CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021752Orig1s030

PROPRIETARY NAME 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
Office of Medication Error Prevention and Risk Management
Division of Medication Error Prevention and Analysis

Medication Error Memo on Proprietary Name

Date:	June 22, 2012
From:	Kellie Taylor, Pharm.D., MPH, Deputy Director **Division of Medication Error Prevention and Analysis**
Through:	Carol Holquist, RPh., Director **Division of Medication Error Prevention and Analysis**
To:	Debra Birnkrandt, MD, Director **Division of Antiviral Products**
Drug Name(s):	Truvada (/Emtricitabine/Tenofovir) Tablets 200 mg/300 mg
Application Type/Number:	NDA 021752/S-30
Applicant/Sponsor:	Gilead Sciences
OSE RCM #:	2012-838

1 INTRODUCTION

This memorandum is to document DMEPA's evaluation of the use of the proprietary name, Truvada, for emtricitabine and tenofovir disoproxil fumarate tablets for the proposed pre-exposure prophylaxis (PrEP) indication .

1.1 BACKGROUND

Truvada is a combination product containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate in a tablet dosage formulation. Truvada was originally approved for use in combination with other antiretroviral agents such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older on August 2, 2004.

The usual dosage and administration is one tablet once daily taken orally with or without food.

The dosing interval of Truvada should be adjusted to every 48 hours in patients with baseline creatinine clearance less than 50 mL/min, and should not be used in patients with creatinine clearance less than 30 mL/min, including those patients requiring Hemodialysis.

The dosing and administration recommendations proposed for the pre-exposure prophylaxis (PrEP) indication is identical to the treatment indication.

At the Antiviral Drugs Advisory Committee (AVDAC) held on May 10, 2012, members proposed that a unique proprietary name for the PrEP indication may be warranted.

Gilead has not proposed a new proprietary name for the PrEP indication and, based on the use of the Truvada name throughout their proposed labeling materials, the firm has made it clear that their intent is to continue using the Truvada proprietary name for both the pre-exposure prophylaxis (PrEP) and treatment indications.

Although the firm, has not proposed a new proprietary name, we considered whether there is sufficient reason from a medication errors perspective to encourage the firm to use a unique proprietary name for the PrEP indication. We also considered whether the use of the Truvada name for the PrEP indication would predispose the product to medication errors.

2 ASSESSMENT AND RECOMMENDATIONS

Although the members of AVDAC recommend a unique proprietary name for the PrEP indication, we do not recommend the use of a unique proprietary name for the following reasons:

- The introduction of a new name for emtricitabine and tenofovir disoproxil fumarate tablets may confuse practitioners who may otherwise understand the drug product due to their familiarity with the product known as Truvada. Such confusion has been reported with other drug products including: Zyban (buproprion) which is also marketed as Wellbutrin, Jantoven (warfarin tablets) which is also marketed as Coumadin, and Revatio (silendifil) which is also marketed as Viagra. The confusion has resulted in adverse events with the drug products due to different types of errors including the inadvertent therapeutic duplications resulting in overdose and the administration of interacting drugs or substances due to a failure of healthcare providers to recognize the drug substance when listed as the lesser-known proprietary name. Based on this post-marketing experience, we would anticipate that the use of a unique proprietary name for emtricitabine/tenofovir disoproxil fumarate tablets has some potential to cause errors.

- The use of a unique proprietary name for the PrEP indication may not help to distinguish the patient populations. Many practitioners, facilities, and databases use the established name of drug products when prescribing, dispensing, profiling, or reporting adverse events with the product.
- We are not aware currently of any name confusion related to the Truvada name. Also, because the dosing is the same for both indications (one tablet daily) the use of the same name is not expected to cause dosing confusion with either indication.

Thus, since there would be some potential for confusion and error with the use of two names and because we do not believe the use of a single name, Truvada, for both indications to predispose this product to error, we recommend that DAVP allow the Applicant to market the name Truvada with the PrEP indication should that indication be approved. Our recommendation differs from the advice of the AVDAC, but we think that you should consider that they did not have the opportunity to consider the points we have raised in this memo when they proposed that a new proprietary name be used for the PrEP indication.

