

October 14, 2003

IMPORTANT DRUG WARNING

RE: High Rate of Virologic Failure in Patients with HIV Infection Treated With a Once-Daily Triple NRTI Regimen containing Didanosine, Lamivudine, and Tenofovir

Dear Health Care Professional,

Gilead Sciences, Inc (Gilead) is writing to inform you of a high rate of early virologic failure and emergence of nucleoside reverse transcriptase inhibitor (NRTI) resistance associated mutations observed in a clinical study of HIV-infected treatment-naïve patients receiving a once-daily triple NRTI regimen containing didanosine enteric coated beadlets (Videx[®] EC, Bristol-Myers Squibb), lamivudine (Epivir[®], GlaxoSmithKline), and tenofovir disoproxil fumarate (Viread[®], Gilead).

These new data are consistent with the high rates of virologic failure observed in several recent clinical studies that have evaluated the use of triple NRTI regimens. Based on these results:

- Tenofovir DF in combination with didanosine and lamivudine is not recommended when considering a new treatment regimen for therapy-naïve or experienced patients with HIV-infection. Patients currently on this regimen should be considered for treatment modification.

In a 24-week, single-site, pilot study (N=24) designed to evaluate the safety and efficacy of a triple NRTI once-daily regimen of didanosine EC (250 mg), lamivudine (300 mg) and tenofovir DF (300 mg) in HIV-infected treatment-naïve patients, Jemsek et al. (Oral Communication, September 2003) have identified a high frequency of virologic failure (91%), which was defined as $< 2 \log_{10}$ reduction in plasma HIV RNA level by Week 12. Resistance testing was performed on 21 patients; 20 patients (95%) had M184I/V and 10 of these patients (50%) had K65R in addition to M184V. As a result of this high early failure rate, study enrollment was stopped.

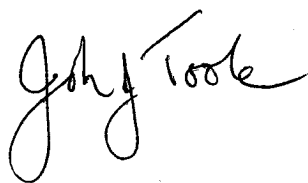
Sub-optimal virologic response has also been reported with the use of the triple NRTI regimen abacavir/lamivudine/zidovudine (Trizivir[®]) (Gulick 2003) and abacavir/didanosine/stavudine (Gerstoft 2003), and similarly early virologic failure and high rates of resistance mutations have been reported with abacavir/lamivudine/tenofovir DF (Farthing 2003, Gallant 2003). Overall, these studies demonstrate a lower response rate in patients on a triple NRTI regimen. Furthermore, they indicate that patients who achieve viral suppression on a triple NRTI regimen have a higher rate of virologic failure.

Reporting of Adverse Events

Please report all adverse events, following or coincident with the use of Viread, to Gilead Global Drug Safety at 1-800-GILEAD-5, option 3, or to the FDA MedWatch Program by phone (1-800-FDA-1088), by fax (1-800-FDA-0178), by mail (using postage-paid form to MedWatch, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787) or via the internet (www.accessdata.fda.gov/scripts/medwatch/).

We hope this information will be helpful to you in caring for your patients. Please consult the enclosed Prescribing Information for complete product information. If you have any additional questions, please contact Gilead Medical Information toll free at 1-800-GILEAD-5, option 2.

Sincerely,

A handwritten signature in black ink that reads "Jay Toole". The signature is written in a cursive, flowing style.

Jay Toole, MD, Ph.D.
Senior Vice President
Clinical Research

References: **Farthing C**, Khanlou H, Yeh V, et al. Early virologic failure in a pilot study evaluating the efficacy of once daily abacavir (ABC), lamivudine (3TC), and tenofovir DF (TDF) in treatment naïve HIV-infected patients (oral presentation). Presented at the 2nd International AIDS Society Meeting, Paris, France, July 13-16, 2003. **Gallant JE**, Rodriguez A, Weinberg W, et al. Early non-response to tenofovir DF (TDF) + abacavir (ABC) and lamivudine (3TC) in a randomized trial compared to efavirenz (EFV) + ABC and 3TC: ESS30009 unplanned interim analysis (oral presentation # H-1722a). Presented at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, September 14-17, 2003. **Gerstoft J**, Kirk O, Obel N, et al. Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine. *AIDS* 2003, 17:2045-2052. **Gulick RM**, Ribaud HJ, Shikuma CM, et al. ACTG 5095: a comparative study of 3 protease inhibitor-sparing antiretroviral regimens for the initial treatment of HIV infection. 2nd IAS Conference on HIV Pathogenesis and Treatment. July 13-16, 2003. Paris. Abstract 41.