

Health Canada Endorsed Important Safety Information on abacavir-containing medicinal products (Pr^rZIAGEN[®] Tablets and Oral Solution; Pr^rKIVEXA[®] Tablets; Pr^rTRIZIVIR[®] Tablets)



June 18, 2008

Dear Health Care Professional:

Subject: Potential risk of cardiac events in patients treated with ZIAGEN[®], KIVEXA[®] and TRIZIVIR[®]

GlaxoSmithKline, in consultation with Health Canada, would like to provide you with new safety information regarding a potential increased risk of myocardial infarction in HIV-infected patients treated with abacavir-containing medicinal products (ZIAGEN[®], KIVEXA[®] and TRIZIVIR[®]).

Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI) which is used in combination with other antiretrovirals in the treatment of human immune deficiency syndrome virus (HIV) infection.

GlaxoSmithKline has provided Health Canada with recent findings published in the April 26, 2008, issue of *The Lancet*¹. This new safety information is based on an ongoing prospective observational study, "*The Data collection of Adverse effects of anti-HIV Drugs (D:A:D) Study*," which was designed to quantify the incidence of myocardial infarction in HIV-infected patients receiving combination antiretroviral therapy. The D:A:D study, initiated in 1999, includes to date more than 33 000 HIV patients within 11 cohorts in Europe, USA, and Australia. Analyses of data collected up to February 1, 2007, suggest that there is a potential increased risk of myocardial infarction in HIV-infected patients treated with abacavir-containing medicinal products.

- Results from the D:A:D study available at this time suggest that current or recent use (within the past 6 months) of abacavir may be associated with a potential increased risk of myocardial infarction. This elevated risk does not appear to increase further over time, and no excess risk was present in patients who had stopped taking abacavir more than 6 months previously.
- At this time, though the available data do not allow a definitive conclusion regarding the association between the use of abacavir and an increased risk of myocardial infarction, it is recommended that physicians discuss the potential benefits and risks of abacavir with their patients.
- The overall benefit-risk profiles of abacavir-containing products should be considered, especially in patients with pre-existing serious cardiovascular diseases.

Results from the D:A:D¹ study suggest that current or recent use (within the preceding 6 months) of abacavir is associated with a potential increased risk of myocardial infarction. The relative risk

of myocardial infarction was estimated to be 1.9 (95% confidence interval (CI), 1.47-2.45; p=0.0001). The absolute myocardial infarction rate was 6.1/1000 patient years of exposure for those recently exposed to abacavir compared to an absolute myocardial infarction rate of 2.6 /1000 patient years of exposure for those not recently exposed. In addition, the absolute myocardial infarction rate ranged from 3.4 to 3.7/1000 patient years of exposure for patients recently exposed to other NRTIs (i.e. zidovudine, stavudine and lamivudine). It should be noted that the D.A.D. study is an observational study which is not designed to establish definitively whether any associations are causal.

GlaxoSmithKline has also conducted a search of its own clinical study databases. GSK's assessment of a pooled analysis of 54 GSK-sponsored clinical trials involving abacavir showed no relationship between use of abacavir and increased risk of myocardial infarction. This analysis included a total of almost 10,000 patients receiving abacavir.

At this time, Health Canada has undertaken the review of this safety data and will advise Canadians if further risk measures are deemed necessary.

GlaxoSmithKline is in contact with Health Canada and this issue will remain under close scrutiny.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any serious or unexpected adverse reactions in patients receiving **ZIAGEN[®] Tablets and Oral Solution; KIVEXA[®] Tablets; TRIZIVIR[®] Tablets** should be reported to GlaxoSmithKline or Health Canada at the following addresses:

GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4
Tel.: 1-800-387-7374
www.gsk.ca

Any suspected adverse reaction can also be reported to:

Canada Vigilance Program
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701C
OTTAWA, Ontario, K1A 0K9
Tel: (613) 957-0337 or Fax: (613) 957-0335
To report an Adverse Reaction, consumers and health professionals may call toll free:
Tel: (866) 234-2345
Fax: (866) 678-6789

CanadaVigilance@hc-sc.gc.ca

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

http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/ar-ei_form_e.html
http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/guide/ar-ei_guide-ldir_e.html

For other inquiries related to this communication, please contact Health Canada at:

Marketed Health Products Directorate

E-mail: MHPD_DPSC@hc-sc.gc.ca

Tel: (613) 954-6522

Fax: (613) 952-7738

Sincerely,

Original signed by

Dr. Tjark Reblin, MD, MBA

Vice President, Medical Division and Chief Medical Officer

GlaxoSmithKline Inc.

REFERENCES

¹D:A:D Study Group, Sabin CA, Worm SW, Weber R, *et al.* (2008) Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet*. Apr 26; **371(9622)**:1417-26.

Comment in:

Lancet. 2008 Apr 26; 371(9622):1391-2.

Lancet. 2008 Apr 26; 371(9622):1413.

[®] *KIVEXA and TRIZIVIR are registered trademarks, used under license by GlaxoSmithKline Shire Canada*

[®] *ZIAGEN is a registered trademark, used under license by GlaxoSmithKline Inc.*