world setting, there is a need to identify other measures of adherence that may be as reliable and, moreover, serve as a tool to help identify individuals likely to have decreased adherence and thus be at greater risk of seroconverting. Validating an adherence questionnaire, given the aforementioned adherence issues identified in the clinical trials, is therefore appropriate for a PMC.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The clinical trials identified that self-reported drug adherence was unreliable. Because greater efficacy correlated with better drug adherence, a reliable assessment of drug adherence is important. The goal of the PMC study is to validate an adherence questionnaire in the context of a CDC demonstration project (trial) using objective measures of adherence such as blood drug levels. Another goal of the study is identify baseline characteristics, using subject demographics and survey responses, that are associated with lower drug adherence, as determined by blood drug levels, and that may be used to identify individuals at risk for seroconversion.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Questionnaire validation study

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other  
Questionnaire validation study
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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KATHERINE SCHUMANN  
07/14/2012

KENDALL A MARCUS  
07/14/2012

## PMC 1906-4

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA # 21-752  
Product Name: TRUVADA®

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PMC Description: Provide nationally representative drug utilization data to FDA of sufficient detail that use of Truvada® for a pre-exposure prophylaxis (PrEP) indication and individuals using Truvada® for a PrEP indication can both be characterized. These data should be submitted to FDA every 6 months for three years, for the combination product emtricitabine/tenofovir disoproxil fumarate, and for the single-ingredient products containing emtricitabine or tenofovir disoproxil fumarate, starting at one year following approval of the PrEP indication. The following analyses should be conducted with the data collected:

- 1) Total number of prescriptions dispensed across all settings of care
  - a. Total number of prescriptions dispensed, stratified by indication, setting of care, and prescriber specialty
  - b. Directions for use (signa) of prescriptions dispensed
- 2) Total number of unique individuals receiving dispensed prescriptions across all settings of care
  - a. Total number of unique individuals receiving dispensed prescriptions, stratified by both indication and setting of care
    - i. Unique incident users every quarter-year
    - ii. Unique prevalent users every quarter-year
  - b. Patient demographics of users of the product
  - c. Clinical characteristics of users of the product
- 3) Duration of therapy, including definitions of gaps in drug therapy
  - a. Total and stratified by indication
  - b. Examination of possible 'intermittent' use
  - c. Number of individuals switching from PrEP to an HIV treatment regimen
  - d. Dose adjustments

Comparison of drug utilization data collected to data collected from demonstration projects (trials) performed in the United States in terms of user demographics, user clinical characteristics, prescriber specialties, settings of care, and geographic region (when available).

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PMR/PMC Schedule Milestones: Final Protocol Submission: 01/2013  
Final Report Submission: 07/2016

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Interim Report Submissions:

07/2013  
01/2013  
07/2014  
01/2015  
07/2015  
01/2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need  
 Life-threatening condition  
 Long-term data needed  
 Only feasible to conduct post-approval  
 Prior clinical experience indicates safety  
 Small subpopulation affected  
 Theoretical concern  
 Other

Because the uptake, patterns of usage, and demographics of uninfected users and prescribers of Truvada for pre-exposure prophylaxis cannot be predicted by the clinical trials, most of which were conducted outside the United States, an assessment of national drug utilization data for Truvada for the pre-exposure prophylaxis indication is appropriate as a PMC.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Because the clinical trials cannot predict who will prescribe and who will use Truvada for pre-exposure prophylaxis in the post-approval period or how the product will be prescribed or used, the goal of the PMC is to provide nationally representative drug utilization data to characterize the individuals and patterns of use of Truvada for the pre-exposure prophylaxis indication in the United States.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - Assess a known serious risk related to the use of the drug?
  - Assess signals of serious risk related to the use of the drug?
  - Identify an unexpected serious risk when available data indicate the potential for a serious risk?
  
- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  
  - Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
  - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  
  - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Collection of drug utilization data in the United States for the pre-exposure prophylaxis indication.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 

- Other  
Drug utilization study
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

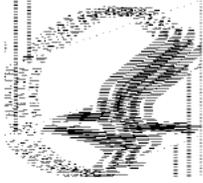
- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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KATHERINE SCHUMANN  
07/14/2012

KENDALL A MARCUS  
07/14/2012



Pediatric and Maternal Health Staff  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-2200  
FAX 301-796-9744

**PEDIATRIC AND MATERNAL HEALTH STAFF,  
MATERNAL HEALTH TEAM REVIEW**

**Date:** 7-9-2012

**From:** Leyla Sahin, M.D.  
Medical Officer,  
Pediatric and Maternal Health Staff, Maternal Health Team

**Through:** Melissa Tassinari, PhD.  
Acting Team Leader,  
Pediatric and Maternal Health Staff, Maternal Health Team

**Through:** Lisa Mathis, M.D.  
Associate Director, Office of New Drugs  
Pediatric and Maternal Health Staff

**To:** Division of Antiviral Products

**Drug:** Truvada® (tenofovir disoproxil fumarate/emtricitabine)

**Application:** NDA 21752/S-30 New Indication for pre-exposure prophylaxis of HIV-1 infection

**Sponsor:** Gilead Sciences, Inc.

**Subject:** Pregnancy and Lactation Labeling; Postmarketing Requirement

**Materials Reviewed:** Sponsor's proposed labeling, literature review

**Consult Question:** Please advise on language to allow physicians to make an informed risk/benefit decision regarding the use of Truvada for a pre-exposure prophylaxis in pregnancy, and on elements of a postmarketing requirement.

## INTRODUCTION

Gilead Sciences Inc. submitted an efficacy supplement on December 14, 2011 for a new indication for pre-exposure prophylaxis of HIV-1 infection (PrEP). Two clinical trials were submitted in support of this indication, one in men-who-have-sex with men (iPrEx), and one in serodiscordant couples (Partners PrEP). The Division of Antiviral Products (DAVP) requested the Pediatric and Maternal Health Staff, Maternal Health Team's assistance in providing recommendations for Pregnancy and Lactation labeling and a postmarketing requirement. This review provides a summary of recommendations that were made regarding labeling for Pregnancy and Lactation, and a request for a postmarketing requirement.

## BACKGROUND

Truvada, a combination of tenofovir and emtricitabine, both nucleoside analog HIV-1 reverse transcriptase inhibitors (NRTIs), and originally approved in 2004, is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.

### *Overview of Truvada*

#### Tenofovir

Tenofovir was approved in 2001, and is labeled pregnancy category B, based on negative reproductive and developmental toxicology studies (rats and rabbits given doses up to 14 and 19 times the human dose based on body surface area). The labeling includes information under Warnings and Precautions regarding a decrease in bone mineral density, and advises bone mineral testing in patients who have a pathologic fracture or risk factors for osteoporosis or bone loss. The labeling also states that the long term effects on bone health and fracture risk are unknown.

The Antiretroviral Pregnancy Registry (APR) report from December 2011 includes 27 birth defects out of 1, 219 births following first trimester exposure with a prevalence of 2.2% (95% CI 1.5%-3.2%). This rate is not greater than the background rate of birth defects in the United States of 2.7%.<sup>1</sup> The APR concludes that sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date.

A recent open-label, nonrandomized study of HIV positive women in Uganda and Zimbabwe<sup>2</sup> who received zidovudine/lamivudine plus either tenofovir or nevirapine during the Development of AntiRetroviral Therapy in Africa (DART) trial, showed that in the 111 infants who were exposed to tenofovir in utero there was no increase in birth defects, low birth weight, infant mortality, bone fractures, kidney problems, or abnormalities in subsequent growth parameters. However follow-up data are based on small sample sizes (n=34 at 48 weeks, n=33 at 72 weeks,

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<sup>1</sup> Centers for Disease Control birth defects surveillance system data in the December 2011 Antiretroviral Pregnancy Registry Report

<sup>2</sup> Gibb DM, et al. Pregnancy and Infant Outcomes among HIV-infected Women Taking Long-Term ART with and without Tenofovir in the DART Trial. PLoS Medicine May 2012;9(5)

n=34 at 96 weeks, and n=31 at 120 weeks for height assessments). No infants were HIV infected. The authors conclude that their findings suggest that tenofovir-containing anti retroviral therapy is a reasonable choice in pregnancy and that tenofovir pre-exposure prophylaxis is also reasonable for women who are at high risk of seroconverting during pregnancy.

### Emtricitabine

Emtricitabine was approved in 2003, and is labeled pregnancy category B, based on negative reproductive and developmental toxicology studies (mice and rabbits given doses up to 60 and 120 times the human dose based on body surface area). The Antiretroviral Pregnancy Registry report from December 2011 includes 18 birth defects out of 764 births following first trimester exposure with a prevalence of 2.4% (95% CI 1.4%-3.7%). This rate is not greater than the background rate of birth defects in the United States of 2.7%. The APR concludes that sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date.

### Use in Pregnancy

According to the Department of Health and Human Services Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States (Perinatal Guidelines), published May 14, 2011, NRTIs are recommended in pregnancy for use as part of combination regimens, usually including two NRTIs with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or one or more protease inhibitor (PI). The preferred NRTI regimen in pregnancy is lamivudine plus zidovudine due to extensive experience and efficacy and safety data. Tenofovir and emtricitabine are listed as alternative NRTIs in pregnancy.

There are published data that show an increased risk of acquiring HIV infection during pregnancy<sup>3,4</sup>.

Women who acquire HIV during pregnancy or lactation are at high risk of transmitting HIV to their infants, probably due to the high viral load during acute infection<sup>5,6,7,8</sup>.

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<sup>3</sup> Gray RH, Li X, Kigozi G, Serwadda D, Brahmbhatt H, et al. (2005) Increased risk of incident HIV during pregnancy in Rakai, Uganda: a prospective study. *Lancet* 366: 1182–1188.

<sup>4</sup> Moodley D, Esterhuizen TM, Pather T, Chetty V, Ngaleka L (2009) High HIV incidence during pregnancy: compelling reason for repeat HIV testing. *AIDS* 23: 1255–1259.

<sup>5</sup> Marinda ET, Moulton LH, Humphrey JH, et al. In utero and intra-partum HIV-1 transmission and acute HIV-1 infection during pregnancy: using the BED capture enzyme-immunoassay as a surrogate marker for acute infection. *Int J Epidemiol.* Aug 2011;40(4):945-954.

<sup>6</sup> Humphrey JH, Marinda E, Mutasa K, et al. Mother to child transmission of HIV among Zimbabwean women who sero-converted postnatally: prospective cohort study. *BMJ.* 2010;341:c6580.

<sup>7</sup> Birkhead GS, Pulver WP, Warren BL, Hackel S, Rodriguez D, Smith L. Acquiring human immunodeficiency virus during pregnancy and mother-to-child transmission in New York: 2002-2006. *Obstet Gynecol.* 2010 Jun;115(6):1247-1255.

<sup>8</sup> Liang K, Gui X, Zhang YZ, Zhuang K, Meyers K, Ho DD. A case series of 104 women infected with HIV-1 via blood transfusion postnatally: high rate of HIV-1 transmission to infants through breast-feeding. *J Infect Dis.* 2009 Sep1;200(5):682-686.

## **SPONSOR'S PROPOSED LABELING**

The sponsor proposed the addition of language that states that Truvada should not be used for pre-exposure prophylaxis (PrEP) in pregnancy (see Appendix A for sponsor's proposed labeling).

## **DISCUSSION AND CONCLUSIONS**

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule while still complying with current regulations. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount. A section for Females and Males of Reproductive Potential may be added containing information regarding pregnancy planning, prevention and/or fertility issues. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

PMHS-MHT participated in the sponsor labeling meeting 5-17-2012, and in the labeling meeting with DAVP 5-22-2012 (see Appendix B for labeling agreed upon by PMHS-MHT and DAVP). PMHS-MHT also recommended that the sponsor include data from the Antiretroviral Pregnancy Registry, and consider adding data from the DART Trial.

The currently approved labeling for Truvada acknowledges that there is limited data in pregnancy but that the use of Truvada in pregnancy should be considered if there is a clear need. The sponsor proposed adding language that states that Truvada should not be used for pre-exposure prophylaxis (PrEP) in pregnancy. The clinical trials of PrEP included women who discontinued Truvada if they became pregnant, but no significant safety concerns were raised. In the PrEP trial involving women reviewed by DAVP, 2 of the 13 women in the Truvada arm who seroconverted became infected while off study drug for >3 months due to pregnancy or breastfeeding. This is consistent with the literature that the risk of infection is increased in pregnancy. The Pediatric and Maternal Health Staff, Maternal Health Team (PMHS-MHT) and DAVP discussed the potential use of PrEP in pregnancy. Recent articles in the medical literature<sup>9</sup>, including an article by the Centers for Disease Control (CDC)<sup>10</sup> discuss pre-exposure prophylaxis as a consideration for HIV-discordant couples attempting conception. The CDC article reviews data that suggest that there are over 140,000 HIV-serodiscordant heterosexual couples in the United States, approximately half of whom want to conceive. Assisted

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<sup>9</sup> Vernazza PL, et al. Preexposure prophylaxis and timed intercourse for HIV discordant couples willing to conceive a child. *AIDS* 2011; 25:2005-2008.

<sup>10</sup> Lampe MA, et al. Achieving safe conception in HIV-discordant couples: the potential role of oral preexposure prophylaxis (prep) in the United States. *AJOG* June 2011;204:488.e1-8.

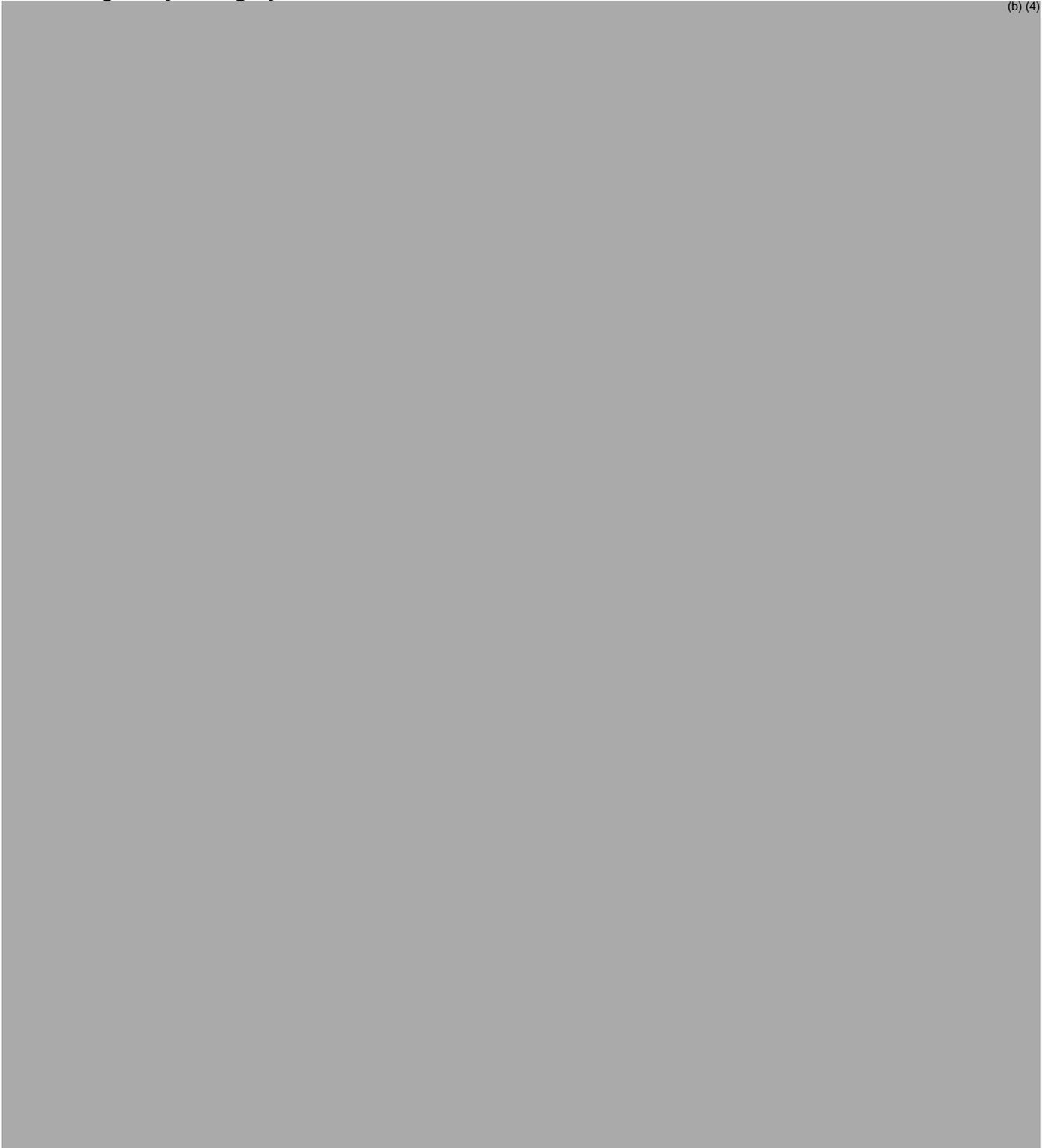
reproductive technology (ART) methods have been developed to reduce the risk of HIV transmission during attempted conception, however, there are barriers to access such as expense, lack of fertility clinics offering services to couples affected by HIV, state laws and regulations barring access to some ART approaches for persons affected by HIV, etc. PMHS-MHT and DAVP concluded that the sponsor's proposed recommendation to not use Truvada for PrEP in pregnancy be removed, as there may be potential benefit, and therefore labeling should reflect the risk-benefit assessment.