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

/s/

KELLIE A TAYLOR
06/22/2012

CAROL A HOLQUIST
06/22/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	June 20, 2012
To:	Debra Birnkrant, MD Director **Division of Antiviral Products (DAVP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TRUVADA (emtricitabine/tenofovir disoproxil fumarate)
Dosage Form and Route:	tablets
Application Type/Number:	NDA 21-752
Supplement Number:	S-030
Applicant:	Gilead Sciences, Inc.

1 INTRODUCTION

On December 15, 2011 Gilead Sciences, Inc. submitted for the Agency's review an Efficacy Prior Approval Supplement (PAS) to their approved New Drug Application, NDA 21-752/S-030, for TRUVADA (emtricitabine/tenofovir disoproxil fumarate) tablets. TRUVADA (emtricitabine/tenofovir disoproxil fumarate) tablets was originally approved on August 2, 2004 with the indication for use in combination with other antiretroviral agents (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infection in adults.

TRUVADA is currently approved with the indication 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. On January 9, 2012, the Division of Antiviral Products (DAVP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for TRUVADA (emtricitabine/tenofovir disoproxil fumarate) tablets.

This review is written in response to a request by DAVP for DMPP to review the Applicant's proposed MG for TRUVADA (emtricitabine/tenofovir disoproxil fumarate) tablets.

2 MATERIAL REVIEWED

- Draft TRUVADA (emtricitabine/tenofovir disoproxil fumarate) tablets MG received on April 11, 2012, and received by DMPP on June 5, 2012.
- Draft TRUVADA (emtricitabine/tenofovir disoproxil fumarate) tablets Prescribing Information (PI) received on December 15, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on June 5, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible

- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the Package Insert (PI) to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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Medication Guide
TRUVADA® (tru-VAH-dah)
(emtricitabine and tenofovir disoproxil fumarate)
tablets

Read this Medication Guide before you start taking TRUVADA and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about TRUVADA?

TRUVADA can cause serious side effects, including:

1. **Build-up of an acid in your blood (lactic acidosis).** Lactic acidosis is a serious medical emergency that can lead to death.

   Lactic acidosis can be hard to identify early, because the symptoms could seem like symptoms of other health problems. **Call your healthcare provider right away if you get the following symptoms which could be signs of lactic acidosis:**

   - feeling very weak or tired
   - unusual muscle pain
   - trouble breathing
   - stomach pain with
     - nausea
     - vomiting
   - feel cold, especially in your arms and legs
   - feel dizzy or lightheaded
   - have a fast or irregular heartbeat

2. **Severe liver problems.** Severe liver problems can happen in people who take TRUVADA. In some cases these liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis) when you take TRUVADA. **Call your healthcare provider right away if you get the following symptoms:**

   - Your skin or the white part of your eyes turns yellow (jaundice)
   - dark “tea-colored” urine
   - light-colored bowl movements (stools)
   - loss of appetite for several days or longer
   - nausea
   - stomach pain

You may be more likely to get lactic acidosis or severe liver problems if you are female, very overweight (obese), or have been taking TRUVADA for a long time.

3. Worsening of your hepatitis B infection. If you have hepatitis B virus (HBV) infection it may become worse (flare-up) if you take TRUVADA and then stop it. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.

- Do not run out of TRUVADA. Refill your prescription or talk to your healthcare provider before your TRUVADA is all gone.
- Do not stop taking TRUVADA without first talking to your healthcare provider.
- If you stop taking TRUVADA, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your HBV infection. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking TRUVADA.

For more information about side effects, see the section **"What are the possible side effects of TRUVADA?"**

TRUVADA is a prescription medicine used:

- with other antiviral medicines to treat Human Immunodeficiency Virus (HIV) in adults and children age 12 years and older. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).
- **with safer sex practices at all times** to reduce the risk of getting HIV in men who have sex with men who are at high risk of getting infected with HIV through sex, and heterosexual couples where one partner has HIV and the other does not. This is sometimes called Pre-Exposure Prophylaxis or PrEP.

