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This is duplicated text of a letter from **GlaxoSmithKline Inc.**
Contact the company for a copy of any references, attachments or enclosures.

**IMPORTANT SAFETY INFORMATION
REGARDING EARLY VIROLOGIC NON-RESPONSE IN PATIENTS WITH
HIV INFECTION TREATED WITH 3TC[®] (LAMIVUDINE), ZIAGEN[®] (ABACAVIR)
AND VIREAD[™] (TENOFIVIR)**



GlaxoSmithKline
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Canada L5N 6L4

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September 30, 2003

Dear Health Care Professional,

3TC[®] (lamivudine) and Ziagen[®] (abacavir), in combination with Viread[™] (tenofovir), should not be used as a triple antiretroviral therapy when considering a new treatment regimen for naïve or pre-treated HIV-1 infected patients.

Any patient currently controlled on therapy with this combination should be closely monitored and considered for modification of therapy.

Any patients using this triple combination with other antiretroviral agents should be closely monitored for signs of treatment failure.

GlaxoSmithKline (GSK) is writing to inform you of a high rate of early virologic non-response observed in a GSK-sponsored clinical study (ESS30009) being conducted in the USA in therapy-naïve adults, receiving once-daily three-drug combination therapy with 3TC[®] (lamivudine) (GlaxoSmithKline Shire BioChem), Ziagen[®] (abacavir) (GlaxoSmithKline) and Viread[™] (tenofovir) (TDF) (Gilead Sciences).

In Canada, 3TC[®] (lamivudine) and Ziagen[®] (abacavir) are approved and marketed products. Viread[™] (tenofovir) is approved (with conditions), but is not currently marketed.

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/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 in viral load from baseline by treatment week 8 or (b) a 1 log increase in viral load 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 \geq 8 weeks	50 / 102 (49%)	5 / 92 (5%)
HIV-1 RNA data for subjects on therapy for \geq 12 weeks	30 / 63 (48%)	3 / 62 (5%)

The precise nature of any interaction leading to non-response in this study is not known.

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 International AIDS Society Conference, Paris, France, July 2003) 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.

The identification, characterization, and management of drug-related adverse events are dependent on the active participation of health care professionals in adverse drug reaction reporting programs. Health care professionals are asked to report any suspected adverse reactions in patients receiving antiretroviral therapy directly to GlaxoSmithKline or to the Marketed Health Products Directorate:

GlaxoSmithKline Inc.
7333 Mississauga Road N
Mississauga, ON
L5N 6L4
Tel: 1-800-387-7374

Your professional commitment in this regard has an important role in protecting the well-being of your patients by contributing to early signal detection and informed drug use.

Any questions from health care professionals may be directed to our Medical Information department via GlaxoSmithKline Customer Service at 1-800-387-7374.

Sincerely,

original signed by

Anne Phillips, M.D., FRCPC
Vice President, Research and Development and Chief Medical Officer
GlaxoSmithKline Inc.

3TC[®] is a registered trademark, used under license by GlaxoSmithKline Shire BioChem.
ZIAGEN[®] is a registered trademark, used under license by GlaxoSmithKline Inc.

Any suspected adverse reactions can also be reported to:

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)

Marketed Health Products Directorate

HEALTH CANADA

Address Locator: 0201C2

OTTAWA, Ontario, K1A 1B9

Tel: (613) 957-0337 or Fax: (613) 957-0335

Toll free for consumers and health professionals:

Tel: 866 234-2345, Fax: 866 678-6789

cadrmp@hc-sc.gc.ca

The [AR Reporting Form](#) and the [AR Guidelines](#) can be found on the TPD web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.