PMHS-MHT concurs with DAVP's decision for a post-marketing requirement study in pregnant women, and provided input on the sponsor's June 27, 2012 proposal (see Appendix C for suggested addition) to conduct a prospective observational cohort study as a nested study within the Antiretroviral Pregnancy Registry, with assessment of additional outcomes such as rates of seroconversion for both the mother and the child. PMHS-MHT recommends that it would also be useful to analyze the data (pregnancy outcomes, infant outcomes, seroconversion for both mother and child) in terms of women who continue Truvada PrEP during pregnancy compared to women who may have been exposed to Truvada PrEP for a short time early in pregnancy, who then choose to discontinue.

**APPENDIX A- SPONSOR'S PROPOSED LABELING**  
(Additions are underlined, deletions are struck out)

**8.1 Pregnancy**

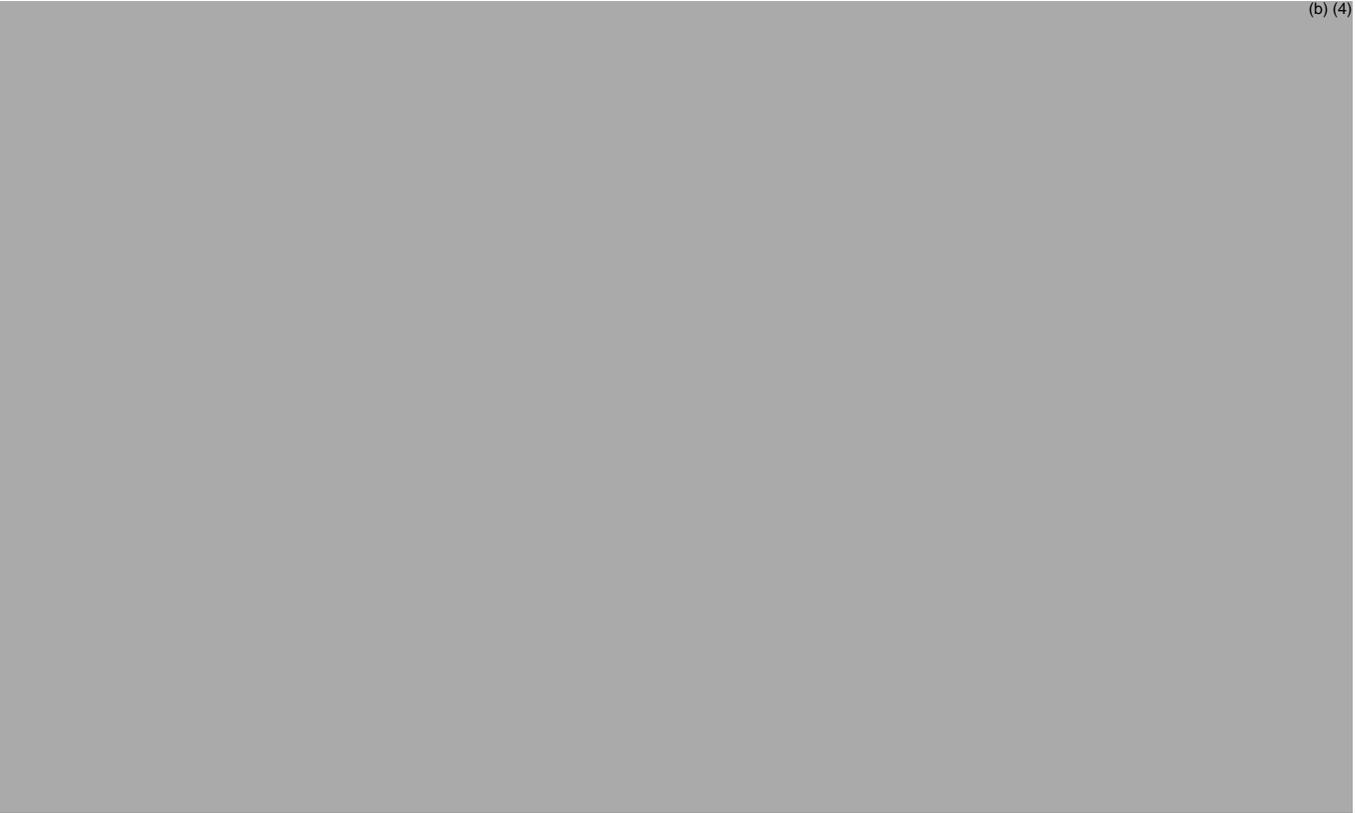
*Pregnancy Category B*



(b) (4)



Medication Guide



## Appendix B- Labeling agreed upon by PMHS-MHT and DAVP on 6-15-2012

### 8.1 Pregnancy

#### *Pregnancy Category B*

*Antiretroviral Pregnancy Registry:* To monitor fetal outcomes of pregnant women exposed to TRUVADA, an Antiretroviral Pregnancy Registry (APR) has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

#### Risk Summary

TRUVADA has been evaluated in a limited number of women during pregnancy and postpartum. Available human and animal data suggest that TRUVADA does not increase the risk of major birth defects overall compared to the background rate. There are, however, no adequate and well-controlled trials in pregnant women. Because the studies in humans cannot rule out the possibility of harm, TRUVADA should be used during pregnancy only if clearly needed. If an uninfected individual becomes pregnant while taking TRUVADA for a PrEP indication, careful consideration should be given to whether use of TRUVADA should be continued, taking into account the increased risk of HIV-1 infection during pregnancy.

#### Clinical Considerations

As of July 2011, the APR has received prospective reports of 764 and 1219 exposures to emtricitabine- and tenofovir- containing regimens, respectively in the first trimester, 321 and 455 exposures, respectively, in second trimester, and 140 and 257 exposures, respectively, in the third trimester. Birth defects occurred in 18 of 764 (2.4%) live births for emtricitabine-containing regimens and 27 of 1219 (2.2%) live births for tenofovir-containing regimens (first trimester exposure) and 10 of 461 (2.2%) live births for emtricitabine-containing regimens and 15 of 714 (2.1%) live births for tenofovir-containing regimens (second/third trimester exposure). Among pregnant women in the U.S. reference population, the background rate of birth defects is 2.7%. There was no association between emtricitabine or tenofovir and overall birth defects observed in the APR.

#### Animal Data

##### *Emtricitabine:*

The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose.

##### *Tenofovir Disoproxil Fumarate:*

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

### 8.3 Nursing Mothers

**Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1.**

Studies in humans have shown that both tenofovir and emtricitabine are excreted in human milk. Because the risks of low level exposure to emtricitabine and tenofovir to infants are unknown, **mothers should be instructed not to breast-feed if they are receiving TRUVADA**, whether they are taking TRUVADA for treatment or to reduce the risk of acquiring HIV-1.

#### *Emtricitabine*

Samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the emtricitabine EC<sub>50</sub> value but 3 to 12 times lower than the C<sub>min</sub> achieved from oral administration of emtricitabine. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown.

#### *Tenofovir Disoproxil Fumarate*

Samples of breast milk obtained from five HIV-1 infected mothers show that tenofovir is secreted in human milk at low levels (estimated neonatal concentrations 128 to 266 times lower than the tenofovir EC<sub>50</sub> value). Tenofovir-associated risks, including the risk of viral resistance to tenofovir, in infants breastfed by mothers being treated with tenofovir disoproxil fumarate are unknown.

### 17.3 Pre-Exposure Prophylaxis

- Women who are pregnant should learn about the risks and benefits of TRUVADA to reduce the risk of acquiring HIV-1 during their pregnancy.

## Medication Guide

### What should I tell my healthcare provider before taking TRUVADA?

#### Tell your healthcare provider if you:

- **are pregnant or planning to become pregnant.** We do not know if TRUVADA can harm your unborn child. You and your healthcare provider will need to decide if TRUVADA is right for you.

**Pregnancy Registry.** There is a pregnancy registry for women who take antiviral medicines during pregnancy. Its purpose is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.

**Do not breastfeed.** You should not breast feed if you are HIV-positive because of the chance of passing the HIV virus to your baby. Also, the drugs in TRUVADA can be passed to your baby in your breast milk, and we do not know whether they could harm your baby. If you are a woman who has or will have a baby, talk with your healthcare provider about the best way to feed your baby.

**Appendix C- Postmarketing Requirement agreed upon by PMHS-MHT and DAVP on 6-29-2012 (additions are underlined)**

**FDA-Requested PMR #2: Prospective Study of Women Take Truvada for PrEP during their Pregnancy**

Prospectively follow 200 women who become pregnant while taking TRUVADA for pre-exposure prophylaxis and choose to continue these drugs during their pregnancies. Collect data on pregnancy outcomes that should include but not be limited to: HIV seroconversions in mother and infants, spontaneous and elective abortions, pre-term deliveries, stillbirths, infant weight (normal or low) and infant outcomes, including the presence or absence of congenital malformations. Data from at least a similarly sized comparator group of pregnant HIV-infected women taking antivirals other than tenofovir/emtricitabine should also be collected.

Timeline: Final protocol submission –Oct 2012  
Study completion – Sept 2014  
Final study report submission – March 2015

Gilead Sciences will conduct the Post Marketing Requirement Pregnant Women on PrEP (PWP) study as per the request from the FDA. This study will be a prospective observational study of pregnant women taking on Truvada<sup>®</sup> for a PrEP indication nested in the Antiretroviral Pregnancy Registry (APR) and will report information on 200 women who fulfill the inclusion criteria and are already enrolled in the prospective registry. A propensity score matched group of pregnancies on a 3:1 ratio from the same registry who are taking other antiretroviral drugs during the same period will be used for comparison purposes.

The following items will be included in the PWP data collection to specifically meet the Agency's request.

- Information regarding pregnancy outcomes among women who choose to continue Truvada for a PrEP indication during their pregnancy
- Information regarding seroconversion for both the mother and the child
- Information about infant outcomes, such as infant weight and the presence or absence of congenital malformations
- an analysis of the data (pregnancy outcomes, infant outcomes, seroconversion for both mother and child) in terms of women who continue Truvada PrEP during pregnancy compared to women who may have been exposed to Truvada PrEP for a short time early in pregnancy, who then choose to discontinue.

It should be noted that two modifications will be requested to the APR protocol.

- The first modification is an addendum to their Registration form, so that section 3 (Clinical Indicators) item D (HIV prophylaxis) is divided into two items i) PEP and ii) PrEP (for reference purposes, a copy of the current APR Registration form is provided as an Attachment 1, below ).
- The second modification is the provision that physicians who have registered PrEP pregnancies are contacted on behalf of APR to document HIV status at delivery for both the mother and the child.

## Appendix 1- Antiretroviral Pregnancy Registry forms

### *The Antiretroviral Pregnancy Registry* Instructions for Completing the REGISTRATION FORMS

**General Guideline:** Date format should always be entered as *DD/MMM/YYYY*

**Patient (Log) ID:** The Registry assigned Log ID number.

**Date first seen during this pregnancy:** Provide the date first seen in *DD/MMM/YYYY* format.

#### 1. Maternal Information

**Clinical Study:** Indicate if the patient is participating in a clinical study by checking "Yes", "No", or "Unknown".

- If no, move to Subsection 1.2
- If yes, provide the study protocol number and check "Yes" or "No" if conducted in pregnant woman

**Last Menstrual Period (LMP):** Provide the LMP date in *DD/MMM/YYYY* format.

**Corrected Estimated Date of Delivery (EDD):** Provide the EDD based on the 20 week prenatal test, especially if this is the date being used to calculate gestational age for medication exposures and outcome.

**Patient Age:** Provide age of the pregnant woman at time of conception.

**Race:** Check the appropriate box for the pregnant woman's race.

#### 2. Prenatal Tests

2.1 **Prenatal Test Done:** Indicate if a prenatal test was done by checking "Yes", "No", or "Unknown".

- If no, move to Section 3: Clinical Indicators.
- If yes, provide the date in *DD/MMM/YYYY* format, or the gestational age, of when the prenatal test was performed and what prenatal test was conducted (ie., Ultrasound, Amniocentesis, MSAFP). If "Other" specify the prenatal test performed.

2.2 **Evidence of a Structural Defect:** Indicate if a structural defect(s) was identified on a prenatal test by checking "Yes", "No" or "Unknown" by each prenatal test done.

- If no, move to Section 3: Clinical Indicators.
- If yes, provide the structural and/or chromosomal defect(s).

#### 3. Clinical Indicators (at the START of pregnancy)

3.1 **Clinical Categories as Defined by the CDC:** [www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm)

Check **all** appropriate categories as they apply as close to the beginning of the pregnancy as possible.

- **Category A:** Consists of one or more of the CDC defined Category A conditions in a person with documented HIV infection. Conditions in Categories B and C must not have occurred.
- **Category B:** Consists of symptomatic conditions in an HIV-infected person not included in Category C and meeting at least one of the two Category B conditions. For classification purposes, someone previously treated for a Category B condition but who is now asymptomatic should be classified in Category B.
- **Category C:** Includes the clinical conditions listed in the AIDS surveillance case definition. For classification purposes, once a Category C condition has occurred, the person will remain in Category C.

3.2 **CD4 + T-cell Categories:** Check the appropriate range for the counts as they were as close to the beginning of the pregnancy (not applicable should be marked if the patient is not HIV positive).

3.3 **Hepatitis Severity Indicator:** Check the appropriate indication for severity of the hepatitis at a time as close to the beginning of the pregnancy as possible (not applicable should be marked if the patient does not have hepatitis or if Pugh score is not yet known).

#### ANTIVIRAL THERAPY DURING PREGNANCY FORM

- **Med Code:** Indicate the code number from the list provided. If a drug is not listed, provide the name of the drug.
- **Total Daily Dose:** Provide the total daily dose with units (e.g., stavudine 80 mg, ZDV (IV) 650 mg).
- **Route:** Provide the code "1" for oral, "2" for IV, and "3" for subcutaneous (sub-Q).
- **Pt taking Meds at Conception?:** "1" if yes at conception, "2" if during pregnancy, "3" if unknown.
- **Gestation Week Course Began:** Indicate the gestation week (if unknown and a date the therapy began is available, that is sufficient) when treatment began.

- **Date Treatment Began or Gestational Age Course Began:**
  - Provide start date in *DD/MMM/YYYY* format, **OR**
  - Provide gestational age course began. If gestational age is known, check the calculation source: LMP or Corrected EDD. This will help to ensure the Registry is calculating from the same date.
- **Date Treatment Stopped or Ongoing:**
  - Provide date, or gestation week, treatment stopped in *DD/MMM/YYYY* format, **OR**
  - Check "Ongoing" if treatment continues following outcome of pregnancy.

**Please write "unk" or "N/A" on the forms if any information is unknown or not applicable.**

The Registry is not designed to monitor all types of events that might occur during pregnancy, labor and delivery, or other neonatal or post- natal events other than defects. If such events occur the provider is encouraged to contact the manufacturer of the individual drug and/or the FDA. FDA can be reached by faxing the information to 800-FDA-0178 or at <http://www.fda.gov/Safety/MedWatch/default.htm>

**Phone Contact:** US/Canada Phone: 800-258-4263 (Toll Free) or 910-256-0238  
 UK, Germany, France Phone: 00800-5913-1359 (Toll Free)  
 International Phone: +910-256-0238 (US) or +32-2-714-5028 (Europe)

**Address:** Research Park, 1011 Ashes Drive, Wilmington, NC 28405

**Internet:** [www.APRegistry.com](http://www.APRegistry.com)

Revised (April 2010)



Address \_\_\_\_\_

Phone \_\_\_\_\_

Fax \_\_\_\_\_

Alternate Contact \_\_\_\_\_

Email \_\_\_\_\_

Provider's Signature \_\_\_\_\_

Date \_\_\_\_\_  
M D Y

# ANTIRETROVIRAL PREGNANCY REGISTRY ANTIVIRAL THERAPY DURING PREGNANCY

(Initiated at registration and completed at follow-up)

Registry ID \_\_\_\_\_

Update

**Patient (Log) ID:** \_\_\_\_\_ *The Registry assigned, non-patient identifying patient ID number or Sponsor MCN*

Complete as much of this page as applicable at Registration. A copy of this form will be sent to you in the expected month of delivery for completion.

