IMPORTANT DRUG WARNING

Subject: FDA-Required Risk Evaluation Mitigation Strategy (REMS) for a new indication for TRUVADA® [TRUVADA for a pre-exposure prophylaxis (PrEP) indication]

A negative HIV-1 test must be confirmed immediately before starting TRUVADA for a PrEP indication. Drug-resistant HIV-1 variants have been identified with the use of TRUVADA for a PrEP indication following undetected HIV-1 infection.

Dear Healthcare Provider:

Gilead Sciences, Inc., would like to inform you of a new indication for TRUVADA (a fixed-dose combination of emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg), approved by the FDA on July 16, 2012, for pre-exposure prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples.

The FDA has determined that a Risk Evaluation Mitigation Strategy (REMS) is necessary to ensure that the benefits of TRUVADA for a PrEP indication outweigh its risks.

The goals of the REMS for TRUVADA for a PrEP indication are:

1. To inform and educate prescribers, other healthcare providers (HCPs), and uninfected individuals at high risk for acquiring HIV-1 infection about:
   - The importance of strict adherence to the recommended dosing regimen
   - The importance of regular monitoring of HIV-1 serostatus to avoid continuing to take TRUVADA for a PrEP indication, if seroconversion has occurred, to reduce the risk of development of resistant HIV-1 variants
   - The fact that TRUVADA for a PrEP indication must be considered as only a part of a comprehensive prevention strategy in order to reduce the risk of HIV-1 infection and that other preventive measures should also be used.
Before initiating TRUVADA for a PrEP indication

You MUST obtain a negative HIV-1 status immediately before prescribing TRUVADA for a PrEP indication in an uninfected individual. Drug-resistant HIV-1 variants have been identified with use of TRUVADA for a PrEP indication following undetected HIV-1 infection.

Do NOT prescribe TRUVADA for a PrEP indication to patients with HIV-1 infection or to individuals with signs or symptoms consistent with acute HIV-1 infection, such as fatigue, fever, sweating, pain, rash, diarrhea or coughing fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and adenopathy (cervical and inguinal).

Prescriber Action

You should review and discuss the content of the Agreement Form for Initiating TRUVADA for Pre-exposure Prophylaxis of Sexually Acquired HIV-1 Infection with an uninfected individual considering or taking TRUVADA for a PrEP indication and refer to the Checklist for Prescribers regarding the management of an uninfected individual taking TRUVADA for a PrEP indication. (Access Agreement Form and Checklist via www.truvadapreprems.com)

The most important information you should know about prescribing TRUVADA for a PrEP indication to reduce the risk of acquiring HIV-1 infection is:

- TRUVADA for a PrEP indication should only be used as part of a comprehensive prevention strategy including consistent and correct use of condoms and risk reduction counseling

- All uninfected individuals at high risk for acquiring HIV-1 should only take TRUVADA for a PrEP indication after HIV-1 negative status is confirmed, to reduce the risk of development of resistant HIV-1 variants

- All uninfected individuals at high risk must strictly adhere to the recommended TRUVADA daily oral regimen
Management of Uninfected Individuals

Uninfected individuals at high risk should:

- Be counseled about safer sex practices that include consistent and correct use of condoms, knowledge of their HIV-1 status and that of their partner(s), and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission.

- Be tested to confirm that they are HIV-1 negative immediately before starting TRUVADA for a PrEP indication.

- Be tested for acute HIV-1 infection and checked for any signs or symptoms consistent with acute HIV-1 infection, such as fatigue, sweating a lot (especially at night), rash, vomiting, diarrhea, joint or muscle aches, headache, sore throat, or enlarged lymph nodes in their neck or groin.

- Be screened at least every 3 months for HIV-1 as determined by their prescriber to confirm that they are HIV-1-negative while taking TRUVADA for a PrEP indication to reduce the risk of acquiring HIV-1.

- Have their creatinine clearance calculated prior to initiating TRUVADA, and not receive TRUVADA for a PrEP indication if creatinine clearance is <60 mL/min. If a decrease in creatinine clearance is observed in uninfected individuals while using TRUVADA for PrEP, the prescriber should evaluate potential causes and potential risks and benefits of continued use.

- Be tested for the presence of hepatitis B virus (HBV) before starting on TRUVADA for a PrEP indication. Severe acute exacerbations of hepatitis B have been reported in individuals who are co-infected with HBV and HIV-1 and have discontinued TRUVADA. Uninfected individuals taking TRUVADA for a PrEP indication who are infected with HBV need close medical follow-up for several months to monitor for exacerbations of hepatitis B in the event TRUVADA is discontinued. HBV-uninfected individuals should be offered vaccination.

- Be informed about the risk of lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, which have been reported. TRUVADA should be suspended in any patient who develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness)
Be informed that TRUVADA has only 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 potential increased risk of HIV-1 infection during pregnancy.

REMS Website (www.truvadapreprems.com)

The REMS website provides access to the following:

- Specific information regarding the risks of TRUVADA for a PrEP indication
- Training and educational materials for prescribers that include safety information for uninfected individuals considering or taking TRUVADA for a PrEP indication, including the Agreement Form for Initiating TRUVADA for Pre-exposure Prophylaxis of Sexually Acquired HIV-1 Infection and Checklist for Prescribers.

Reporting Adverse Events

To report any adverse events, suspected to be associated with the use of TRUVADA for a PrEP indication, contact:

- Gilead Pharmaceuticals, Inc at 1-800-445-3235 and/or
- FDA’s MedWatch reporting system by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), or online (https://www.accessdata.fda.gov/scripts/medwatch/)

This letter is not intended as a comprehensive description of the risks associated with the use of TRUVADA for a PrEP indication. Please read the enclosed Full Prescribing Information and Medication Guide for a complete description of safety risks.

Sincerely,

Hans Reiser, MD
Senior Vice President, Medical Affairs