July 2003

IMPORTANT DRUG WARNING

RE: Early Virologic Non-Response in Patients with HIV Infection Treated With Lamivudine, Abacavir and Tenofovir

Dear Health Care Provider,

GlaxoSmithKline (GSK) is writing to inform you of a high rate of early virologic non-response observed in a GSK-sponsored clinical study (ESS30009) of therapy-naive adults receiving once-daily three-drug combination therapy with lamivudine (Epivir®, GlaxoSmithKline), abacavir (Ziagen®, GlaxoSmithKline) and tenofovir (Viread(tm), TDF, Gilead Sciences). Based on these results:

* Abacavir and lamivudine in combination with tenofovir should not be used as a triple antiretroviral therapy when considering a new treatment regimen for naive or pre-treated patients.
* Any patient currently controlled on therapy with this combination should be closely monitored and considered for modification of therapy.
* Any usage of this triple combination with other antiretroviral agents should be closely monitored for signs of treatment failure.

Study ESS30009 is a randomized, open-label, multi-center study of the safety and efficacy of efavirenz (EFV 600mg daily, Sustiva®, Bristol-Myers Squibb Co.) versus tenofovir (TDF 300mg daily) when administered in combination with an investigational abacavir/lamivudine (ABC 600mg daily plus 3TC 300mg daily) fixed-dose combination tablet as a once-daily regimen in antiretroviral-naïve HIV-1 infected adults. Shortly after initiation of this study, GlaxoSmithKline received reports from investigators of poor efficacy in patients receiving TDF+3TC+ABC. An urgent, unplanned interim analysis was conducted to assess virologic non-response, defined as either (a) failure to achieve a 2 log decrease from baseline by treatment week 8 or (b) a 1 log increase above nadir on any subsequent treatment visit. Results are shown in the following table:

Number (%) of Patients Meeting the Definition of Virologic Non-Response	TDF + 3TC + ABC	EFV +3TC+ ABC
HIV-1 RNA data for subjects on therapy for > 8 weeks	50 / 102 (49%)	5 / 92 (5%)
HIV-1 RNA data for subjects on therapy for > 12 weeks	30 / 63 (48%)	3 / 62 (5%)

The precise nature of any interaction leading to non-response in this study is not known. Preliminary genotypes of viral isolates from 14 patients with non-response taking the TDF+3TC+ABC regimen have shown all 14 isolates had the M184V mutation in HIV reverse transcriptase. In addition, 8 of the 14 (57%) isolates also had the K65R mutation.

On review of these results, GSK promptly informed all participating clinical investigators and terminated the TDF+3TC+ABC arm in this study. Clinical investigators are working with patients to change therapy based on genotype and clinical judgement. The once daily EFV+3TC+ABC arm performed well and continues unchanged in this clinical study.

In addition to study ESS30009, a pilot study by Farthing et al. (2nd annual meeting of the International AIDS Society, July, 2003, Paris, France) provided data in 20 patients receiving TDF+3TC+ABC once daily for initial therapy. As in ESS30009, a high rate of virologic non-response was documented.

GlaxoSmithKline is committed to providing you with current product information for the management of your patients with HIV infection. You can assist us in monitoring the safety of our products by reporting adverse reactions to GlaxoSmithKline's Product Surveillance Department at 1-888-825-5249 or to FDA's MedWatch program by telephone at 1-800-332-1088, by fax at 1-800-332-0178, via www.FDA.gov/medwatch, or by mail to MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857.

If you have questions about the new information or want additional medical information, please contact the GlaxoSmithKline Customer Response Center at 1-888-825-5249. Thank you.

Sincerely,

Douglas J. Manion, M.D.
Vice President, Clinical Development and Medical Affairs