## 4. ANTIVIRAL THERAPY DURING PREGNANCY

1. Use the med. codes below for antiviral medication taken during pregnancy. If not coded, **Specify Medication**.

- |   |  |
|---|--|
| <p>1. Abacavir (ZIAGEN<sup>®</sup>, ABC)</p> <p>1.1 Abacavir generic - Hetero</p> <p>2. Didanosine (VIDEX<sup>®</sup>, VIDEX<sup>®</sup> EC, ddl)</p> <p>2.1 Didanosine generic – Teva Pharmaceuticals</p> <p>2.2 Didanosine generic – Aurobindo</p> <p>2.3 Didanosine generic - Mylan</p> <p>2.99 Didanosine (unknown manufacturer)</p> <p>3. Efavirenz (SUSTIVA<sup>®</sup>, EFV)</p> <p>3.1 Efavirenz (STOCRIN<sup>®</sup>, EFV)</p> <p>3.2 Efavirenz generic - Hetero</p> <p>3.99 Efavirenz (unknown manufacturer)</p> <p>4. Lamivudine (EPIVIR<sup>®</sup>, 3TC)</p> <p>4.1 Lamivudine generic – Hetero</p> <p>4.2 Lamivudine+tenofovir df generic – Hetero</p> <p>4.3 Lamivudine generic – Apotex</p> <p>4.4 Lamivudine generic - Aurobindo</p> <p>4.99 Lamivudine (unknown manufacturer)</p> <p>5. Lamivudine+zidovudine (COMBIVIR<sup>®</sup>, ZDV+3TC)</p> <p>5.1 Lamivudine+zidovudine generic - Hetero</p> <p>5.2 Lamivudine+zidovudine generic – Teva Pharmaceuticals</p> <p>5.99 Lamivudine+zidovudine (unknown manufacturer)</p> <p>6. Nelfinavir (VIRACEPT<sup>®</sup>, NFV)</p> <p>7. Nevirapine (VIRAMUNE<sup>®</sup>, NVP)</p> <p>7.1 Nevirapine generic - Hetero</p> <p>7.99 Nevirapine (unknown manufacturer)</p> <p>8. Ritonavir (NORVIR<sup>®</sup>, RTV)</p> <p>9. Saquinavir (FORTOVASE<sup>®</sup>, SQV-SGC)</p> <p>10. Saquinavir mesylate (INVIRASE<sup>®</sup>, SQV-HGC)</p> <p>11. Stavudine (ZERIT<sup>®</sup>, d4T)</p> <p>11.1 Stavudine generic – Mylan</p> <p>11.2 Stavudine generic – Aurobindo</p> <p>11.3 Stavudine generic – Cipla</p> <p>11.4 Stavudine generic - Hetero</p> <p>11.99 Stavudine generic – unknown manufacturer</p> <p>12. Zalcitabine (HIVID<sup>®</sup>, ddC)</p> <p>13. Zidovudine (RETROVIR<sup>®</sup>, ZDV)</p> | <p>13.1 Zidovudine oral generic - Ranbaxy</p> <p>13.2 Zidovudine oral generic – Teva/GSK</p> <p>13.3 Zidovudine oral generic – Roxane/BI</p> <p>13.4 Zidovudine oral generic – Aurobindo</p> <p>13.5 Zidovudine oral generic – Cipla</p> <p>13.6 Zidovudine oral generic – Mylan</p> <p>13.7 Zidovudine oral generic – Hetero</p> <p>13.8 Zidovudine oral generic – HEC Pharm</p> <p>13.99 Zidovudine oral (unknown manufacturer)</p> <p>14. Amprenavir (AGENERASE<sup>®</sup>, APV)</p> <p>15. Indinavir (CRIXIVAN<sup>®</sup>, IDV)</p> <p>16. Delavirdine mesylate (RESCRIPTOR<sup>®</sup>, DLV)</p> <p>17. Lopinavir+ritonavir (KALETRA<sup>®</sup>, ALUVIA<sup>®</sup>, LPV/r)</p> <p>18. Abacavir+lamivudine+zidovudine (TRIZIVIR<sup>®</sup>, TZV)</p> <p>19. Tenofovir disoproxil fumarate (VIREAD<sup>®</sup>, TDF)</p> <p>19.1 Tenofovir disoproxil fumarate generic - Hetero</p> <p>19.99 Tenofovir disoproxil fumarate (unknown manufacturer)</p> <p>20. Adefovir dipivoxil (HEPSERA<sup>®</sup>, ADV)</p> <p>21. Enfuvirtide (FUZEON<sup>®</sup>, T-20)</p> <p>22. Atazanavir sulfate (REYATAZ<sup>®</sup>, ATV)</p> <p>23. Emtricitabine (EMTRIVA<sup>®</sup>, FTC)</p> <p>24. Fosamprenavir calcium (LEXIVA<sup>®</sup>, FOS)</p> <p>25. Abacavir+lamivudine (EPZICOM<sup>®</sup>, EPZ)</p> <p>26. Tenofovir disoproxil fumarate+emtricitabine (TRUVADA<sup>®</sup>, TVD)</p> <p>27. Entecavir (BARACLUDE<sup>®</sup>, ETV)</p> <p>28. Tipranavir (APTIVUS<sup>®</sup>, TPV)</p> <p>29. Efavirenz+tenofovir disoproxil fumarate+emtricitabine (ATRIPLA<sup>™</sup>, ATR)</p> <p>30. Telbivudine (TYZEKA<sup>®</sup>, SEBIVO<sup>®</sup>, LdT)</p> <p>31. Darunavir (PREZISTA<sup>™</sup>, DRV)</p> <p>32. Raltegravir (ISENTRRESS<sup>™</sup>, RAL)</p> <p>33. Maraviroc (SELZENTRY<sup>™</sup>, CELENTRI<sup>™</sup>, MVC)</p> <p>34. Etravirine (INTELENCE<sup>™</sup>, ETR)</p> <p>35. Rilpivirine (EDURANT<sup>™</sup>, TMC278)</p> <p>36. Rilpivirine+Emtricitabine+Tenofovir Disoproxil Fumarate (COMPLERA<sup>®</sup>, CPA; EVIPLERA<sup>®</sup>, EPA)</p> |
|---|--|

2. In the following table, describe each course or change in route for each applicable therapy.

Med. Code (1-34) or if no code indicated, please write medication name and indicate if generic	Total Daily Dose (mg/day or mg/kg/hr)	Route (enter code) 1 = oral 2 = IV 3 = sub-Q	Pt Taking Med. at Conception? 1 = Yes 2 = No 3 = Unknown	Date Treatment Course Began (DD/MMM/YYYY)  OR Gestational Age Course Began (0 weeks = prior to conception) If gestational age, calculation source: ( LMP )   (corrected EDD)	Date Treatment Stopped (DD/MMM/YYYY) OR Ongoing? (Note: Ongoing = ongoing Follow-up delivery)
Course					<input type="checkbox"/> or <input type="checkbox"/> or ongoing
					<input type="checkbox"/> or <input type="checkbox"/> or ongoing
					<input type="checkbox"/> or <input type="checkbox"/> or ongoing

Phone: (US, Canada) 800-258-4263 (Toll Free) or 910-256-0238

Phone: (International) +910-256-0238 or (UK, Germany, France) 00800-5913-1359 (Toll Free) Phone: (Europe): +32-2-714-50

Internet www.APRRegistry.com

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/s/  
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LEYLA SAHIN  
07/09/2012

MELISSA S TASSINARI  
07/09/2012

LISA L MATHIS  
07/16/2012

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Professional Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** June 25, 2012

**To:** Katherine Schumann, MS, Regulatory Project Manager  
Division of Antiviral Products (DAVP)

**From:** Jessica Fox, PharmD, Regulatory Review Officer  
Sheila Ryan, PharmD, Group Leader  
Division of Professional Drug Promotion (DPDP)

**Subject:** NDA 021752/S-30 – Truvada (emtricitabine/tenofovir disoproxil fumarate) tablets, for oral use

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As requested in DAVP's consult dated January 9, 2012, DPDP has reviewed the proposed Truvada prescribing information (PI) and container label, sent via email by DAVP on June 6, 2012. The proposed labeling provides for a new indication for pre-exposure prophylaxis to reduce the risk of sexually acquiring HIV-1 in adults at high risk.

DPDP's comments are provided directly below in the proposed substantially complete version of the PI. DPDP has no comments on the proposed container label at this time.

Thank you for your consult. If you have any questions, please contact Jessica Fox at 6-5329 or at Jessica.Fox@fda.hhs.gov.

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/s/

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JESSICA M FOX  
06/25/2012

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Consumer Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

**Memorandum**

**Date:** June 25, 2012

**To:** Katherine Schumann, Regulatory Project Manager  
Division of Antiviral Products (DAVP)

**From:** Kemi Asante, PharmD, Regulatory Review Officer  
Division of Consumer Drug Promotion (DCDP)

**Subject:** TRUVADA (emtricitabine/tenofovir disoproxil fumarate) – NDA  
21752/S-30

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As requested in DAVP's consult dated January 9, 2012, DCDP has reviewed the Truvada medication guide (MG).

DCDP's review is provided below and is based on DMPP's edits to the substantially complete version of the MG that was sent via email by Sharon Mills on June 22, 2012.

Thank you for your consult. If you have any questions please contact Kemi Asante at 6-7425 or at [Kemi.Asante@fda.hhs.gov](mailto:Kemi.Asante@fda.hhs.gov).

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/s/  
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OLUWASEUN A ASANTE  
06/25/2012

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

**DATE:** May 25, 2012

**TO:** Katherine Schumann, M.S., Regulatory Health Project Manager  
Peter Miele, M.D., Medical Officer  
Division of Antiviral Products

**FROM:** Antoine El-Hage, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**THROUGH:** Susan Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**THROUGH:** Lauren Iacono-Connors, Ph.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 21-752/S-030

**APPLICANT:** Gilead Sciences.

**DRUG:** Truvada (tenofovir/ emtricitabine)

**NME:** No

**THERAPEUTIC CLASSIFICATION:** Priority Review

**INDICATION:** Pre-exposure prophylaxis (PrEP) to reduce the risk of acquiring HIV-1

**CONSULTATION REQUEST DATE:** January 19, 2012  
**INSPECTION SUMMARY GOAL DATE:** June 1, 2012

DIVISION ACTION GOAL DATE: June 15, 2012

PDUFA DATE: June 15, 2012

## **I. BACKGROUND:**

The sponsor, Gilead Sciences, Inc. submitted a New Drug Application (NDA) for the use of oral Truvada PrEP in HIV-1 infected partners (male or female) to prevent seroconversions in adults. HIV-1-infected patients are routinely being treated with combinations of 3 or 4 drugs, including nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs/NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) in order to reduce the risk of viral resistance development. The HIV-1 pandemic continues to have the greatest impact on adults and children living with HIV/AIDS worldwide. Given the long timelines, need for large clinical efficacy trials, and obstacles for distribution of new pharmacological products, availability of vaccines to prevent HIV-1 acquisition is likely over a decade away. In the meantime, there is a critical public health need for a widely available, safe, non-contraceptive method to prevent HIV-1 seroconversions within heterosexual HIV-1 discordant relationships worldwide and especially in Africa.

Currently, both tenofovir (TDF) and emtricitabine (FTC) are nucleoside reverse transcriptase inhibitors approved by the FDA for the treatment of HIV-1 infection. According to the applicant, co-formulated TDF and FTC (Truvada) has important characteristics that make them suitable for consideration as chemoprophylaxis, including prolonged intracellular half-lives, once daily dosing, potent antiviral effects, and high tolerability.

The applicant proposes that Truvada PrEP will combine the convenience of once daily dosing with acceptable antiviral effects and a higher barrier to resistance as compared to currently approved NNRTIs. Development of new, potent antiretroviral compounds with different and improved resistance and safety profiles remains a significant unmet need, especially in treatment-experienced HIV-1 infected population.

The sponsor submitted an NDA supplement for a co-formulated drug product FTC/TDF that makes it suitable for chemoprophylaxis in HIV-1 discordant couples. The sponsor sought approval by submitting data from two pivotal study protocols (CO-US-104-0380 and CO-US-104-0288) to support approval of the pending application.

The two protocols detail three-arm, placebo-controlled, proof-of-concept, phase III safety and efficacy trials of once daily TDF, FTC/TDF, or placebo taken by HIV-1 uninfected partners within heterosexual HIV-1 discordant couples for prevention of HIV-1 transmission, with follow-up of HIV-1 uninfected participants (on study drug, unless held/discontinued for pregnancy/breastfeeding or for toxicity) for a minimum of 24 and up to a maximum of 36 months, with follow-up of HIV-1 seroconverters (study drug stopped at the time of detection of HIV-1 seroconversion) for at least 12 months after seroconversion.

In study Partners PrEP CO-US-104-0380, TDF and FTC/TDF were chosen because they have long half-lives, permitting once daily dosing, and excellent safety and tolerability profiles, including lack of significant drug interactions with hormonal contraceptives and antituberculosis drugs, which are commonly used in target populations for PrEP. In this study HIV-1 uninfected partners will be assigned at random in a 1:1:1 ratio to one of three arms:

TDF, FTC/TDF, or placebo. Those randomized to the TDF arm took active TDF 300 mg orally once daily+ placebo FTC/TDF once daily. Those randomized to the FTC/TDF arm took 200 mg/300 mg orally once daily. Those randomized to the placebo arm took placebo TDF orally once daily + placebo FTC/TDF orally once daily. All participants and study staff were blinded to each participant’s randomization group assignment throughout the study.

The primary objective of Study Partners PrEP CO-US-104-0380 was to measure the efficacy of once daily PrEP with TDF or FTC/TDF in preventing HIV-1 acquisition among HIV-1 uninfected persons within the heterosexual HIV-1 discordant couples.

The secondary objectives were: 1) to assess the efficacy of PrEP by gender of the HIV-1 uninfected partner, and 2) to measure the effect of other factors, including CD4 count of the HIV-1 infected partner and, for both partners, herpes simplex virus type 2 serostatus, sexually transmitted infections, and male circumcision.

In study iPrEx CO-US-104-0288, TDF or FTC/TDF were taken by homosexual men (MSM) for HIV-1 prevention. In this study HIV-1 uninfected partners were assigned at random in a 1:1 ratio to one of two arms: FTC/TDF, or placebo. Those randomized to the FTC/TDF arm took 200mg/300mg orally once daily. Those randomized to the placebo arm took placebo orally once daily+ FTC/TDF orally once daily. All participants and study staff were blinded to each participant’s randomization group assignment throughout the study.

The primary objective of study CO-US-104-0288 was to determine if daily oral FTC/TDF is associated with comparable rates of adverse events compared to placebo among HIV-1 uninfected men who have sex with men (MSM). Another primary objective was to determine if daily oral FTC/TDF reduces seroincidence among HIV-1 uninfected MSM.

The secondary objectives were to determine if hepatic viral flares occur in participants who have active hepatitis B infection during and after FTC/TDF chemoprophylaxis.

The review division requested inspection of 4 clinical investigators for the two pivotal protocols (4 sites: 2 foreign sites to cover Study iPrEx (CO-US-104-0288) and 2 foreign sites to cover Study Partners PrEP (CO-US-104-0380)) as data from the two protocols are considered essential to the approval process. These sites were targeted for inspection due to: 1) enrollment of a relatively large number of subjects, and 2) higher site-specific efficacy compared to other sites in their respective trials and thus, significant contribution to the overall efficacy determination.

Gilead Sciences is the Applicant for this application.

**II. RESULTS (by protocol/site):**

<b>Name of CI, site # and location</b>	<b>Protocol and # of subjects</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
Juan V. Guanira Carranza, M.D. Asociacion Civil Impacta Salud y Education Putumayo 171, Urb, Pando Lima 32, Peru Site# 90	Protocol iPrEx (CO-US-104-0288) Number of subjects: 440	3/26-30/2012	Pending  Preliminary: VAI

<b>Name of CI, site # and location</b>	<b>Protocol and # of subjects</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
Telmo E. Fernandez Cadena, M.D., MSc. Fundacion Ecuatoriana Equida Quisquis 921 y Garcia Moreno Guayaquil Guayas, Ecuador Site# 93	Protocol iPrEx (CO-US-104-0288)  Number of subjects: 300	4/2-6/2012	Pending  Preliminary: NAI
James Campbell, M.D. Partners Center Tororo C/O Taso Tororo Tororo District Hospital Campus Station Road Tororo, Uganda Site# 50	Protocol Partners PrEp (CO-US-104-0380) Number of subjects: 638	4/23-27/2012	Pending  Preliminary: NAI
Elizabeth A. Bukusi, MBChB, MMed, M.P.H., Ph.D CIS project CMR, KEMRI-UCSF Bldg. Agoi St. Lumumba Health Center Box 614 Kisumu, 40100 Kenya Site# 56	Protocol Partners PrEP (CO-US-104-0380) Number of subjects: 629	4/30-5/4/2012	Pending  Preliminary: NAI

#### Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

**Note: Observations noted below for the four sites (Drs. Carranza, Cadena, Campbell and Bakusi) are based on an e-mail communication from the field. The EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

#### Protocol Study iPrEx (CO-US-104-0288)

##### **1. Juan V. Guanira Carranza, M.D. Lima 32, Peru**

- a. What Was Inspected:** At this site, a total of 1,274 subjects were screened, and 834 subjects were reported as screen failures. Four hundred and forty (440) subjects were randomized, and 274 subjects completed the study. The number of subjects that were seroconverters (positive HIV-1) at this site was 33 subjects. Review of Informed

Consent Documents for 42 subjects records verified that subjects signed prior to enrollment.