Before taking TRUVADA to help prevent you from getting HIV:

- **You must get tested to be sure you are HIV-negative**. It is important that you also get tested at least every 3 months as recommended by your healthcare provider while taking TRUVADA. **Do not take TRUVADA to reduce the risk of getting HIV unless you are confirmed to be HIV-negative.**
- Tell your healthcare provider if you have any the following symptoms before or at any time while taking TRUVADA:
  - tiredness
  - fever
  - sweating a lot (especially at night)
  - pain
  - rash
  - vomiting
  - diarrhea
  - joint or muscle aches
  - headache
  - sore throat
  - enlarged lymph nodes in the neck or groin

These may be signs of HIV infection and may need to have a different kind of test to diagnose HIV.

- **TRUVADA by itself is not a complete treatment for HIV**. If you already have HIV or get HIV and take TRUVADA by itself without other medicines, you may develop resistance to TRUVADA.
- **Just taking TRUVADA may not keep you from getting HIV**. **TRUVADA does not always prevent HIV.**
- **You must still practice safer sex at all times**. **Do not have any kind of sex without protection**. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **You must also use other prevention methods to keep from getting HIV.**
    - Know your HIV status and the HIV status of your partners. While taking TRUVADA, get tested at least every 3 months for HIV, as recommended by your healthcare provider. Ask your partners to get tested.
    - Get tested for other sexually transmitted infections such as syphilis and gonorrhea. These infections make it easier for HIV to infect you.
    - Get information and support to help reduce risky sexual behavior.
    - Have fewer sex partners.
    - **Do not miss any doses of TRUVADA. Missing doses increases your risk of getting HIV.**
    - **See the section "What is TRUVADA?" and talk to your healthcare provider for more information about how to prevent HIV infection.**

What is TRUVADA?

TRUVADA contains the prescription medicines emtricitabine (EMTRIVA®) and tenofovir disoproxil fumarate (VIREAD®). TRUVADA is used:

- with other antiviral medicines to treat Human Immunodeficiency Virus (HIV) in adults and children age 12 years and older. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).
- **with safer sex practices at all times,** to reduce the risk of getting HIV in men who have sex with men who are at high risk of getting infected with HIV though sex, and heterosexual couples where one partner has HIV and the other does not. This is sometimes called Pre-Exposure Prophylaxis or PrEP.

It is not known if TRUVADA is safe and effective in children with HIV-1 infection who are under 12 years of age or who weigh less than 77 pounds.

When used with other HIV medicines to treat HIV-1 infection, TRUVADA may help:

1. Reduce the amount of HIV in your blood. This is called "viral load."
2. Increase the number of CD4+ (T) cells in your blood that help fight off other infections.

   Reducing the amount of HIV and increasing the CD4+ (T) cells in your blood may help improve your immune system. This may reduce your risk of death or infections that can happen when your immune system is weak (opportunistic infections).

TRUVADA does not cure HIV infection or AIDS. If you have HIV infection, you must stay on continuous HIV therapy to control HIV infection and decrease HIV-related illnesses.

Avoid doing things that can increase your risk of getting HIV infection or spreading HIV infection to other people:

- **Do not share or re-use needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Ask your healthcare provider if you have any questions on how to prevent getting HIV infection or spreading HIV infection to other people.

Who should not take TRUVADA?

Do not take TRUVADA to prevent HIV infection if you are HIV positive or if your HIV status is not known.

What should I tell my healthcare provider before taking TRUVADA?

See "What is the most important information I should know about TRUVADA?"

Before taking TRUVADA, tell your healthcare provider if you:

- have liver problems including hepatitis B virus infection
- have kidney problems or receive kidney dialysis treatment
- have bone problems
- have any other medical conditions
- **are pregnant or plan to become pregnant.** It is not known if TRUVADA can harm your unborn baby.

