DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Rebecca Coleman, Pharm.D.
Director, Regulatory Affairs
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

RE: NDA 21-356
Viread (tenofovir disoproxil fumarate) Tablets
MACMIS ID # 10666

Dear Dr. Coleman:

This letter notifies Gilead Sciences (Gilead) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified promotional activities that are in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Specifically, representatives of Gilead made both false and misleading oral statements about Viread at Gilead's promotional exhibit booth at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) held in Chicago, Illinois in December 2001.

False or Misleading Statements and Minimization of Important Risk Information

Gilead's representatives engaged in false and misleading promotional activities about a boxed warning in Viread's approved product labeling (PI). The boxed warning states that "Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals."

One Gilead representative failed to provide any risk information and instead made the following false or misleading statements about Viread to DDMAC reviewers at Gilead's promotional exhibit booth at ICAAC:

- "no toxicities"
- "extremely safe"
- "extremely well-tolerated"

Two additional Gilead representatives made the following statements:

- The boxed warning is a "product class warning, and there are no problems but it was put into the PI as a 'wait and see' warning."
- Viread "does not affect mitochondria; therefore, you would not expect to see lactic acidosis."
- The warning "is a class effect" and "our PI is the only one that does not name the drug because Viread is a nucleotide, not a nucleoside."

These statements are in violation of the Act because they minimize the boxed warning for Viread and misleadingly suggest that the drug is safer than has been demonstrated by substantial evidence. In fact, there have been case reports of lactic acidosis in patients receiving Viread in clinical trials and the expanded access program. Additionally, although in vitro studies may suggest a lack of mitochondrial toxicity, it is misleading to suggest that these conclusions from nonclinical studies have clinical significance when such has not been demonstrated by substantial evidence. Furthermore, Viread functions as a nucleoside analogue and, therefore, carries the same class warnings as other nucleoside reverse transcriptase inhibitors (NRTIs).

Furthermore, these statements are inconsistent with other risk information in the PI. Viread's PI contains a warning not to administer the drug to patients with renal insufficiency, and various precautions, such as potential drug interactions when Viread is concomitantly administered with didanosine or with drugs that reduce renal function or compete for active tubular secretion. The PI also states that treatment-related adverse events that occurred in patients receiving Viread include mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting, and flatulence.

Overstatement of Efficacy

A fourth Gilead representative also engaged in false or misleading promotional activities about the efficacy of Viread. Specifically, this representative stated that Viread "is approved for a broad indication" and characterized it as a "miracle drug." In fact, Viread was approved by the Food and Drug Administration under accelerated approval status, and the clinical benefit of Viread in HIV patients has not yet been determined. Moreover, there are substantial limitations to Viread's indication as stated in the PI:

> "VIREAD is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in a controlled study of VIREAD of 24 weeks duration and in a controlled, dose ranging study of VIREAD of 48 weeks duration. Both studies were conducted in treatment experienced adults with evidence of HIV-1 viral replication despite ongoing antiretroviral therapy. Studies in antiretroviral naïve patients are ongoing; consequently the risk-benefit ratio for this population has yet to be determined.
>
> Additional important information regarding the use of VIREAD for the treatment of HIV-1 infection:

- There are no study results demonstrating the effect of VIREAD on clinical progression of HIV.
- The use of VIREAD should be considered for treating adult patients with HIV strains that are expected to be susceptible to tenofovir as assessed by laboratory testing or treatment history."

The above oral statements made by the Gilead representative are misleading, and therefore in violation of the Act because they overstate the efficacy of Viread, and fail to communicate material facts with respect to the limitations of its indication.

Requested Actions

Gilead should immediately cease making such violative statements and should cease the distribution or use of any promotional materials for Viread that contain the same or similar violative statements. Gilead should submit a written response to DDMAC on or before March 28, 2002, describing its intent and plans to comply with the above. In its letter to DDMAC, Gilead should include the date on which this and other similarly violative materials were discontinued.

Gilead should direct its response to me by facsimile at (301) 594-6771 or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42, Room 17B-20, 5600 Fishers Lane, Rockville, MD 20857. In all future correspondence regarding this matter, please refer to MACMIS ID #10666 in addition to the NDA number. DDMAC reminds Gilead that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Laura L. Pincock, Pharm.D.
LT, USPHS
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Laura Pincock
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