A review of the medical records/source documents was conducted. The medical records for 42 randomly selected subjects were reviewed in detail, including drug accountability records, vital signs, laboratory test results, IRB records, inclusion/exclusion criteria, and use of concomitant medications. Source documents were compared to case report forms and to data listings, to include primary efficacy endpoints and adverse events.

- b. General observations/commentary:** At the conclusion of the inspection, a one item Form FDA 483 was issued to Dr. Guanira Carranza. Our investigation found that for Subject 90-1069-1, an additional informed consent for seroconverter was not obtained after HIV status was confirmed positive according to protocol. Dr. Guanira Carranza acknowledged the inspectional observation in a letter dated 3/26/2012. The clinical investigator stated that “in future protocols conducted at his site, issues that are left under consideration by a study participant for potential resigning of the Informed Consent Document will be documented, tracked, and addressed at each visit until the participant decides if they would like to consent or opt-out of the corresponding activity”. The proposed corrective action in his written response appears acceptable if implemented. With the exception of the Informed Consent issue, the medical records reviewed were found to be in order and the data verifiable. There were no deaths and no under-reporting of adverse events. There were no known limitations to the inspection. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the pending application.
- c. Assessment of Data Integrity:** The data, in support of clinical efficacy and safety at Dr. Guanira Carranza’s site, are considered reliable and appear acceptable in support of the pending application.

Note: Observations noted above are based on an e-mail communication from the field; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

## **2. Telmo E. Cadena, M.D. MSc. Guayas, Ecuador**

- a. What Was Inspected:** At this site, a total of 751 subjects were screened, and 451 subjects were reported as screen failures. Three hundred (300) subjects were randomized and 223 subjects completed the study. The number of subjects that were seroconverters (positive HIV-1) was 26. Review of the Informed Consent Documents for 34 subjects verified that subjects signed consent forms prior to enrollment.

The medical records/source data for 34 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB records, prior and

current medications, and inclusion/exclusion criteria. Source documents were compared to CRFs and data listings for primary efficacy endpoints and adverse events listing.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued. The medical records reviewed were verifiable based on the information available at the site. There were no known limitations to the inspection. There were no deaths and no under-reporting of adverse events. The study appears to have been conducted adequately, and the data generated by this site can be used to support the pending application.
- c. Assessment of Data Integrity:** The data, in support of clinical efficacy and safety at Dr. Cadena's site are considered reliable and appear acceptable in support of the pending application.

Note: Observations noted above are based on an e-mail communication from the field; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

Protocol Study Partners PrEP (CO-US-104-0380)

**3. James Campbell, M.D.  
Entebe, Uganda**

- a. What Was Inspected:** At this site, a total of 1073 couples were screened, 435 couples were reported as screen failures, and 638 couples were randomized into the study. The Informed Consent Documents for 17 couples records were reviewed, and it was verified that all subjects signed Informed Consent Documents prior to enrollment.

The medical records/source documents for 17 couples were reviewed and all 17 couples were found to be seroconverters. The medical records for 17 couples were reviewed for evidence of initial, duplicate, positive rapid HIV results, as well as the confirmatory positive results as documented on the laboratory requisition form and the case report forms (CRFs). In addition, drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria, and use of concomitant medications were reviewed. Source documents for couples/subjects were compared to case report forms and data listings, to include primary efficacy endpoints and adverse events

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Campbell. Our investigation found no evidence of protocol violations and no evidence of under reporting of adverse events.
- c. Assessment of Data Integrity:** The data from Dr. Campbell's site are considered reliable and appear acceptable in support of the pending application.

Note: Observations noted above are based on an e-mail communication from the field: an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

**4. Elizabeth Bakusi, M.D.  
Kisumu, Kenya 40100**

- a. What was Inspected:** At this site, a total of 1337 couples were screened, 708 couples were reported as screen failures, and 629 couples were randomized into the study. Review of Informed Consent Documents for 14 couples/subjects, verified that all subjects signed Informed Consent Documents prior to enrollment.

The medical records/source documents for 14 subjects were reviewed and all 14 couples were found to be seroconverters. The medical records for 14 couples were reviewed for evidence of initial, duplicate, positive rapid HIV results, as well as the confirmatory positive results as documented on the laboratory requisition form and the CRFs. In addition, drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria, and use of concomitant medications were reviewed. Source documents for subjects were compared to case report forms and data listings, to include primary efficacy endpoints and adverse events

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Bakusi. Our investigation found no evidence of protocol violation and no evidence of under reporting of adverse events.
- c. Assessment of Data Integrity:** The data from Dr. Bakusi's site are considered reliable and appear acceptable in support of the pending application.

Note: Observations noted above are based on an e-mail communication from the field: an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

**III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

Four foreign clinical investigators were inspected in support of this application. The inspections of Drs. Cadena, Campbell and Bakusi revealed no regulatory violations and the pending classifications for these inspections are No Action Indicated (NAI). While a regulatory violation was identified during the inspection of Dr. Guanira Carranza, the findings are not likely to critically impact primary efficacy and safety analyses; therefore, OSI does not consider the effect on overall data integrity to be significant. The pending classification for the inspection of Dr. Carranza is Voluntary Action Indicated (VAI). Overall, the data submitted from these sites are considered acceptable in support of the pending application.

**Note: Observations noted above for the four sites inspected are based on an e-mail communication from the field; the EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

*{See appended electronic signature page}*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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ANTOINE N EL HAGE  
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05/25/2012

LAUREN C IACONO-CONNORS  
05/30/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**Drug Utilization Review**

Date: April 6, 2012

Reviewer(s): Grace Chai, Pharm.D.  
Drug Utilization Data Analysis Team Leader  
Division of Epidemiology II

Team Leader: Hina Mehta, Pharm.D.  
Drug Utilization Data Analysis Team Leader  
Division of Epidemiology II

Deputy Director: Laura Governale, Pharm.D., MBA  
Deputy Director for Drug Use  
Division of Epidemiology II

Subject: Truvada<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate)  
Drug Utilization

Drug Name(s): Truvada<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate)

Application Type/Number: NDA 21752 S-030

Applicant/sponsor: Gilead

OSE RCM #: 2012-639

\*\*This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.\*\*

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## EXECUTIVE SUMMARY

As part of the review for NDA 21752/S-030, Truvada<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate), a new efficacy supplement for pre-exposure prophylaxis (PrEP) of HIV-1, the Division of Antiviral Products (DAVP) is requesting a review of postmarketing drug utilization patterns for Truvada<sup>®</sup> to determine if there is current use for the PrEP indication. In support of this request, this review provides U.S. outpatient retail pharmacy drug utilization patterns for Truvada<sup>®</sup>, from years 2004 through 2011.

### *Summary of findings from years 2004 through 2011:*

- A total of approximately (b) (4) prescriptions were dispensed and (b) (4) patients received a dispensed prescription for Truvada<sup>®</sup> from U.S. outpatient retail pharmacies from years 2004-2011, cumulative.
  - Truvada<sup>®</sup> prescriptions increased over (b) (4)-fold from (b) (4) prescriptions dispensed in year 2004 to approximately (b) (4) prescriptions dispensed in year 2011.
  - The number of patients who received prescriptions for Truvada<sup>®</sup> increased by nearly (b) (4) fold from (b) (4) patients in year 2004 to (b) (4) patients in year 2011.
- Infectious Disease and Internal Medicine were the top prescribing specialties, accounting for (b) (4) % of prescriptions dispensed, respectively.
- Approximately (b) (4) % or (b) (4) Truvada<sup>®</sup> drug occurrences, (95% CI, (b) (4) (b) (4)) as reported by office-based physicians, was for Truvada<sup>®</sup> to be used alone, without a concomitant medication.
  - Approximately (b) (4) Truvada<sup>®</sup> drug occurrences (95% CI, < (b) (4) (b) (4)) when “used alone” or monotherapy were reported to be for “prophylaxis”.
- The majority of medications reported to be used concomitantly with Truvada<sup>®</sup> were other HIV medications for the desired action of “suppress HIV” or “decrease viral load”.

Since much of HIV treatment may not occur in physicians’ offices and retail pharmacies, but rather in specialty HIV clinics across the country, it is important to note that these estimates may not be representative of all treatment for HIV in the U.S. and should be interpreted with caution.

## 1 INTRODUCTION

### 1.1 BACKGROUND

As part of the review for NDA 21752/S-030, Truvada<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate), a new efficacy supplement for pre-exposure prophylaxis (PrEP) of HIV-1, the Division of Antiviral Products (DAVP) is requesting a review of postmarketing drug utilization patterns for Truvada<sup>®</sup> to determine, if possible, current use

for the PrEP indication. For a PrEP indication, Truvada<sup>®</sup> would be prescribed without other antiretroviral drugs. However, it is possible, though unlikely, that Truvada<sup>®</sup> is also being prescribed off-label for hepatitis B.

In support of this request, the Division of Epidemiology II (DEPI II) was requested to provide drug utilization patterns for Truvada<sup>®</sup>, specifically, by top prescribing specialties, use alone or with concomitant medications, as well as the desired actions reported for the use of Truvada<sup>®</sup>. Using the currently available proprietary drug use databases licensed by the Agency, this review provides U.S. outpatient retail pharmacy drug utilization patterns for Truvada<sup>®</sup> from years 2004 through 2011.

## 1.2 PRODUCT INFORMATION

Truvada<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate), a combination of Emtriva<sup>®</sup> (emtricitabine) and Viread<sup>®</sup> (tenofovir disoproxil fumarate), was approved in August 2004 for use *in combination* with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.<sup>1</sup>

The recommended dose for Truvada<sup>®</sup> is 1 tablet daily. One tablet contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate.

In December 2010, an article was published in *The New England Journal of Medicine* reporting the findings from an efficacy trial with Truvada<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate) for pre-exposure prophylaxis of HIV-1 in men.<sup>2</sup> This study found that oral use of emtricitabine/tenofovir disoproxil fumarate provided protection against the acquisition of HIV infection among their subjects. A second trial has not been published yet but a press release was issued in July 2011.<sup>3</sup> The data in the second trial was discussed at the 2012 Conference on Retroviruses and Opportunistic Infections (CROI) in early March 2011. It was reported that this study found that taking a daily tablet containing an HIV medication – either the antiretroviral medication tenofovir or tenofovir in combination with emtricitabine – experienced significantly fewer HIV infections than those who received a placebo pill.

## 2 METHODS AND MATERIALS

### 2.1 DETERMINING SETTING OF CARE

The IMS Health, IMS National Sales Perspectives<sup>TM</sup> database (see *Appendix 2* for full database description) was used to determine the various retail and non-retail channels of distribution for Truvada<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate). Sales data for

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<sup>1</sup> Truvada<sup>®</sup> package insert. Gilead Sciences Inc. July 2011. Accessed March 2012.

<sup>2</sup> Grant R, et.al. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. *The New England Journal of Medicine*. Vol 363(27). December 30, 2010.

<sup>3</sup> International Clinical Research Center(ICRC) (2011). PIVOTAL STUDY FINDS THAT HIV MEDICATIONS ARE HIGHLY EFFECTIVE AS PROPHYLAXIS AGAINST HIV INFECTION IN MEN AND WOMEN IN AFRICA.[Press release]. Retrieved from [http://depts.washington.edu/uwicrc/research/studies/files/PrEP\\_PressRelease-UW\\_13Jul2011.pdf](http://depts.washington.edu/uwicrc/research/studies/files/PrEP_PressRelease-UW_13Jul2011.pdf)

year 2011 indicated that approximately (b) (4) % of Truvada<sup>®</sup> bottles were distributed to outpatient retail pharmacies; (b) (4) % to non-retail settings, and (b) (4) % to mail-order/specialty pharmacies<sup>4</sup>. Retail pharmacies include chain stores, independent pharmacies, and food store pharmacies. As a result, outpatient retail pharmacy utilization patterns were examined. Neither mail order/specialty nor non-retail settings data were included in this analysis.

## 2.2 DATA SOURCES USED

Proprietary drug use databases licensed by the Agency were used to conduct this analysis (see *Appendix 2*).

U.S. outpatient utilization and patient demographics for Truvada<sup>®</sup> were obtained from the IMS, Vector One<sup>®</sup>: National (VONA) and Total Patient Tracker (TPT) from years 2004 through 2011. From these two sources, nationally projected estimates of the number of prescriptions dispensed by outpatient retail pharmacies and the number of patients who received a dispensed prescription for Truvada<sup>®</sup> were obtained.

Additional analyses were conducted for years 2010 through 2011, aggregated, to assess patterns of use since the publication of the pivotal studies. The top prescribing specialties for Truvada<sup>®</sup> were obtained from the IMS, Vector One<sup>®</sup>: National (VONA), years 2010 through 2011, aggregated. The use of Truvada<sup>®</sup>, and comparators tenofovir (Viread<sup>®</sup> as well as its generic), and Epzicom<sup>®</sup> (abacavir sulfate/lamivudine), with concomitant medications, and the desired actions as reported by prescribers were obtained from SDI's, Physician Drug and Diagnosis Audit (PDDA) with Pain Panel, from years 2010 through 2011, aggregated.

## 3 RESULTS

### 3.1 TRUVADA<sup>®</sup> PRESCRIPTION AND PATIENT DATA

*Table 1* and *Figure 1* in *Appendix 1* provides the nationally estimated number of prescriptions dispensed and patients who received a dispensed prescription for Truvada<sup>®</sup> from U.S. outpatient retail pharmacies from years 2004 through 2011. A total of approximately (b) (4) prescriptions were dispensed and (b) (4) patients received prescriptions for Truvada<sup>®</sup> during the examined time period, from approval in 2004 to year 2011. Truvada<sup>®</sup> prescriptions increased over (b) (4)-fold from (b) (4) prescriptions dispensed in year 2004 to approximately (b) (4) prescriptions dispensed in year 2011. The number of patients who received prescriptions for Truvada<sup>®</sup> increased by nearly (b) (4) fold from (b) (4) patients in year 2004 to (b) (4) patients in year 2011.

### 3.2 PRESCRIBING SPECIALTIES

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<sup>4</sup> IMS Health, IMS National Sales Perspectives™ Database. Year 2011. Extracted March 2012. File: NSPC 2012-639 Truvada Y2011.xlsx.

**Table 2 in Appendix 1** provides the nationally estimated number of prescriptions dispensed for Truvada<sup>®</sup> by prescribing specialties from U.S. outpatient retail pharmacies, years 2010 and 2011, aggregated. During the examined time period, “Infectious Diseases” was the top prescribing specialty, accounting for approximately (b) (4) prescriptions) of total dispensed prescriptions for Truvada<sup>®</sup>. “Internal Medicine” and “General Practice/Family Medicine” followed with approximately (b) (4) prescriptions) and (b) (4) prescriptions) of total dispensed prescriptions, respectively.

### 3.3 CONCOMITANT MEDICATIONS AND DESIRED ACTIONS

**Table 3 in Appendix 1** provides the number of drug occurrences<sup>5</sup> for Truvada<sup>®</sup> and comparators, tenofovir (Viread<sup>®</sup> and its generic), and Epzicom<sup>®</sup> (abacavir sulfate/lamivudine), used alone or with concomitant medications, stratified by the desired actions as reported by U.S. office-based physician surveys during years 2010 through 2011, cumulative. Approximately (b) (4) % of drug occurrences for Truvada<sup>®</sup> ((b) (4) drug occurrences, 95% CI, (b) (4)) were reported as “used alone” or monotherapy by office-based physician practices. The top desired actions for Truvada<sup>®</sup> when “used alone” were to “decrease viral load” ((b) (4) % of drug occurrences) or “suppress HIV” ((b) (4) % of drug occurrences). However, there were (b) (4) drug occurrences (95% CI, (b) (4)) or (b) (4) of the drug occurrences when Truvada<sup>®</sup> was “used alone” for the desired action of “prophylaxis” as reported by physicians. These results were below the acceptable count allowable to provide a reliable estimate of national use and therefore, the results must be interpreted with caution as the sample size was very small with correspondingly large confidence intervals.

Comparators tenofovir (brand and generic Viread<sup>®</sup>) and Epzicom<sup>®</sup> (abacavir sulfate/lamivudine) were included in the analysis. Approximately (b) (4) of drug occurrences for tenofovir products were reported to be “used alone” while there were no drug occurrences reported of Epzicom<sup>®</sup> to be “used alone” during the examined time. There were no drug occurrences captured with references to “prophylaxis” for either comparator during the examined time.

