DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Naumann Chaudry, Pharm.D.
Director, Regulatory Affairs Advertising and Promotion
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

RE: NDA 21356, 22577
VIREAD® (tenofovir disoproxil fumarate) Tablets and Powder, for oral use
MA # 285, 3

Dear Dr. Chaudry:

As part of its routine monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed Gilead Sciences Incorporated's (Gilead) sponsored link on the internet search engine, Google.com[1], for VIREAD® (tenofovir disoproxil fumarate) tablets and powder, for oral use (Viread). The sponsored link provides evidence that Viread is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use, which renders Viread misbranded within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act) or otherwise makes its distribution violative. *See* 21 U.S.C. 355(a); 352(f); 331(a), (d); 21 CFR 201.5; 201.100; 201.115; 201.128. In addition, the sponsored link is misleading because it makes representations and/or suggestions about the efficacy of Viread, but fails to communicate any risk information associated with the use of this product. Thus, the sponsored link misbrands the drug within the meaning of the FD&C Act, and makes its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). *See* 21 CFR 202.1(e)(5). Furthermore, the sponsored link for Viread fails to present the required established name, *see* 21 CFR 201.10(g)(1); 202.1(b)(1), and Gilead did not comply with 21 CFR 314.81(b)(3)(i).

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Viread.[2] According to the INDICATIONS AND USAGE section of the FDA-approved Viread product labeling (PI) (in pertinent part):

> Viread is indicated for the treatment of chronic hepatitis B in adults and pediatric patients 12 years of age and older.

[1] http://www.google.com: Last accessed June 27, 2014.
[2] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece(s) cited in this letter.

The following points should be considered when initiating therapy with VIREAD for the treatment of HBV infection:

- The indication in adults is based on safety and efficacy data from treatment of subjects who were nucleoside-treatment-naïve and subjects who were treatment-experienced with documented resistance to lamivudine. Subjects were adults with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease.

- VIREAD was evaluated in a limited number of subjects with chronic hepatitis B and decompensated liver disease.

- The numbers of subjects in clinical trials who had adefovir resistance-associated substitutions at baseline were too small to reach conclusions of efficacy.

Viread is associated with a number of serious risks. According to the PI, Viread has a Boxed Warning regarding lactic acidosis and severe hepatomegaly with steatosis and post treatment exacerbation of hepatitis. The PI for Viread includes warnings and precautions regarding new onset or worsening of renal impairment, coadministration with other products, patients coinfected with HIV-1 and HBV, bone effects, fat distribution, immune reconstitution syndrome and early virologic failure. The most common adverse reactions in HBV-infected subjects were abdominal pain, nausea, insomnia, pruritis, vomiting, dizziness, and pyrexia.

Lack of Adequate Directions for Use

The sponsored link presents the following claim about Viread (bolded emphasis in original; underlined emphasis added):

- **Hepatitis B Prevention** – viread.com
  www.viread.com/Treating HBV
  Looking for A **Hep** B Treatment Option? Click to Learn More!

This claim misleadingly suggests that Viread is safe and effective for use in the prevention of hepatitis B. According to the PI, "Viread is indicated for the **treatment** of chronic hepatitis B in adults and pediatric patients 12 years of age and older" (bolded emphasis added). The approved labeling for Viread does not provide instructions for, or otherwise indicate that Viread will be safe and effective if used for the prevention of hepatitis B. Information sufficient to demonstrate that Viread is safe and effective for this new intended use has not been submitted to FDA in an application.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

The sponsored link cited above makes representations and/or suggestions about the efficacy of Viread (e.g., Hep B Treatment Option), but fails to communicate **any** risk information. By omitting the serious risks associated with the drug, including the Boxed Warning regarding fatal cases of lactic acidosis and severe hepatomegaly with steatosis and post treatment exacerbation of hepatitis, the sponsored link misleadingly suggests that Viread is safer than has been demonstrated. We note that the sponsored link contains a link to the product's website, www.viread.com. However, this does not mitigate the misleading omission of risk information from this promotional material.

Inadequate Presentation of Established Name

The sponsored link fails to present the established name for Viread (tenofovir disoproxil fumarate), despite the requirement to do so in direct conjunction with the proprietary name. *See* 21 CFR 201.10(g)(1); 202.1(b)(1).

Failure to Submit Under Form FDA-2253

FDA regulations require companies to submit any labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling. A copy of the Viread sponsored link was not submitted to OPDP under cover of Form FDA-2253 at the time of initial publication as required by 21 CFR 314.81(b)(3)(i).

Conclusion and Requested Action

For the reasons discussed above, the sponsored link provides evidence that Viread is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use, which renders Viread misbranded or otherwise makes its distribution violative. *See* 21 U.S.C. 355(a); 352(f); 331(a), (d); 21 CFR 201.5; 201.100; 201.115; 201.128. The sponsored link also misbrands Viread within the meaning of the FD&C Act, and makes its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). *See* 21 CFR 202.1(e)(5). Furthermore, the sponsored links for Viread fail to present the required established name, *see* 21 CFR 201.10(g)(1); 202.1(b)(1), and Gilead did not comply with 21 CFR 314.81(b)(3)(i).

OPDP requests that Gilead immediately cease violating the FD&C Act, as discussed above. Please submit a written response to this letter on or before July 11, 2014, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Viread that contain presentations such as those described above, and explaining your plan for discontinuing use of such materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include

a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA # 285, 3 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Viread comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Kemi Asante, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Samuel M. Skariah, Pharm.D.
Team Leader
Office of Prescription Drug Promotion

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

/s/

OLUWASEUN A ASANTE
06/27/2014

SAMUEL M SKARIAH
06/27/2014