  If you are a female who is taking TRUVADA to prevent HIV infection and you become pregnant while taking TRUVADA, talk to your healthcare provider about whether you will continue taking TRUVADA.

Pregnancy Registry. There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of this registry 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.

- **are breastfeeding or plan to breastfeed. Do not breastfeed** if you take TRUVADA.
    - You should not breastfeed if you have HIV because of the risk of passing HIV to your baby.
    - TRUVADA can pass to your baby in your breast milk.

  Talk with your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. TRUVADA may affect the way other medicines work, and other medicines may affect how TRUVADA works.

Do not take TRUVADA if you also take:
- other medicines that contain tenofovir (ATRIPLA, COMPLERA, EMTRIVA, VIREAD)
- medicines that contain lamivudine (Combivir, Epivir, Epirvir-HBV, Epzicom, Trizivir)
- adefovir (HEPSERA)

Especially tell your healthcare provider if you take:
- didanosine (VIDEX, VIDEX EC)
- atazanavir (REYATAZ)
- lopinavir with ritonavir (KALETRA)

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take TRUVADA?

- Take TRUVADA exactly as prescribed.
- **Do not change your dose or stop taking TRUVADA without first talking with your healthcare provider**. Stay under a healthcare provider's care when taking TRUVADA.
- TRUVADA is usually taken 1 time each day. If you have kidney problems, your healthcare provider may tell you to take TRUVADA less often.
- **When used to treat HIV-1 infection, TRUVADA is always used with other HIV-1 medicines.**
- **If you take TRUVADA to reduce the risk of getting HIV, you must also use other methods to reduce your risk of getting HIV. See "What is the most important information I should know about TRUVADA?"**
- Take TRUVADA by mouth, with or without food.

- Take TRUVADA at the same time each day.
- If you miss a dose of TRUVADA, take it as soon as you remember that day. Do not take more than 1 dose of TRUVADA in a day. Do not take 2 doses at the same time to make up for a missed dose. Call your healthcare provider or pharmacist if you are not sure what to do.
- It is important that you do not miss any doses of TRUVADA or your other HIV-1 medicines.
- When your TRUVADA supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to TRUVADA and become harder to treat.
- If you take too much TRUVADA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of TRUVADA?

TRUVADA may cause the following serious side effects, including:

- **See "What is the most important information I should know about TRUVADA?"**
- **New or worse kidney problems,** including kidney failure. If you have had kidney problems in the past or need to take another medicine that can cause kidney problems, your healthcare provider may need to do blood tests to check your kidneys before you start and while you are taking TRUVADA. Your healthcare provider may tell you to take TRUVADA less often, or to stop taking TRUVADA if you have kidney problems.
- **Bone problems** can happen in some people who take TRUVADA. Bone problems include bone pain, softening or thinning (which may lead to fractures). Your healthcare provider may need to do tests to check your bones.
- **Changes in body fat can happen in people who take HIV medicines**. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these problems are not known.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having any new symptoms after starting your HIV medicine.

The most common side effects of TRUVADA include:

- diarrhea
- nausea
- tiredness
- headache
- dizziness
- depression
- problems sleeping
- abnormal dreams
- rash

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of TRUVADA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TRUVADA?

- Store TRUVADA at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep TRUVADA in its original container and keep the container tightly closed.
- Do not use TRUVADA if seal over bottle opening is broken or missing.

Keep TRUVADA and all other medicines out of reach of children.

General information about TRUVADA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TRUVADA for a condition for which it was not prescribed. Do not give TRUVADA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about TRUVADA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about TRUVADA that is written for health professionals. For more information, call 1-800-GILEAD-5 or go to www.TRUVADA.com.

What are the ingredients in TRUVADA?

Active ingredients: emtricitabine and tenofovir disoproxil fumarate

Inactive ingredients: Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch (gluten free). The tablets are coated with Opadry II Blue Y-30-10701 which contains FD&C Blue #2 aluminum lake, hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide, and triacetin.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Issued Month Year

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/s/

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06/20/2012

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