DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

**TRANSMITTED VIA FACSIMILE**

John C. Martin, Ph.D.
President and Chief Executive Officer
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

**Re: NDA 21-356**
**Viread® (tenofovir disoproxil fumarate) Tablets**
**MACMIS # 11723**

# WARNING LETTER

Dear Dr. Martin:

This Warning Letter objects to Gilead Sciences, Inc.'s ("Gilead") promotional activities for Viread (tenofovir disoproxil fumarate) Tablets. Through routine monitoring and surveillance, the Food and Drug Administration's ("FDA" or the "Agency") Division of Drug Marketing, Advertising, and Communications ("DDMAC") has concluded that Gilead's promotion of Viread violates the Federal Food, Drug, and Cosmetic Act (the "Act") and its implementing regulations.

Specifically, a representative of Gilead made oral representations at Gilead's promotional exhibit booth during the 15th National HIV/AIDS Update Conference in Miami, Florida, on March 31-April 2, 2003, that minimized important risk information and broadened the indication for Viread. Your failure to disclose the fatal risks of lactic acidosis and severe hepatomegaly with steatosis reported with the use of nucleoside analogues raises significant public health and safety concerns. This conduct is particularly troubling because the more than 1,500 attendees of this conference included social workers, AIDS educators, and patients with HIV/AIDS, and you had previously been warned not to engage in such activities.

## Background

Viread was approved under the Subpart H (accelerated approval) regulations, 21 CFR 314.510, on October 26, 2001, for the following indication:

*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. 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.*

Viread is a nucleotide that shares similar structural and functional properties with nucleoside analogues approved for the treatment of HIV infection, such as its prodrug status that requires metabolic activation by cellular enzymes to form the pharmacologically active metabolite, the triphosphate form. The triphosphate form competes with the physiological substrate dATP for incorporation into nascent DNA, and causes chain termination due to lack of a sugar moiety. Viread does not require the initial phosphorylation by the nucleoside kinase of the host cells, a property that distinguishes it from currently approved nucleoside analogues. However, this property of Viread has not been demonstrated to FDA to convey a clinical advantage over nucleoside analogues.

Because Viread functions as a nucleoside analogue, the approved product labeling (PI) for Viread includes a box warning that states, "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." This warning is identical to the labeling warnings for nucleoside analogues. In vitro studies may suggest a lack of mitochondrial toxicity, but we are not aware of any studies that demonstrate that these results are predictive of in vivo lack of toxicity. Moreover, lactic acidosis has been observed in clinical trials and in your expanded access program.

On October 26, 2001, a conference call took place between Dr. Jean-Ah Choi from DDMAC and Dr. [ ] Dr. Choi provided advisory comments regarding proposed launch materials for Viread. Gilead noted the following points in its November 7, 2001, correspondence/written meeting minutes to DDMAC:

- "Dr. Choi advised that referring to Viread as a nucleotide in a way that conveyed that this confers an advantage over other drugs was not acceptable. In promotional materials references to the mechanistic descriptor "nucleotide analog" will be used without conveying that this is an advantage."
- "Comparison statements (safer than other regimens) are not supported by data and would be acceptable only if studies have been performed evaluating those questions specifically."
- Dr. Choi advised Gilead to include the "most common and most serious findings" regarding safety[1]. The most serious findings are the boxed warnings for lactic acidosis and severe hepatomegaly with steatosis.
- Dr. Choi informed Gilead that "all promotional information describing the activity of Viread should include the limitations of the data as represented in the indication."

[1] 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.

On March 14, 2002, DDMAC issued an Untitled Letter to Gilead regarding promotional activities that violate the Act. The letter explained that 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 on December 2001. Specifically, a Gilead representative failed to provide any risk information and made false or misleading representations by describing Viread as "extremely safe," "no toxicities," and "extremely well-tolerated." Two other Gilead representatives minimized the important risk information for Viread by referring to the boxed warning as a "product class warning" and "class effect." The Gilead representatives described Viread as a "nucleotide, not a nucleoside," thereby suggesting that the same safety issues do not apply. Additionally, the representatives claimed that Viread "does not affect the mitochondria," thereby implying that lactic acidosis would not be expected with Viread. Furthermore, a fourth Gilead representative grossly overstated the efficacy of Viread by characterizing it as a "miracle drug" that "is approved for a broad indication."