## 4 DISCUSSION

Although Truvada<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate) is currently indicated for use *in combination* with other antiretroviral agents for the treatment of HIV-1 infection, approximately (b) (4) % of drug occurrences for Truvada<sup>®</sup> were reported as “used alone”. Approximately (b) (4) of Truvada<sup>®</sup> drug occurrences when “used alone” were reported to be for “prophylaxis”. However, these results are survey-based and were below the acceptable count allowable to provide a reliable estimate of national use;

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<sup>5</sup> Drug occurrences refer to the number of times a product has been reported on a patient information form during an office-based patient visit for that period. It is important to note that a “drug occurrence” does not necessarily result in a prescription being generated.

therefore, the results must be interpreted with caution as the sample size was very small with correspondingly large confidence intervals.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that Truvada<sup>®</sup> products were distributed primarily to the outpatient retail pharmacy setting based on the IMS Health, IMS National Sales Perspectives<sup>™</sup>. This review does not include community health centers, outpatient clinics, and various other clinical settings where patients may receive outpatient health care. Sales data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use. *We did not include mail-order or non-retail settings data in this analysis, which may represent important sources of care for patients with HIV infection.* Since non-retail settings such as specialty clinics are not included in the current analyses, these results may not be representative of all care provided for patients with HIV and should therefore be interpreted with caution. The estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate, and may be due to random error. The universe of retail pharmacies are used to make national projections for dispensed prescriptions and patients receiving dispensed prescriptions.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study.

Concomitant use and desired action data were obtained using SDI's PDDA, a monthly survey of 3,200 office-based physicians. Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and outpatient prescription data are best used to evaluate utilization trends over time. SDI recommends caution when interpreting nationally projected estimates of annual uses or mentions that fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

PDDA uses the term "drug occurrences" to refer to the number of times a product has been reported on a patient information form during an office-based patient visit for that period. It is important to note that a "drug occurrence" does not necessarily result in a prescription being generated. A "drug occurrence" can result from a prescription written, a sample given, a recommendation for OTC products, recommendation with sample, a product dispensed or administered in the office, a hospital order, a nursing home order or a combination of these.

PDDA can only measure one level of concomitant drug activity. The relationship that the database is capable of handling is a one-to-one relationship. That is to say that if three products are prescribed concurrently and an analysis is performed on Product A, Product B and C will each receive one concurrent drug occurrence. Consequently, concurrent and

concomitant products will almost always add to greater than 100% of the total product occurrences. This also pertains to “desired action” because the doctor may have noted more than one “desired action” on the patient survey form.

## 5 CONCLUSIONS

There were approximately (b) (4) prescriptions dispensed and (b) (4) patients who received a dispensed prescription for Truvada<sup>®</sup> from U.S. outpatient retail pharmacy settings in year 2011. Although Truvada<sup>®</sup> is currently indicated for use *in combination* with other antiretroviral agents for the treatment of HIV-1 infection, approximately (b) (4) of drug occurrences reported for Truvada<sup>®</sup> were for monotherapy or “used alone”; among these, about (b) (4) of drug occurrences were reported with a desired action of “prophylaxis”. Although the data are based on a small sample and subject to many limitations, it suggests that there is use, however small, of Truvada<sup>®</sup> alone for the desired action of “prophylaxis” during years 2010 through 2011. The true extent of use for this indication is unknown.

**APPENDIX 1: TABLES AND FIGURES**

**Table 1:**

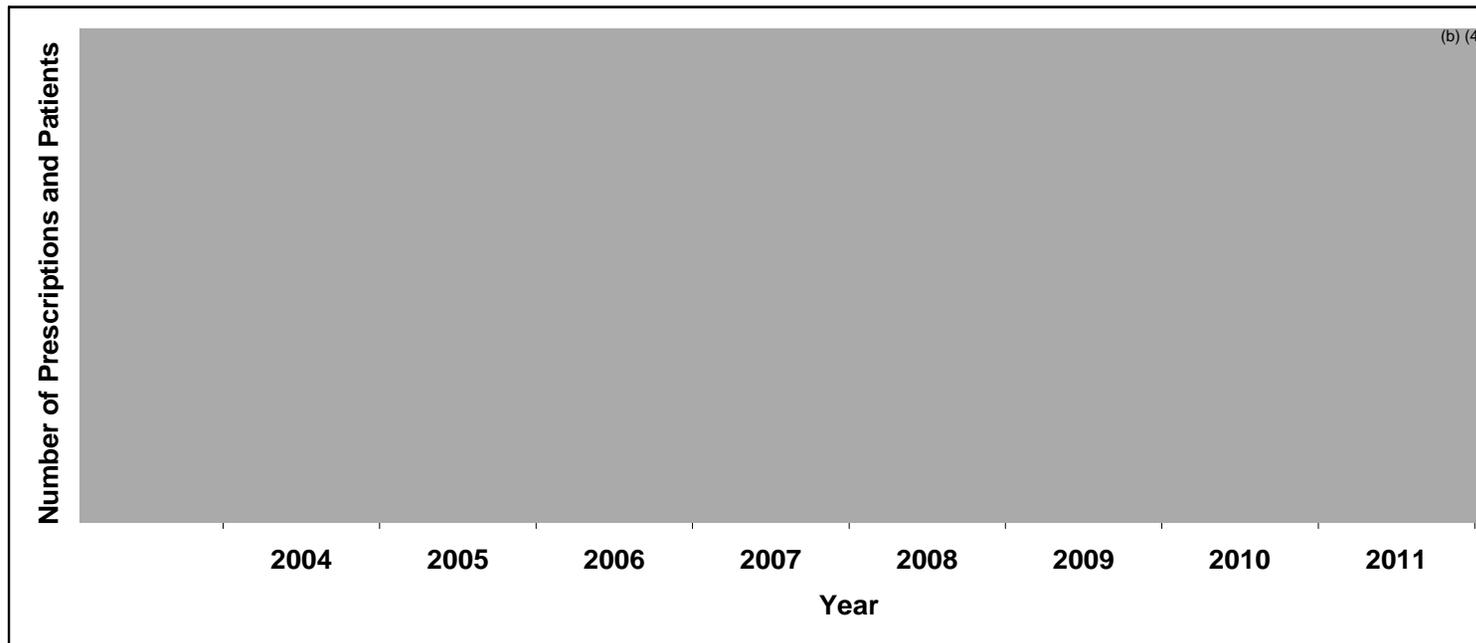
**Nationally Estimated Number of Prescriptions and Patients Who Received Prescriptions for Truvada® Dispensed from U.S. Outpatient Retail Pharmacies, Years 2004-2011**

	2004	2005	2006	2007	2008	2009	2010	2011	Total: 2004-2011
<b>Truvada Prescriptions</b>	(b) (4)								
<b>Truvada Patients</b>	(b) (4)								

Source: IMS, Vector One®: National (VONA) and Total Patient Tracker (TPT). Extracted March 2012. Files: VONA 2012-639 Truvada TRx 2004-2011.xls and TPT 2012-639 Truvada pts display 2004-2011.xls, and TPT 2012-639 Truvada pts total 2004-2011.xls

**Figure 1:**

**Nationally Estimated Number of Prescriptions and Patients Who Received Prescriptions for Truvada® Dispensed from U.S. Outpatient Retail Pharmacies, Years 2004-2011**



Source: IMS, Vector One®: National (VONA) and Total Patient Tracker (TPT). Extracted March 2012. Files: VONA 2012-639 Truvada TRx 2004-2011.xls and TPT 2012-639 Truvada pts display 2004-2011.xls

**Table 2:**

**Nationally Estimated Number of Prescriptions by Prescribing Specialty for Truvada® Dispensed from U.S. Outpatient Retail Pharmacies, Years 2010-2011**

	Years 2010-2011	
	TRxs	Share%
Truvada		(b) (4)
ID		
IM		
GP/FM/DO		
NP		
UNSPEC		
PA		
PED		
HOSP		
OTHER		
GE		
All Others		

Source: IMS, Vector One®: National (VONA). Extracted March 2012. Years 2010-2011.

File: VONA 2012-639 Truvada TRx by MD 2010-2011.xls

ID=Infectious Diseases, IM=Internal Medicine, GP/FM/DO=General Practice/Family Medicine/Osteopathy

**Table 3:**

**Nationally Estimated Number of Drug Occurrences Associated with the Use of Truvada® and Comparators, Tenofovir (Viread®) and Epzicom®, by Concomitant Medications and Desired Action as Reported by Office-Based Physicians, Years 2010-2011**

Years 2010-2011	Years 2010-2011	Years 2010-2011
Occurrence	Occurrence	Occurrence

(b) (4)

## **APPENDIX 2: DRUG USE DATABASE DESCRIPTIONS**

### **IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail**

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

### **IMS, Vector One®: National (VONA)**

The IMS, Vector One®: National (VONA) database measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. There are over 800,000 physicians in the VECTOR One database, which supplies VONA, TPT, & DET. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. IMS receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

### **IMS, Vector One®: Total Patient Tracker (TPT)**

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

### **SDI Physician Drug & Diagnosis Audit (PDDA) with Pain Panel**

SDI's Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based

physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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GRACE CHAI  
04/06/2012  
cleared by data vendors

HINA S MEHTA  
04/06/2012  
Drug use data cleared

LAURA A GOVERNALE  
04/08/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**Provision of Pharmacovigilance Data**

**Date:** March 29, 2012

**Reviewer(s):** Paula Gish, R Ph, Safety Evaluator,  
Division of Pharmacovigilance II

**Team Leader(s):** Kelly Cao, Pharm D, Safety Evaluator Team Leader,  
Division of Pharmacovigilance II

**Product Name(s):** Viread® (tenofovir), Truvada® (emtricitabine + tenofovir)

**Subject:** AERS reports of adverse events in hepatitis B patients without  
reported co-infection with HIV-1

**Application Type/Number:** Viread® (tenofovir) - NDA 21-356 tablets, 22-577 powder

**Supplement:** Truvada® (emtricitabine + tenofovir) - NDA 21752 S-030

**Applicant/Sponsor:** Gilead

**OSE RCM #:** 2012-636

## 1 INTRODUCTION

The Division of Antiviral Products (DAVP) requested the Division of Pharmacovigilance (DPV) II conduct data mining of the postmarketing Adverse Event Reporting System (AERS) data base for tenofovir disoproxil fumarate (tenofovir DF) and the hepatitis B indication. This response provides the following data; no analysis has been performed:

- Data mining scores with an EB05 > 2 of adverse event Preferred Terms (PTs) reported in association with tenofovir under the hepatitis B indication.
- Crude counts for most commonly reported PTs associated with tenofovir under the hepatitis B indication
- Summaries of adverse event reports with tenofovir in hepatitis B patients (without co-infection with HIV-1) for selected PTs with data mining EB05 scores > 2

Tenofovir DF (Viread®) is a nucleotide analog HIV-1 and HBV reverse transcriptase inhibitor and was initially approved 2001 in combination with other antiretroviral agents for the treatment of HIV-1 infection. Viread was also approved in 2008 for the treatment of chronic hepatitis B in adults. In 2004 a fixed dose combination of emtricitabine plus tenofovir DF (Truvada®) was approved in combination with other antiretroviral agents for the treatment of HIV-1 infection.

DAVP is evaluating an efficacy supplement for Truvada® in which the sponsor proposes a new indication for HIV pre-exposure prophylaxis (PREP) in healthy patients. Per DAVP patients with hepatitis B are more representative of healthy patients than HIV-1 infected patients. DAVP is interested in adverse events reported in association with tenofovir DF in hepatitis B patients without HIV-1 co-infection because it may inform them in their NDA supplement risk/benefit assessment of the HIV PREP indication.

## 2 METHODS AND MATERIALS

### 2.1 DATA MINING

The Empirica Signal database was searched with the strategy described in Table 1.<sup>1</sup>

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<sup>1</sup> OSE uses Empirica Signal software, which uses the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm, to perform analyses on AERS data and identify patterns of associations or unexpected occurrences (i.e., “potential signals”) in large databases. MGPS analyzes the records in AERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in AERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on AERS data, limitations relating to AERS data also apply to data mining-derived data.

<b>Table 1. Data Mining Search Strategy</b>	
Data Refresh Date	2/16/2012
Product Terms	Tenofovir
Empirica Signal Run Name	7122: Generic name + Indication PT + PT Where: EB05 > 2.0
Indication	<i>Hepatitis B</i>

## 2.2 AERS

The Adverse Event Reporting System (AERS) was searched with the strategy described in Table 2.<sup>2</sup>

<b>Table 2. AERS Search Strategy</b>	
Date of search	16-Mar-2012
Time period of search	26-Oct-2001* to 16-Mar-2012
Product Terms	Tenofovir, Viread
MedDRA Search Terms	For AERS crude counts: all PTs  For summaries of reports with PTs of EB05 >2: <i>abortion spontaneous, osteoporosis, renal failure, blood creatinine increased, pancytopenia, leukopenia, thrombocytopenia, rhabdomyolysis</i> Plus: <i>osteomalacia, osteopenia, renal failure acute, Fanconi syndrome, Fanconi syndrome acquired</i>
Indication	<i>Hepatitis B, Congenital hepatitis B infection, Hepatitis B antibody positive, Hepatitis B antigen positive, Hepatitis B core antibody positive, Hepatitis B DNA assay positive, Hepatitis B surface antibody positive, Hepatitis B surface antigen positive, Hepatitis B virus test positive</i>

\* Initial US Approval date

## 3 DATA

### 3.1 DATA MINING

<sup>2</sup> AERS is a database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. AERS data do have limitations (e.g., variable quality and quantity of information provided, cannot determine causality, voluntary reporting system, reporting biases). Additionally, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

## Tenofovir DF: Hepatitis B Indication

### Data mining PTs with EB05 > 2

*AERS data as of 2-16-2012*

**Configuration:** CBAERS BestRep (S) (v2) **Run :** 7122 w/o sourc dup (3D) D-E-I **Run ID:** 7122

**Dimension:** 3 **Selection Criteria:** Generic name(Tenofovir) + Indication PT(Hepatitis B) + PT **Where:** EB05 > 2.0

Generic name	Indication PT	PT	N	EBGM	EB05	EB95	INTSS	RR
Tenofovir	Hepatitis B	Viral load increased	11	3552.0	2086.8	5735.2	30.5	8371.3
Tenofovir	Hepatitis B	Abortion spontaneous	10	1034.5	590.0	1711.0	11.4	1352.1
Tenofovir	Hepatitis B	Osteoporosis	6	1150.7	514.9	2271.1	9.95	2116.8
Tenofovir	Hepatitis B	Renal failure	12	200.0	102.1	445.6	1.97	355.5
Tenofovir	Hepatitis B	Blood creatinine increased	8	122.7	67.6	238.1	1.31	295.8
Tenofovir	Hepatitis B	Bone pain	5	155.6	57.4	731.9	1.11	666.5
Tenofovir	Hepatitis B	Pancytopenia	5	97.1	48.4	188.1	0.934	329.2
Tenofovir	Hepatitis B	Leukopenia	5	87.0	44.3	159.1	0.855	232.4
Tenofovir	Hepatitis B	Rhabdomyolysis	5	81.6	41.7	148.0	0.806	190.6
Tenofovir	Hepatitis B	Alanine aminotransferase increased	6	74.9	40.3	130.2	0.778	128.5
Tenofovir	Hepatitis B	Thrombocytopenia	5	75.7	38.8	136.6	0.750	153.8
Tenofovir	Hepatitis B	Drug ineffective	10	52.1	31.6	82.0	0.610	59.2
Tenofovir	Hepatitis B	Pyrexia	5	38.2	19.6	68.6	0.379	41.4
Tenofovir	Hepatitis B	Nausea	6	33.5	18.0	58.1	0.348	34.2

These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

## 3.2 AERS

**Tenofovir DF: Hepatitis B Indication****Crude report counts<sup>1</sup> for most commonly reported MedDRA Preferred Terms (PTs)***From dates of product marketing through 3-16-2012*

Comments:

<b># of rpts<sup>1</sup> all adverse events for hepatitis B indication</b>	257	257 reported under hepatitis B indication out of 9433 total reports for tenofovir (including combination products) for all indications
<b># of rpts<sup>1</sup> (% of total rpts) for the most commonly reported PTs:</b>		
<i>Renal failure</i>	18 (7%)	Labeled to have occurred in clinical trials for hepatitis B. 23 cases reported under PTs blood creatinine increased, Fanconi syndrome, Fanconi syndrome acquired, renal failure, renal failure acute in hepatitis B patients without co-infection with HIV-1. 15/23 report pre-existing renal impairment, diabetes mellitus, prior renal toxicity with adefovir or renal events in conjunction with deteriorating liver function (3 deaths). One other death in case with very little information.
<i>Viral Load Increased</i>	17 (6.6%)	N/A
<i>Drug ineffective</i>	14 (5.45%)	N/A
<i>Abortion Spontaneous</i>	12 (4.7%)	Unlabeled. 10 cases in hepatitis B patients without co-infection. Maternal age 31-40 years. 9/10 in first trimester. One at 16 weeks.
<i>Alanine aminotransferase increased</i>	12 (4.7%)	Labeled to have occurred in clinical trials for hepatitis B.
<i>Hepatitis B</i>	11 (4.3%)	N/A- indication.
<i>Blood Creatinine Increased</i>	10 (3.9%)	Labeled to have occurred in clinical trials for hepatitis B. See comments under renal failure.
<i>Osteoporosis</i>	9 (3.5%)	Labeled for HIV-1 infected patients. "The bone effects of VIREAD have not been studied in patients with chronic HBV infection." 9 cases reported under PTs osteoporosis, osteopenia, and osteomalacia in hepatitis B patients without co-infection. Two study patients (no fractures). Seven non-study patients. Two with fractures.
<i>Genotype Drug Resistance Test Pos.</i>	8 (3.1%)	N/A
<i>Hepatitis B DNA Increased</i>	8 (3.1%)	N/A
<i>Nausea</i>	7 (2.7%)	Labeled to have occurred in clinical trials for hepatitis B patients.
<i>Pancytopenia</i>	7 (2.7%)	Unlabeled. 6 cases in hepatitis B patients without co-infection.
<i>Asthenia</i>	6 (2.3%)	Labeled to have occurred in clinical trials for HIV-1 patients.
<i>Bone Pain</i>	6 (2.3%)	Labeled for HIV-1 infected patients. "The bone effects of VIREAD have not been studied in patients with chronic HBV infection." See comments under osteoporosis.
<i>Hepatic Failure</i>	6 (2.3%)	9 cases reported under PTs acute hepatic failure, hepatic failure in hepatitis B patients without co-infection. All cases report patients with cirrhosis, liver transplant rejection, hepatic cancer, or hepatitis B reactivation following Rituxan treatment for lymphoma.
<i>Pyrexia</i>	6 (2.3%)	Labeled to have occurred in clinical trials for hepatitis B patients.
<i>Rhabdomyolysis</i>	6 (2.3%)	Labeled post marketing. 5 cases in hepatitis B patients without co-infection.
<i>Thrombocytopenia</i>	6 (2.3%)	Unlabeled. 5 cases in hepatitis B patients without co-infection. One reports history of cirrhosis.

