CONFIDENTIAL

23 April 2008

Direct Healthcare Professional Communication on results pertaining to abacavir and didanosine from the D:A:D study

Summary

GlaxoSmithKline and Bristol-Myers Squibb, in agreement with the European Medicines Agency (EMEA) and the Irish Medicines Board (IMB) would like to provide you with new safety information concerning:

- abacavir sulfate -containing medicinal products[1] (ZIAGEN Tablets and Oral Solution; KIVEXA Tablets; TRIZIVIR Tablets), and
- didanosine -containing medicinal products[2] (VIDEX Gastro-resistant Capsules)

The D:A:D Study (Data collection of Adverse effects of anti-HIV Drugs Study) is an ongoing prospective observational study following HIV patients included within 11 cohorts in Europe, USA and Australia. The study was initiated in 1999 with the primary objective of quantifying the incidence of myocardial infarction in HIV patients who are receiving combination antiretroviral therapy.

The most recent analysis (see Lancet reference in Annex 1) from this study comprised 33,347 patients, of whom 517 developed a first myocardial infarction. Of these 517 patients, 192 had taken abacavir and 124 had taken didanosine, in the 6 months prior to their myocardial infarction:

- The relative risk of myocardial infarction associated with recent use of abacavir (within the preceding 6 months or current) was 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.
- The relative risk of myocardial infarction associated with recent use of didanosine (within the preceding 6 months or current) was 1.49 (95% CI, 1.14-1.95; p=0.003). The absolute myocardial infarction rate was

[1] Ziagen, Kivexa and Trizivir were authorised by the European Commission following the adoption of the Opinion by the EMEA scientific committee CHMP (centralised authorisation procedure)

[2] Videx was authorised by regulatory authorities in Member States (national authorisation procedure)

4.5/1000 patient years of exposure for those recently exposed to didanosine.

- No significant increased risk of myocardial infarction was noted in patients who had stopped taking these medicines more than 6 months previously, suggesting that any risk of myocardial infarction is reversible.

Further information on the safety concern

No biological mechanism linking abacavir or didanosine treatment with myocardial infarction has so far been identified.

Previous comparative clinical trials sponsored by GSK (abacavir sulfate containing medicinal products) and by BMS (didanosine containing medicinal products) have not shown increased risk for myocardial infarction with either of these medicines:

- In a pooled analysis of 54 clinical trials involving abacavir no increased risk of myocardial infarction with the use of abacavir was observed. This analysis comprised 12,498 patient years of observation (9639 subjects received abacavir containing combination antiretroviral therapy, 5044 subjects received non-abacavir containing combination antiretroviral therapy) and showed a relative risk of myocardial infarction of 0.9 (95% CI, 0.40-1.86; p=0.7) for patients treated with abacavir containing antiretroviral regimens (myocardial infarction rate: 2.0/1000 patient years of exposure) versus patients treated with non-abacavir containing regimens (myocardial infarction rate: 2.4/1000 patient years of exposure).

- In a pooled analysis of 7 clinical trials involving didanosine (almost 1500 patients, 1286 patient years of exposure) no increased myocardial infarction risk with the use of didanosine was observed.

After examination of all currently available data, the EMEA[3] and the national competent authorities[4] have considered that, presently, no definitive conclusion can be drawn on the potential association between abacavir or didanosine use and the risk of myocardial infarction. The EMEA and the national competent authorities have therefore determined that no changes to the product information are considered necessary at this time.

This issue will continue to be kept under close scrutiny. Further information on the potential association between nucleoside analogues and the risk of myocardial infarction

---

[3] The EMEA reviewed the relevant information on the centrally authorised products: Ziagen, Kivexa and Trizivir

[4] The regulatory authorities in Members States reviewed the relevant information on the nationally approved product Videx.

from other ongoing observational studies is expected later this year. The EMEA has requested the relevant information from the investigators in charge of these studies.

Further information on recommendations to healthcare professionals

Prescribers are reminded of the importance of taking appropriate action to minimise or control modifiable cardiovascular risk factors, such as smoking, hypertension, hyperlipidaemia and diabetes mellitus.

Call for reporting

GlaxoSmithKline and Bristol-Myers Squibb encourage healthcare professionals to continue to report suspected adverse reactions, pregnancy, overdose and unexpected benefits to the respective companies.

In the case of suspected adverse reactions please report to the companies using the following contact details:

For abacavir and abacavir containing medicinal products please contact GlaxoSmithKline (Ireland) Ltd., Stonemasons Way, Rathfarnham, Dublin 18 (Freephone 1800 244 255, Fax 01 4938839 or e-mail ireland.drugsurveillance@gsk.com).

For Videx Gastro-resistant Capsules please contact Bristol Myers Squibb, South County Business Park, Leopardstown, Dublin 18 (Phone number 01 291 3800 or Freephone 1800 749 749. Fax: 00 44 1895 533677 or e-mail medical.information@bms.com).

Alternatively, suspected adverse reaction reports can be sent directly to the Irish Medicines Board in the usual way.

Communication information

The latest analysis of the D:A:D study was presented as a poster at 15th Conference on Retroviruses and Opportunistic Infections (CROI) [Sabin et al, 2008], and has been published in the Lancet [D:A:D Study Group].

For further information regarding abacavir and abacavir containing medicinal products please contact GlaxoSmithKline (Ireland) Ltd., Stonemasons Way, Rathfarnham, Dublin 18 (Freephone 1800 244 255).

For further information regarding Videx Gastro-resistant Capsules please contact Bristol Myers Squibb, South County Business Park, Leopardstown, Dublin 18 (Phone number 01 291 3800 or Freephone 1800 749 749. Fax 00 44 1895 533677 or e-mail medical.information@bms.com).

Dr. Tracy Cunningham MB FRCPI AFPM
Medical Director
GlaxoSmithKline Ireland

Siobhán Mitchell.

Dr. Siobhan Mitchell BSc PhD
Medical Director
Bristol Myers Squibb Ireland

Annexes:

Annex 1: LITERATURE REFERENCE

Sabin C, Worm S, Weber R et al. Do Thymidine Analogues, Abacavir, Didanosine and Lamivudine Contribute to the Risk of Myocardial Infarction? The D:A:D Study. 15th Conference on Retroviruses and Opportunistic Infections, Boston, MA, February 3-6, 2008, Abstract 957c.

D:A:D Study Group. 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* 2008; published online April 2. DOI:10.1016/S0140-6736(08)60423-7.