On March 21, 2002, Gilead responded to DDMAC's March 14, 2002, Untitled Letter. Your letter states that "Gilead has issued a memorandum to U.S. sales and marketing personnel, medical affairs staff, and all Gilead attendees at ICAAC" regarding the violations outlined in DDMAC's March 14, 2002, letter and "reminding them that such violations are inconsistent with Gilead's promotional policies." Additionally, your letter states that "Gilead takes very seriously the policy that all oral and written product promotion accurately represents the approved indication and labeling, and provides fair balance of risks and benefits of the product," and that the letter "constitutes Gilead's commitment to ensure that future violative statements are not made in the promotion of Viread." Despite your assurance that violative promotional activities would cease, your sales representative continues to violate the Act.

**Promotional Activities by Gilead's Sales Representative**

On April 2, 2003, at Gilead's promotional exhibit booth during the 15th National HIV/AIDS Update Conference, your sales representative made oral statements that minimized the risk information and broadened the indication for Viread.

Minimization of Important Risk Information

Your sales representative greatly minimized the important safety information for Viread. Your representative failed to provide **any** risk information from Viread's boxed warning concerning reported fatal cases of lactic acidosis and severe hepatomegaly with steatosis linked to the use of nucleoside analogues. Your representative claimed that the boxed warning is a "class effect warning on all nucleoside analogues" and did not apply to Viread. Furthermore, your representative referred to the totality of the adverse reactions associated with Viread as "benign." By failing to include any of the important risk information, Gilead misleadingly suggests that Viread is safer than has been demonstrated by substantial evidence or substantial clinical experience. This omission of the boxed warning together with other important risk information for Viread is particularly concerning given the serious risks associated with the drug.

Your representative also stated that because Viread is a nucleotide, not a nucleoside, it is "more potent," has "fewer side effects," and is "safer." As discussed above, it is misleading to suggest that Viread confers any clinical advantages over nucleoside analogues without supporting data. Moreover, Viread functions as a nucleoside analogue and, therefore, carries the same warnings as nucleoside

analogues. Furthermore, the Agency is not aware of any data from head-to-head clinical trials to substantiate claims of more favorable safety or efficacy with Viread over other drug products.

Broadened Indication

Your representative misleadingly broadened the indication for Viread. Your representative failed to convey that Viread is only approved for use in combination with other antiretroviral agents. It is imperative to emphasize that patients take Viread as part of an antiretroviral combination regimen because monotherapy can lead to rapid development of resistant virus, thereby decreasing the therapeutic effectiveness of the drug and reducing the susceptibility of the HIV virus to the drug. Emergence of drug resistance is a major concern in the treatment of HIV patients.

Your sales representative also stated that Viread "improves lipid parameters." FDA is not aware of substantial evidence or substantial clinical experience that supports the claim that Viread has a positive impact on patients' lipid profiles.

These oral statements by your representative recommending or suggesting use of Viread for a use other than that for which FDA has reviewed safety and effectiveness data create a new "intended use" for which adequate directions must be provided in approved product labeling. 21 U.S.C. 352(f)(1); 21 C.F.R. 201.5, 201.100, 201.128. Absent such directions, your product is misbranded. 21 U.S.C. 352(f)(1).

**Conclusions and Requested Actions**

Gilead's sales representatives have repeatedly omitted or minimized material facts regarding the safety profile of Viread, and have broadened Viread's approved indication. Due to the significant public health and safety concerns raised by these repetitive promotional activities, we request that you provide a detailed response to the issues raised in this Warning Letter. This response should contain an action plan that includes:

1) The date on which Gilead ceased dissemination of the above statements and all promotional materials that contain the same or similar statements.

2) A plan of action to disseminate accurate and complete information to the audience(s) that received the promotional statements described above.

3) A written statement of your intent to comply with "1" and "2" above.

4) A commitment to retrain your sales representatives to ensure that their promotional activities comply with your firm's policies and with applicable requirements of the Act and regulations, and an explanation of why/how you expect this retraining to succeed.

Gilead should submit a written response to DDMAC by August 12, 2003, describing its intent and plans to comply with DDMAC's request. If you have any questions or comments, please contact Debi Tran, Pharm.D. or Lesley Frank, Ph.D., J.D. by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857.

We remind you that only written communications are considered official. In all future correspondence regarding this particular matter please refer to MACMIS ID 11723 in addition to the NDA number.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your promotional campaign for Viread and may determine that additional measures will be necessary to address other conduct.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

*{See appended electronic signature page}*

Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

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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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Barbara Chong
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Signed for Thomas W. Abrams