<sup>1</sup> Crude counts: may contain duplicate reports; reports have not been individually reviewed for a drug-event association. One report may have more than one Preferred Term.

## Tenofovir DF: Hepatitis B Indication (no reported co-infection with HIV-1)

### Summaries of selected adverse events with EB05 > 2

*From dates of product marketing through 3-16-2012*

**Abortion spontaneous (N=10)** - (crude count 12 reported under PT *abortion spontaneous*, 2 cases excluded [#6591896, 700119] due to hepatitis B and HIV-1 co-infection). Maternal age: 31 to 40 years. Two of the 10 cases are from the Antiretroviral Pregnancy Registry (APR) and two involve study patients from GS –US-203-0101 “Randomized double blinded tenofovir DF monotherapy vs. emtricitabine plus tenofovir DF for the treatment of chronic hepatitis B”. Nine of the 10 spontaneous abortions occurred in the first trimester. One occurred at 16 weeks.

**Osteoporosis, osteomalacia, or osteopenia (N=9)** - (crude count 13 reported under PTs *osteoporosis, osteomalacia, osteopenia*, 4 cases excluded [#6132477, 6426197, 7304067, 8346967] due to hepatitis B and HIV-1 co-infection). Two of remaining 5 are study patients and report no fractures. Seven non-study patients report osteoporosis, osteopenia or osteomalacia. Two report fractures.

- Case 7083963 – 53-year-old female with chronic hepatitis B and history of amenorrhea (including menopause) or oligomenorrhea and wasting or weight loss who commenced Viread on 27-Nov-08. The patient was not taking any concomitant medication, and it was reported that the patient had not received corticosteroids, bisphosphonates, anticonvulsants or hormone replacement. The patient had no history of cigarette smoking, immobilization or prolonged bed rest, bone disease, renal disease, Cushing’s syndrome, gastrointestinal disease, hyperlipidemia, drug or alcohol abuse, thyroid disease, parathyroid disease or vitamin D deficiency. The patient had been post-menopausal for 7 years and bone scintigraphy after menopause did not reveal osteoporosis. After 3 months of tenofovir DF the patient had whole body and bone pain which she had never experienced before. On [REDACTED] <sup>(b) (6)</sup> days after commencing tenofovir DF, the patient experienced osteopenia on neck of femur and osteoporosis on forearm confirmed whole body bone mineral density measurement by scintigraphy. She was hospitalized. The patient had a metal implant in her lumbar vertebra and her osteoporosis score could not be measured. Tenofovir DF was discontinued and switched to another medicine.
- Case 7326437 – STUDY GS-US-174-0103 “A Randomized, Double-Blind, Controlled Evaluation of Tenofovir DF versus Adefovir Dipivoxil for the treatment of HBeAg positive Chronic Hepatitis B.” 23-year-old Asian male with chronic hepatitis B infection diagnosed with osteoporosis of left hip and lumbar spine with high fracture risk (DEXA scan) after > 3 years of treatment with blinded and open label tenofovir DF.
- Case 7346140 - STUDY GS-US-174-0102 “A Randomized, Double-Blind, Controlled Evaluation of Tenofovir DF versus Adefovir Dipivoxil for the treatment of Presumed Pre-core Mutant Chronic Hepatitis B.” 59-year-old Caucasian male with hepatitis B started open-label tenofovir DF 16-Mar-2007. Concomitant medications included

Nerisone (diflucortovalerate), desloratadine, pristnamycin used for treatment of rash on legs. Patient denied use of corticosteroids, bisphosphonates, anticonvulsants, and hormone replacement medication. Patient was negative for cigarette smoking, immobilization, bone disease, renal disease, Cushing's syndrome, gastrointestinal disease, hyperlipidemia, drug or alcohol abuse, wasting or weight loss, thyroid disease, parathyroid disease, testosterone deficiency, liver disease and vitamin D deficiency. On 26-Sep-2006 patient was noted to have hypophosphatemia intermittently with a phosphorus level of 1.6 which required treatment. Creatinine level increased from 74 umol/L 11-Apr-2006 to 82 umol/L 15-Dec-2009. On 09-Feb-2010 a DEXA scan indicated vertebral bone mineral density corresponding to osteopenia and densitometric osteoporosis on hip. Patient began treatment with risendronate.

- Case 7750945 – 49-year-old Caucasian male with chronic hepatitis B and chronic osteomyelitis, type II diabetes mellitus and immobilization/prolonged bed rest. Patient began tenofovir DF and on an unspecified date developed osteoporosis. On 21-Oct-2010 DEXA scan of hip and spine revealed lumbar T-score of -3.0 (osteoporosis and high fracture risk) and a femur neck T-score of -1.5 (osteopenia, fracture risk increased). 26-Nov-2010 creatinine was 0.85mg/dL (0.8-1.2), alk phos was 468 u/L (5-270), inorganic phosphorous was 2.6mg/dL (2.7-4.5), calcium 9.1mg/dL (8.8-10.2). Patient was treated with risendronate, calcium with D vitamin and cholecalciferol. Tenofovir DF was discontinued and switched to another medicine.
- Case 8383936 – 53-year-old male with hepatitis B, alcoholism, diabetes, cirrhosis, dyslipidemia, hyperlipidemia, arterial hypertension, testosterone deficiency, hemosiderosis, liver disease, vitamin D deficiency, polyneuropathy, incipient diabetic nephropathy with proteinuria, diabetic retinopathy. Active smoker for 40 years/package. Patient began treatment with adefovir on 13-Mar-2008. After two months viral load of virus B decreased. In January 2010 patient was diagnosed with vertebral fracture – crushing at the level of the vertebra L1. Adefovir was discontinued and patient was put on tenofovir DF. In September 2011 patient presented with multiple atraumatic fractures. Lumbar bone densitometry showed multiple focus of hypercaptation in ribs, condyle and neck of femur, tarsus and ankle and the head of the humerus. Imperfect osteogenesis genetic study was negative. Rheumatology specialist diagnosed secondary osteomalacia to tenofovir DF and incomplete Fanconi syndrome. Tenofovir DF was discontinued. *(also reported under renal events)*
- Case 7650511 - 29-year-old male patient with hepatitis B who commenced Viread (tenofovir DF) on 06 April 2009 (one dosage form orally daily). Concomitant medications included lamivudine and Hepsera (adefovir dipivoxil) (dates not provided). The patient's medical history was significant for entecavir therapy started in 2007 but discontinued in 2008 when the patient's HBV DNA became negative. On 06 April 2009, the patient's HBV DNA level was 1.7x1000000IU and the patient was HBEAG negative. AST and ALT levels were increased but not more than two times. Therapy with tenofovir DF was initiated as a result. In the first 3 three months of therapy, HBV DNA became negative. After 6 months HBV DNA was 989IU. It was reported that the patient's medical history did not include any of the following: cigarette smoking,

immobilization/prolonged bed rest, bone disease, renal disease, Cushing's syndrome, gastrointestinal disease, hyperlipidemia, drug or alcohol abuse, weight loss, thyroid disease, parathyroid disease, testosterone deficiency or vitamin d deficiency. However the patient did have a medical history of liver disease. The patient was not receiving any corticosteroids, bisphosphonates, anticonvulsants or hormone replacement. On 14 January 2010, approximately 9 months after commencing tenofovir DF, the patient developed viral breakthrough (HBV DNA 12000IU). Neither non-compliance to therapy or resistance to lamivudine, entecavir or adefovir were detected. Biochemical test results were normal. In August 2010, the patient started to complain of widespread bone pain and went to a specialist. On 20 September 2010, a bone densitometry was performed which revealed a T-score of 2.2, a Z-score of 2.2 in total body and T-score of 2.8 and an L2 Z-score of 2.8 in L2. The patient was diagnosed with osteopenia and fosavance therapy was initiated. At the time of this report, treatment with tenofovir DF and fosavance were ongoing. On an unspecified date, lab tests revealed that HBV DNA level of patient was decreased, therefore the reporter no longer suspected a virologic breakthrough. The reporter considered that it was due to it non-compliance of HBV therapy in the beginning. At the time of this report, the osteopenia had stabilized and was not progressing.

- Case 7751090 - 60-year-old male patient with chronic hepatitis B, who commenced Viread (tenofovir DF tablets, 245mg, orally) on 22 October 2008. Concomitant medications included olmesartan, insulin and OAD (for diabetes - not further specified). The patient's medical history included renal function disorder (it was reported that the patient was monitored very closely), hypertension and diabetes (for 12 years at time of this report). On an unspecified date, while receiving tenofovir DF, the patient developed osteopenia and received treatment (not further specified). On 01 June 2009, the patient experienced an increase in creatinine levels at 1.4 (units and normal range not specified). On 17 February 2010, creatinine was 1.3. On 26 May 2010, the patient experienced proteinuria (+++). On 20 July 2010, creatinine was 1.5. On 28 December 2010, tenofovir DF and olmesartan were discontinued. The patient was switched to entecavir. The patient was currently closely monitored by the nephrology department of the hospital. The reporter was expecting to see the patient again in February 2011. At the time of this report, the physician stated that the events were not progressing since tenofovir DF was discontinued. The final etiology for the events of proteinuria, osteopenia and increased creatinine were due to both the patient's diabetes mellitus and treatment with tenofovir DF. The reporter considered that the events were likely to be associated with the use of tenofovir DF due to the fact that they occurred within a few months of the initiation of tenofovir DF. (*also reported under renal events*)
- Case 7903579 - a female patient (age and race not provided) with hepatitis B (HBV) infection who commenced therapy with Viread (tenofovir disoproxil fumarate) on an unspecified date; treatment details not provided. Concomitant medications and medical history were not provided. On an unspecified date, the patient experienced osteomalacia bone pain. Treatment and outcome not provided. Additional information not provided.

- Case 8351355 - a male (age unspecified) patient with hepatitis B, who commenced tenofovir DF on an unspecified date. The patient's medical history and concomitant medications were not reported. While receiving long term tenofovir therapy, on an unspecified date the patient was referred by his gastroenterologist to the reporting physician with generalized aches and pains and insufficiency fractures. The gastroenterologist had suspected osteoporosis however the reporting physician believed that the patient's presentation was consistent with osteomalacia. No information on renal parameters or renal monitoring was available. The outcome of the osteomalacia was not reported.

**Renal events (N=23)** -(crude count 32 under the PTs *renal failure, blood creatinine increased, acute renal failure, Fanconi syndrome, Fanconi syndrome acquired*, 7 cases excluded [#4042090, 6359454, 6566947, 6574983, 6860769, 7304067, 7361950] due to hepatitis B and HIV-1 co-infection and another 2 cases excluded (#6107597, 6647819) because renal events occurred prior to tenofovir DF)

See table at end of this document with detailed description of each of the 23 cases.

**Pancytopenia (N=6)** – (crude count 7 under PT *pancytopenia*. One is a duplicate report.)

- Case 6281195 - 71-year-old female with hepatitis B and liver cirrhosis with ascites. Concomitant medications include lamivudine, ciprofloxacin, lansoprazole, Pabrinex (glucose, ascorbic acid, nicotinamide, paracetamol/pyridoxine, riboflavin, thiamine), spironolactone, thiamine, vitamin K. Four months later developed pancytopenia. Tenofovir DF discontinued, patient recovering.
- Case 6962910 (dup 6965480) - 52-year-old male with chronic hepatitis B and urothelium carcinoma not active, diagnosed in 1992. CLL diagnosed in Nov 2000 given chemotherapy in 2005, 2007, 2008. Concomitant medications include telbivudine. After 7 mos tenofovir DF treatment (in 2009) developed severe pancytopenia. Tenofovir, telbivudine discontinued, patient recovered.
- Case 7244054 - 53-year-old male with hepatitis B and D, cirrhosis of liver, history of acute renal failure (b)(6) liver transplant (b)(6), clostridium difficile colitis, proteinuria and pancytopenia since July 2009. Started tenofovir July 09. Concomitant medications included tacrolimus, sirolimus and ursodeoxycholic acid post liver transplant, pantoprazole, ramipril, vancomycin. Developed Fanconi syndrome, tenofovir discontinued. Renal tubular acidosis is not resolved. Outcome unknown. (*also reported under renal events*)
- Case 7371992 – female (age unk) with hepatitis B and history of dialysis began tenofovir DF once weekly post dialysis. Concomitant medications unknown. One month after beginning tenofovir DF patient experienced pancytopenia. Tenofovir was discontinued. Patient remained on other medications. Outcome unknown.

- Case 7495086 – 35-year-old male patient with hepatitis B began tenofovir DF. Concomitant medications and history not reported. Over 6 months physician noted a decrease in white count, platelet count and hemoglobin. No findings on ultrasound. Patient admitted to hospital for 4 days. Tenofovir DF was discontinued but no effect noted at all. Patient instructed to follow-up when discharged but did not return-lost to follow up.
- Case 7716809 – 48-year-old female with hepatitis B and history of breast cancer (T1N0M0) developed pancytopenia while on therapy with entecavir. She received adefovir from Mar 2005-Feb 2009 and tenofovir from July 2010 to Aug 2010. 23-Jul-2010 WBC 2.61, Hgb 10.4 g/dl, platelet count 96K. The patient was treated with entecavir beginning 20-Aug-2010. On Dec 2010 patient was found to have pancytopenia (11-Dec-2010 WBC 3.1, hgb-10.6 g/dl platelets 107K) and was treated with packed red blood cells. Entecavir was discontinued.

#### **Leukopenia (N=5) – (crude count 5 under PT *leukopenia*)**

- Case 6882472 - male (age unknown) with hepatitis B, cirrhosis, pre-existing leukoneutropenia. One month after tenofovir leukocytes decreased from 3000 to 1200/mm<sup>3</sup>, neutrophils 500/mm<sup>3</sup>. Tenofovir discontinued. Biological work up “became normal”. Leukocytes increased to 4100/mm<sup>3</sup>.
- Case 7217507 – 48-year-old male with hepatitis B treated with tenofovir two weeks. Admitted for pneumonia and started on levaquin and Tamiflu. Concomitant medications include Xanax, Lexapro, Lamictal and Inderal. Found with thrombocytopenia. Underwent a “bronch” with washings. WBC 2.7. Tenofovir discontinued. Lovenox also on hold because of thrombocytopenia. Leukopenia resolving at discharge. (*also reported under thrombocytopenia*)
- Case 7658116 – 51-year-old male with hepatitis Delta, no history of pericardial disease in the past began peg interferon alfa on 15 Jun 09. On unreported date patient developed leucopenia, anemia. On 29 Mar 2010 patient began tenofovir. On 3-Sep 2010 patient developed febrile infection and was treated with ciprofloxacin. Patient hospitalized <sup>(b) (6)</sup> days later due to thoracic pain and fever 39 C, dyspnea. Pericardial rub was found and pericarditis diagnosed. X-ray showed chronic bronchitis. Treated with diclofenac and pericarditis, pericardial effusion resolved. Leukopenia and anemia persisted. Outcome unknown.
- Case 7958892 – 51-year-old male with chronic hepatitis B since 1978, lamivudine resistance began tenofovir in February 2011. On an unspecified date he experienced leukopenia 1600 cell/uL and neutropenia 200 cells/uL. The patients HBV DNA level was below detection limit. The patient informed the reporting physician that a control label outside the hospital showed the patient had a normal blood count and the physician said a lab error should be considered if “too long period of rest in the lab automat.”

- Case 8168552 – male patient (age unk) with hepatitis B began tenofovir on 01-Apr-2009. Due to “some dental problems” the patient was treated with antibiotics, anti-inflammatory drugs and possibly with analgesics in Aug 2011. On an unspecified date the patient experienced slight leukopenia that resolved on 18-Oct-2011. Tenofovir was continued throughout the events.

**Rhabdomyolysis (N=5)** – (crude count 6 under PT *rhabdomyolysis*, one report excluded [#7361950] due to hepatitis B and HIV-1 co-infection.)

- Case 7005655 – young male patient (age unknown) with hepatitis B who was “a (b) (6),” was treated with lamivudine and tenofovir. Patient had increased CPK 1.5N less than 3 months after starting tenofovir. The patient did not discontinue tenofovir. Symptoms disappeared. The patient eventually discontinued treatment with tenofovir and started adefovir. No further info provided.
- Case 7575487 – GX-FR-174-0130 “a multicentre, non-interventional study of the management and follow-up of patients with chronic hepatitis B treated by tenofovir DF in routine clinical practice in France”. 61-year-old male patient with hepatitis B, psoriatic rheumatism and otospongiosis began Viread 16-Feb-2010. No concomitant medications. On 15-Mar-2010 patient experienced grade 3 osteo-articular pain, depressive syndrome, difficulty walking, moderate loss of weight, exacerbation of psoriasis and visual disorders. Patient treated with betamethasone dipropionate, and betaderm. Patient also developed muscular weakness and asthenia suggesting rhabdomyolysis. Tenofovir was discontinued and patient recovered.
- Case 8780172 – 42-year-old male of African descent with chronic hepatitis B began Viread in November 2010. No concomitant medications. No medical history provided. In December 2010 patient experienced CK increase of 878 IU/ml and myalgia. Diagnosed with rhabdomyolysis. Hospitalized and treated with fluid replacement. Tenofovir was discontinued. CK values had not improved 3 mos after discontinuation.
- Case 8162717 – 25-year-old female with hepatitis B who commenced Viread. Patient became pregnant. Patient experienced an increase in CPK at 3N and continued had diffuse pains. Eventually tenofovir was discontinued. 15 days after discontinuation increased CPK and once venous lactates were noted. CPK was still slightly elevated but was decreasing.
- Case 8329456 – 68-year-old female with hepatitis B and history of lymphoma, diabetes mellitus, CNS disease, cardiac disease and liver disease. Concomitant medications included glimepiride, simvastatin, Plavix, lisinopril, amlodipine, HCTZ, and metoprolol. No history of hypertension, drug or alcohol abuse, renal disease, gastrointestinal disease or other endocrine disease, musculoskeletal or connective tissue, fluid or electrolyte imbalance or poor nutrition. On 23-Dec-2011 initiated tenofovir DF due to hepatitis B reactivation following Rituxan treatment. Her creatinine was 1.75 mg/dL (0.5-1.3 mg/dL). Approximately (b) (6) later patient developed rhabdomyolysis. Patient was hospitalized. On (b) (6) creatinine was 1.92 mg/dL. On (b) (6) CPK 1351

u/L (25-170 u/L). Patient was treated with fluids. On [REDACTED] Viread was discontinued. On [REDACTED] creatinine was 1.25 mg/dL. On [REDACTED] myoglobin 6784 ng/ml (9-82 ng/ml). On [REDACTED] CPK 1375 u/L, creatinine 0.97 mg/dL and myoglobin 3059 ng/ml. On [REDACTED] myoglobin 190 ng/ml. On [REDACTED] CPK 24 u/L, creatinine 0.86 mg/dl. Rhabdomyolysis resolved.

**Thrombocytopenia (N=5)** – (crude count 6 under PT *thrombocytopenia*. One is a duplicate report.)

- Case 5948235 (dup 5958602) - 22-year-old North African male study patient (study: GS-US-174-0103 Randomized double blind controlled evaluation of tenofovir vs. adefovir for treatment of HBeAG pos chronic hepatitis B). Patient platelet count 30K at study week 4, continued study drug and platelets improved to 144K.
- Case 7217507– 48-year-old with hepatitis B treated with tenofovir two weeks. Admitted for pneumonia and started on Levaquin and Tamiflu. Concomitant medications included Xanax, Lexapro, Lamictal and Inderal. Found with thrombocytopenia. Underwent a “bronch” with washings. WBC 2.7. Tenofovir discontinued. Lovenox also on hold because of thrombocytopenia. Leukopenia resolving at discharge. (*also reported under leukopenia*)
- Case 7511861 – 27-year-old male with HBV but no other illnesses or medical history began tenofovir 15-Jan-2010. No concomitant medications. On 19 Jul 2010 185 days after beginning tenofovir patient presented with thrombocytopenia. Tenofovir discontinued. On 20 Jul 2010 thrombocyte count 74K. On 22 Jul 2010 thrombocyte count 180K. Restarted tenofovir 22 Jul 2010. On 04-Aug-2010 thrombocyte count low 117K. Normal peripheral blood count. No evidence of cirrhosis in patient. Tenofovir was discontinued and patient switched to another oral antiviral agent. Platelet levels were normal for two months.
- Case 7613680 – 66-year-old male with hepatitis B and hepatocellular carcinoma, cirrhosis and gastric ulcer. Seven months prior his first hepatocellular carcinoma was resected. In April he 2010 he received chemembolization for a new left lobe lesion. 12-July 2010 began tenofovir. 13-Jul 2010 MRI showed a gastric varix in the fundus. [REDACTED] underwent trans arterial chemoembolization for left lobe lesion. Pre-op tests showed 79K platelets, PT 14.8 and INR 1.18. Patient discharged next day after surgery. [REDACTED] experienced vomiting blood, hospitalized for blood transfusion. Endoscopy revealed bleeding ulcer. Tenofovir discontinued 17-Aug 2010. Patient said he was feeling better since discontinuing tenofovir. Outcome unknown.
- Case 8061412 – 32-year-old male with chronic hepatitis B began tenofovir on 02-Aug-2010. 08-Mar 2011 platelet count 41.1 (units not reported). On 19-Jul-2011 platelet count was 43. Treatment with tenofovir continued and event had not resolved. Outcome unknown.

### Tenofovir DF

#### AERS cases of renal events\* in hepatitis B patients with no reported HIV-1 co-infection

N=23

\*Reported under MedDRA Preferred Terms: *blood creatinine increased, Fanconi syndrome, Fanconi syndrome acquired, renal failure, renal failure acute*

AERS data as of 3-16-2012

ref #	AERS case # Age/sex	Preferred terms (PTs)	Concomitant medications	Narrative/comments
1	3857946 Male (age unk)	Renal failure	NR	Male patient (age unknown) with hepatitis B and history of severe hepatic failure started tenofovir DF 300mg once daily on 1-Oct-2002. Soon after the patient developed renal failure. Hemodialysis was planned. On 4-Oct-2002 tenofovir DF was interrupted and re-initiated at 300mg every 3 days. The patient died (cause not reported). Per the reporting physician the "death was probably not related to tenofovir DF because the patient was critically ill before receiving tenofovir DF"
2	5921805 58M	Alanine aminotransferase increased, blood albumin decreased, blood bilirubin increased, coagulopathy, condition aggravated, drug resistance, hepatic failure, international normalized ratio increased, rebound effect, renal failure, sepsis, viral infection, viral mutation identified	NR	Literature: 58-year-old Middle Eastern male with chronic hepatitis B and history of lamivudine-resistant HBV and decompensated cirrhosis (awaiting liver transplant) and osteomyelitis began adefovir (Hepsera). Concomitant medications included lamivudine. Two months after the detection of adefovir-resistant mutation, salvage therapy was implemented, switching the patient to tenofovir DF. Despite the change the patient had worsening liver failure evidenced by "rising bilirubin levels, worsening coagulopathy and renal failure" and died two months later.
3	6313932 56F	Fluid retention, hepatic steatosis, hypokalaemia, metabolic syndrome, renal cyst, renal failure, urinary tract infection	Spironolactone, lisinopril, metformin, furosemide, ciprofloxacin	56-year-old female with hepatitis B since 1975, and history of hyperhydropexis (dates not provided), diabetes mellitus since 1999, arterial hypertension since 2000 and chronic renal failure began adefovir in July 2003. The patient was hospitalized on (b) (6) due to increasing renal insufficiency (ser cr 2.9mg/dL). Sonography revealed renal cyst on the left and no hydronephrosis. After interrupting spironolactone, lisinopril, metformin and adefovir the patient's creatinine dropped to 1.8mg/dL. On 29-Sep-2006 adefovir was switched to tenofovir. A urinary infection was treated with ciprofloxacin. The patient's creatinine rose to 2.9mg/dL. Tenofovir dose was reduced to 300mg every 4 days and creatinine recovered to 1.24mg/dl. Patient did not tolerate tenofovir DF "very well" and in Feb 2007 was switched back to adefovir every 3 days.
4	6629521 60M	Renal failure	Furosemide, Vitamin K, Luvion, entecavir, Lactulose	60-year-old male Caucasian with hepatitis b and cirrhosis, history of jaundice, oedema, oliguria, ascites, hepatic encephalopathy and allergy to azithromycin began tenofovir DF 300mg daily on 27-Mar-2008 (creatinine clearance was 135 mL/min) (b) (6) days later patient developed worsening of jaundice, severe deterioration of liver and renal function and was hospitalized. Renal dysfunction characterized as predominantly tubular disease. Creatinine 4.55mg/dL, creatinine clearance was 33.4 mL/min, bilirubin was 52.8mg/dL, viral load was 4.766 x

### Tenofovir DF

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				10 <sup>6</sup> copies/mL. Tenofovir DF dose was reduced but the patient's condition continued to deteriorate. Patient was evaluated for a liver transplant. Haemodialysis was continued. On (b) (6) patient died due to hepatic and renal failure.
5	6855074 51M	Renal failure	Entecavir, ciclosporine, furosemide	51-year-old male with hepatitis B, and history of kidney transplant began tenofovir DF in combination with entecavir in Nov-2007 (Ser cr 104 micromole/liter, GFR 52ml.min). The patient had a urinary tract infection in Nov 2008. On 13-Nov-2008 the patient experienced stage IV renal insufficiency. The renal insufficiency improved to stage III on 04-Dec-2008 (GFR 38 ml/min). The dose of entecavir was reduced.
6	6914094 75M	Blood creatinine increased, drug ineffective	Lamivudine	75-year-old male with chronic hepatitis B and cirrhosis confirmed by liver biopsy. After 15 mos after adding tenofovir DF to ongoing lamivudine therapy the patient developed a rise in serum creatinine to 140 (units not given) and a GFR of 30-40 mL/min. Tenofovir DF was reportedly adjusted to "300mg every day". The patient is still viremic with a viral load of 8800 copies/mL.
7	7010485 32M	Blood creatinine increased	NR	32-year-old male switched from adefovir to tenofovir DF in October 2008. Prior to start of adefovir baseline cr was 1.2. After switching to adefovir creatinine was 1.33. There was no significant medical history of hypertension or renal disease. After 6 mos with tenofovir DF creatinine increased to 1.7, glucose was 2+ and 24 hour urine test revealed 1.3 grams of protein. Tenofovir DF was dc'd and patient was started on etravirine as well as enalapril.
8	7060322 59M	Back pain, pyrexia, renal failure	Nimesulide, tetracosactide, "FANS and corticosteroids"	Un-sponsored clinical trial "multicenter open label study to explore efficacy and tolerability of tenofovir DF in chronic hepatitis B, HBeAg positive or negative, patients with suboptimal response to adefovir or ADC/LAM treatment" Italy: 59-year-old male began tenofovir DF on 19-Nov-2008. Nimesulide was started on 28-Mar-2009. On (b) (6) days after commencing tenofovir DF the patient presented with fever, shivering, lumbar pain. Tenofovir DF and nimesulide were dc'd and patient was hospitalized. Ser Cr was 3.59 mg/dL and BUN was 79. Patient was diagnosed with renal failure and dehydration. A backbone X-ray and RMN showed multiple lumbar discal protrusions in the patient with spondylosis and osteochondrosis. Treatment with tenofovir DF was restarted 29 May 2009. On (b) (6) the patient was re-hospitalized for acute renal failure, hydronephrosis due to lithiasis of left pyelo-ureteral joint. Creatinine was 1.8mg/dL. Urine analysis showed specific gravity 1020, pH at 6, proteins at 30mg/dL and WBC at 22,400. Serum creatinine at discharge was 1.3mg/dL.
9	7072264 74M	Metabolic acidosis, renal failure acute, vomiting	Losartan, Zeffix (lamivudine), hidrosaluretil, omeprazole, dianben	74-year-old male with hepatitis B, history of hypertension, type 2 diabetes mellitus, and renal insufficiency experienced worsening renal function while treated with tenofovir DF and lamivudine. Treated with periodic haemodialysis and bicarbonate.

### Tenofovir DF

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AERS data as of 3-16-2012

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10	7075758 53F	Fanconi syndrome acquired, hyperparathyroidism, renal failure	Lithium, lamivudine, bromazepam, tamoxifen, risendronate	53-year-old female with chronic hepatitis B diagnosed in 1992, history of depression, Hodgkin's disease in 1972 treated by splenectomy and radiotherapy, "inguinal relapse" in 1973 leading to osteoporosis and early menopause. In 2003 patient was diagnosed with "colic" cancer treated by surgery, in 2004 patient developed ductal carcinoma in situ. 2005 patient diagnosed with bilateral breast cancer treated with tumorectomy, radiotherapy. 2006 diagnosed with ovarian cancer treated by surgery and chemotherapy. Evidence of primary hypoparathyroidism, hypocalcemia and hypophosphatemia were all present before initiation of tenofovir DF. On an unspecified date in May 2009, eight months after commencing tenofovir DF, the patient was hospitalized for abdominal pain vomiting, deterioration of general status with 10kg weight loss in two months and biological renal insufficiency with hyponatremia at 132, hypokalemia 3.3 and hypocalcemia at 2. On 22 May 2009 tenofovir DF and lithium were dc'd. Patient was diagnosed with Fanconi's syndrome. Urine was positive for amino acids and glucose. A conclusion of Viread induced Fanconi's syndrome and lithium induced hyperparathyroidism in context of tumoral osteomalacia was made. On an unspecified date the events resolved.
11	7244054 53M	Fanconi syndrome acquired, pancytopenia, renal tubular acidosis	Tacrolimus, sirolimus, ursodeoxycholic acid, pantoprazole, ramipril, vancomycin	53-year-old male with hepatitis B and D, cirrhosis of liver, history of acute renal failure (b) (6), liver transplant (b) (6) clostridium difficile colitis, proteinuria and pancytopenia since July 2009. Started tenofovir July 09. On unspecified date tneofovir DF dose interval had been reduced to 3 times weekly due to impaired renal function in anamnesis and liver transplantation. In Jan 2010 a non respiratory acidosis was first diagnosed (suspected tubular acidosis, suspected Fanconi syndrome). Patient transferred to the ICU and administered high amounts of electrolytes resulting in rapid amelioration within a few hours. Tenofovir dc'd on 07-Jan 2010. Ser cr 1.8mg/dL, potassium 3 mmol/L (3.5-5.1), glucose 68 mg/dL (83-100), chloride 129 mmol/L (98-107), pH 7.08 (7.35-7.45), cHCo3 4.5 mmol (normal 24-32). Renal tubular acidosis was reported as not yet not resolved. Outcome unknown. (also reported under pancytopenia)
12	7326102 75M	Renal failure	Actraphane penfil '20-0-20 units'	75-year-old male patient was enrolled in the GEMINIS study (protocol GX-DE-174-0129) - 'A multicenter non-interventional prospective cohort study of chronic Hepatitis B (CHB) monoinfected patients treated with tenofovir DF'. The patient commenced tenofovir DF (one dosage form, orally, daily) on 26 Nov 2009. The patient was previously treated with adefovir and lamivudine. The patient's medical history included renal insufficiency since 17 Aug 2009 and diabetes mellitus. On 19 Nov 2009, creatinine was 1.43 mg/dl (range 0.60-0.90), glomerular filtration rate (by MDRD) was 38 ml/min (normal range 90-140 ml/min), haemoglobin was 12.6g/dL, leukocytes 3.3/uL (4.3-10.0/uL) and albumin was 66.8% (55.8-66.1). The reporter stated that at the time of enrollment into the study, the patient's serum creatinine value was 'not much too high'. On 01 March 2010, the patient experienced grade 3 (severe) aggravation of renal insufficiency. On the same date, creatinine was 4.57mg/dl, albumin was 64.3%, leukocytes were 4.3/uL and glomerular filtration rate (by MDRD) was 10

### Tenofovir DF

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*AERS data as of 3-16-2012*

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				ml/min. The reporter stated that the event was aggravation of a 'concomitant disease, known since 17 August 2009' and 'an aggravation of blood values'. On 08 March 2010, tenofovir DF was 'interrupted'. On 09 March 2010, the patient's creatinine was 4.58mg/dL. The patient was receiving co-treatment by a nephrologist however findings were still outstanding. The reporter stated that the event was continuing however it was also noted that the event abated on discontinuation of the drug. On 29 April 2010, the patient's creatinine was 2.93mg/dL.
13	7345522 37F	Blood creatinine increased, abdominal pain	NR	37-year-old female with hepatitis B, hx of hepatoma hx of resection. Started on Viread -tenofovir- 300 mg po daily -Scr baseline 0.9-. Later admitted for abd pain, also found to have acute rise scr about two weeks after starting Viread. Admit Scr 2.2. No other etiology could be identified for acute rise Scr. Suspect Viread -this was discontinued-. Scr eventually resolved to baseline.
14	7414781 60F	Fanconi syndrome acquired, bone pain, glomerular filtration rate decreased	Lamivudine	60-year-old female patient with HBV (e antigen positive), for 15 years, who commenced adefovir on 04 March 2004 and Viread (tenofovir DF, 245 mg, orally) on 20 August 2008. Concomitant medications included Lamivudine. The reporter stated that the patient was cirrhotic in 1995. After receiving treatment with lamivudine for three years, the patient developed resistance to lamivudine. As a result, treatment with adefovir dipivoxil was introduced on 04 March 2004, as an 'add on' therapy to lamivudine. The patient was treated with a combination of lamivudine and adefovir dipivoxil for four years and achieved e antigen seroconversion. On an unspecified date, renal function and eGFR (estimated Glomerular Filtration Rate) deteriorated gradually. Adefovir dipivoxil was discontinued on 20 May 2008, and the patient commenced treatment with tenofovir DF on 20 August 2008 'to prevent further renal damage'. The reporter stated that although renal function had improved, subsequently the patient's serum phosphate dropped to 0.4. On 14 January 2009, the patient experienced Fanconi syndrome with symptomatic bone pain. On 19 March 2009, tenofovir DF was discontinued and entecavir was introduced. The reporter stated that since then, the patient's symptoms have improved, phosphate level normalized and her viral load is undetectable. On 18 March 2010, the event of Fanconi syndrome was considered resolved. The patient is currently having three monthly follow up to monitor viral load and biochemistry, and six monthly follow-up for hepatocellular surveillance.
15	7575205 38F	Pancreatitis acute, renal failure acute	Steroids (5-8mg, daily, not further specified)	38-year-old female patient who commenced tenofovir DF, 1x1, orally on an unspecified date in May 2005. The patient's medical history included multiple illnesses (not further specified). The patient had one kidney and bilateral adrenal glands were taken during a cholecystectomy. On (b) (6), the patient developed pancreatitis and experienced acute tubular necrosis with anuria and was hospitalised. A suprarenalectomy was performed 'at the same time'. On the same day, creatinine was 7.5, amylase was 300, c-reactive protein (CRP) was 158.3 (units and normal range not specified) and tenofovir DF was discontinued. When the patient was taken to hospital steroid level had decreased to 16mg. On an unspecified date, amylase increased to 600 and CRP decreased to 13.9mg/L. On an unspecified date labs were as follows; sedimentation 87ml/h, lipase 669U/L, albumin 3.15/dL, leukocyte count 12900 (units not specified), AST 18U/L, ALT 13U/L and urea 144mg/dL

### Tenofovir DF

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				(normal ranges not specified). An abdominal ultrasound revealed 'the size of screened pancreas was increased and it was in heterogen echo form'. No oral nutrition was given during hospitalisation. Sulbactam+cefeperezon were given to treat the events and as a result of intensive liquid supplement the patient's renal failure recovered. Mineralcorticoids were taken 'whilst she was leaving hospital'. On 27 July 2010, the events were considered resolved and tenofovir DF was re-started without dosing adjustment.
16	7751090 60M	Osteopenia, proteinuria, blood creatinine increased	Olmesartan, insulin, OAD (for diabetes - not further specified)	60-year-old male patient with chronic hepatitis B, who commenced tenofovir DF tablets, 245mg, 22 October 2008. The patient's medical history included renal function disorder (it was reported that the patient was monitored very closely), hypertension and diabetes (for 12 years at time of this report). On an unspecified date, patient developed osteopenia and received treatment (not further specified). On 01 June 2009, the patient experienced an increase in creatinine levels at 1.4 (units and normal range not specified). On 17 February 2010, creatinine was 1.3. On 26 May 2010, the patient experienced proteinuria (+++). On 20 July 2010, creatinine was 1.5. On 28 December 2010, tenofovir DF and olmesartan were discontinued. The patient was switched to entecavir. The patient was currently closely monitored by the nephrology department of the hospital. The reporter was expecting to see the patient again in February 2011. At the time of this report, the physician stated that the events were not progressing since tenofovir DF was discontinued. The reporter also stated that the final etiology for the events of proteinuria, osteopenia and increased creatinine were due to both the patient's diabetes mellitus and treatment with tenofovir DF due to the fact that they occurred within a few months of the initiation of tenofovir DF. <i>(also reported under osteopenia)</i>
17	7880102 77M	Renal failure, cerebrovascular accident	Levothyroxine, omeprazole, perindopril, simvastatin, sertraline, allopurinol	77-year-old male patient with hepatitis B, hepatocellular carcinoma, history of neurological disorder (nos), hepatic disease, stroke, hypertension, viraemia, arteriosclerosis, hypercholesterolemia (for several years) and sporadic intake of alcohol drink (for several years). It was unknown if the patient had drug or alcohol abuse. The patient was negative for the following: renal disease, diabetes mellitus, other endocrine diseases, gastrointestinal disease, muscular and connective tissue, fluid or electrolyte disorders, cardiac disease and poor nutrition. On an unknown date in 2009, the patient started NEXAVAR (sorafenib) 200mg orally for an unspecified indication. On an unknown date in 2009, the patient started tenofovir DF 245mg orally (daily dose unspecified) for the indication of hepatitis B. The patient responded well to the tenofovir DF, with viraemia negativation and maintained the treatment with both drugs for about one year. During this same time, the patient had a stroke which debilitated him even more. On an unspecified date in Sep 2010, while received tenofovir DF, the patient was admitted to the hospital due to creatinine level of 5.44 mg/dL (normal range not specified). On 27-Sep-2010, the tenofovir DF was discontinued due to the renal insufficiency and it was decided to initiate therapy with lamivudine. The patient had advanced hepatocellular carcinoma that was worsening with a poor prognosis in the short/medium term and with low probability of resistance according to recent history. With supporting therapy and venous hydration, the patient recovered from the renal insufficiency and creatinine values were normal or

### Tenofovir DF

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				just slightly above normal. The patient continued to be followed in external appointments. Throughout this time, the hepatitis B became stable. The patient had some worsening of his general condition and also signs that showed that the hepatocellular carcinoma had progressed. Creatinine remained stable with normal values.
18	7951439 Male (age unk)	Blood creatinine increased	Entecavir	Male patient (age unkown) developed increased serum creatinine while on entecavir and tenofovir therapy. The patient was receiving entecavir 0.5mg for two years for hepatitis B. During entecavir therapy the patient's viral load was found to be undetectable. The physician prescribed tenofovir in addition to entecavir, following which the patient developed increased serum creatinine. Therapy with tenofovir was discontinued and patient was scheduled to have additional lab work within the next few weeks from the time of this report. Outcome unknown.
19	8095040 40M	Death, renal failure	NR	40-year-old male patient who commenced tenofovir DF, dosage not reported for an assumed indication of hepatitis B, on an unspecified date approximately a year ago (at the time of this report). Concomitant medications were not reported. The patient was reported to have decompensated liver disease. On an unspecified date, while receiving tenofovir DF, the patient experienced renal failure. On a further unspecified date, the patient died. No further information was provided.
20	8259671 60M	Electrolyte imbalance, renal failure, chest pain	NR	60-year-old male patient with Hepatitis B, who commenced VIREAD "a few years" ago. Concomitant medications were not reported. The patient's medical history included Hepatitis B. The patient had been on VIREAD for "a few years" and was doing fine. Then on or around Sep-2011, while receiving VIREAD, the patient experienced Renal failure, Chest pain and Electrolyte issues. His creatinine level was 3 (units and normal range unspecified). Treatment with VIREAD was discontinued. At the time of this report, the patient was maintained on a low dose Baraclude (entecavir) 0.25 milligram (mg) and was doing well. The outcomes of the Renal failure, Chest pain and Electrolyte issues were considered to be resolved.
21	8346899 39M	Blood creatinine increased, renal failure, asthenia, blood phosphorus abnormal, renal tubular disorder, glomerular filtration rate decreased	Emtricitabine	39-year-old male patient re-started on tenofovir treatment due to abnormal liver function and increasing viral load. Progressive tubular toxicity following administration of Tenofovir in combination with Emtricitabine for treatment of hepatitis B. Treatment started 8 months previously. Fluctuation of phosphate level detected 5 months into treatment with significant asthenia. Creatinine mild elevation detected 7 months into treatment, with worsening at 8 months including reduced estimated glomerular filtration rate and phosphate leak. Patient out of the country but contacted to stop medication and have renal function monitoring: results sent shows improvement.
22	8383936 53M	Osteoporosis, fracture, Fanconi syndrome acquired	Hypolipidemic drug (not further specified), insulin, oral anti-	53-year-old-male patient with Hepatitis B (diagnosed in 2004), cirrhosis, dyslipidemia, hyperlipidemia, arterial hypertension, testosterone deficiency (hypogonadism and deficit of GH in follow-up by endocrinology), hemosiderosis (heterozygous for the mutation H63D probably secondary to chronic alcoholism that has required the completion of 3 phlebotomies), liver disease, vitamin D deficiency, diabetes mellitus type 2 (with poor

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			diabetes drugs, enalapril, simvastatin	<p>metabolic control which presented organic complications: peripheral polyneuropathy, incipient diabetic nephropathy with proteinuria but with preserved renal function and diabetic retinopathy which has required photocoagulation) and polyneuropathy secondary to diabetes. The patient was noted to be a significant consumer of alcohol (chronic enolism of 60 grams) and tobacco (active smoker for 40 years/package). Patient commenced tenofovir DF, dose not specified in January 2010. Prior to commencing treatment with tenofovir DF, the patient was treated with adefovir beginning March 2008. Analytics on 28 November 2007 showed: glucose 142, creatinine 0.9, Na/K 139 5, AST/ALT 117, 126, GGT 338, FA 71, ferritin 92, Saturations 28%, Leukocytes 7,82, Hb 14.8 mg/dL, platelets 96000, alpha-fetoprotein 4.9 IU/mL, quick 91 %. HBsAg: positive, HBs AC: negative, HBcore Ac: positive, HBe Ag: Negative, HBe AC: Positive, anit HCV: negative, anti HDV: negative, viral load virus B on 25 July 2007 was 4000 IU/mL. Abdominal echo showed: hepatomegaly with hyperechogenic liver bright suggesting steatosis. Absence of space-occupying Lesions, portal vein permeable of 14.5 mm of diameter, Absence of splenomegaly. Rest unaltered. After 2 months of starting adefovir treatment the viral load of virus B decreased to 109 IU/mL and with persistence of the elevation of the transaminases (AST/ALT: 211/166, GGT: 918, total bilirubin: 0.9 ,g/dL). In January 2010, the patient went to see his consultant because he had been diagnosed with a vertebral fracture - crushing at the level of the vertebra L1 and he was remitted for assessment by orthopedic surgery or orthopedics (rachis unit). At the time, the patient presented an undetectable viral load with high transminases (AST: 111/ ALT: 68, GGT: 1823, FA: 129) And it was decided to change the antiviral treatment of adefovir 10 mg/day to tenofovir 300 mg/day. During evolution, the patient presented a progressive improvement of transaminases. In December 2010, analytical values of AST/ALT: 51/47, F/GGT: 618/718, total bilirubin: 0.33. In September 2011, the patient was evaluated for rheumatology for presenting multiple atraumatic fractures. A lumbar bone densitometry performed had showed a T score of -3.6 and a bone scan showed multiple focus of hypercaptation in ribs, condyle and neck of femur, tarsus and ankle as well as the head of the humerus, a genetic study of imperfect osteogenesis was negative. The rheumatology specialist oriented the case as a secondary osteomalacia to tenofovir and incomplete Fanconi syndrome. For this reason, the patient decided to stop the medication in September 2011. In December 2011, the patient will go to the liver unit for consultation for regular control. The patient's current laboratory results were as follows; glucose: 138, urea: 32 mg/dL, creatinine: 1.17, NA: 137, K: 6.7, Ca/q: 9.1/2.6, cholesterol: 138, triglycerides: 67000, AST/ALT: 22/11, GGT/FA: 169/397, bilirubin: 0.47, amylase lipase: 64/26, leukocytes: 5.77, Hb: 13.2, platelets: 124000, albumin: 38.8, INR: 1.22. Viral load of virus B: 44.107 IU/mL. Abdominal echo showed enlarged liver size with normal contour and diffuse alteration of the echogenicity in relation to chronic liver disease, without space-occupying lesions. Gallbladder alitiasica. Spleen of normal size. Rest without complications. At present the patient does not want any other treatment for hepatitis B virus and he decides to go for the next control in March 2012, to assess the use of other antiviral for the treatment of chronic</p>

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#### AERS cases of renal events\* in hepatitis B patients with no reported HIV-1 co-infection

N=23

\*Reported under MedDRA Preferred Terms: *blood creatinine increased, Fanconi syndrome, Fanconi syndrome acquired, renal failure, renal failure acute*

*AERS data as of 3-16-2012*

ref #	AERS case # Age/sex	Preferred terms (PTs)	Concomitant medications	Narrative/comments
				infection by virus B. The outcome of the osteoporosis, bone fracture and incomplete Fanconi Syndrome were not reported. <i>Also reported under osteoporosis.</i>
23	8426195 Female (age unk)	Clostridium difficile colitis, renal failure acute	Prograf	Female patient (age not reported) with hepatitis B (diagnosed on an unspecified date), who commenced tenofovir DF; dose not reported on an unspecified date (reported as 'since shortly'). The patient's medical history included a kidney transplant. On an unspecified date, the patient experienced Clostridium difficile pseudo-membranous colitis and on an unspecified day in December 2011, the patient experienced acute renal failure. On an unspecified date, tenofovir DF was discontinued. The reporter stated that the acute renal failure was resolved and the patient was better at the time of this report. Her renal function had normalized but her nephrologist was reluctant to re-start tenofovir DF. The outcome of the Clostridium difficile pseudo-membranous colitis was unknown.

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/s/  
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PAULA L GISH  
03/29/2012

KELLY Y CAO  
03/29/2012

# REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

**Application:** NDA 21752 S-030

**Name of Drug:** Truvada<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate) Tablets, 200mg and 300mg

**Applicant:** Gilead Sciences, Inc.

## Labeling Reviewed

**Submission Date:** December 14, 2011

**Receipt Date:** December 15, 2011

## Background and Summary Description

NDA 21752 S-30 for TRUVADA (emtricitabine/tenofovir disoproxil fumarate) Tablets was submitted on December 14, 2011 and received December 15, 2011. This supplemental application proposes a new indication for the use of TRUVADA (emtricitabine/tenofovir disoproxil fumarate) tablets, pre-exposure prophylaxis of HIV-1 infection (PrEP).

At the request of the Division, the sponsor is proposing a new REMS with a Medication Guide. Therefore, the labeling submitted to this supplement includes a package insert (PI) and a Medication Guide.

## Review

The submitted labeling was reviewed in accordance with 21 CFR 201.56 and 201.57 and relevant labeling guidance. Labeling issues are identified on the following pages with an “X.”

## Recommendations

All labeling issues identified on the following pages with an “X” will be conveyed to the applicant.

Katherine Schumann

Regulatory Project Manager

Date

Victoria Tyson

Chief, Project Management Staff

Date

# Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

## Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission. (*already granted*)
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information) <b>needs ROA</b>
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, **route of administration (ROA)**, and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and

Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:  
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)” must be present. Only include toll-free numbers.**

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).** Ask for exact wording

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

## Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)” **not exact wording**
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

25 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KATHERINE SCHUMANN  
02/24/2012

VICTORIA L TYSON  
02/27/2012