EMEA PUBLIC STATEMENT

High rate of virologic failure in patients with HIV infection treated with a once-daily triple nucleosides/nucleotide reverse transcriptase inhibitors combination containing didanosine, lamivudine and tenofovir

This is new information as compared to the Public Statement of 30 July 2003 (EMEA/20194/03) regarding a different triple nucleosides/nucleotide combination containing abacavir, lamivudine and tenofovir

The European Medicines Evaluation Agency (EMEA) and its scientific committee (CPMP) have been made aware of reports of a high rate of early virologic failure and emergence of nucleoside/nucleotide reverse transcriptase inhibitor resistance associated mutations, observed in a clinical study of HIV-infected treatment-naïve patients, receiving a once-daily triple combination containing tenofovir (Viread\(^1\), TDF), lamivudine (Epivir\(^2\), 3TC), and didanosine enteric coated beadlets (Videx\(^3\) EC, ddl EC). The precise nature of any interaction leading to non-response in this study is not known.

For details of this study (Jemsek et al., oral communication, September 2003), see Annex 1.

The CPMP considered the results of the above mentioned study on 15 October 2003, and requested the marketing authorisation holder to explore further the nature of these interactions. More details on this study and study reports of any relevant ongoing studies have also been requested. As soon as available, the results will be assessed by the competent authorities and the public will be updated accordingly.

\(^1\) On 05 February 2002, the European Commission issued a marketing authorisation valid throughout the European Union for the medicinal product Viread, which contains tenofovir disoproxil fumarate. The marketing authorisation holder responsible for this medicinal product is Gilead Sciences International Ltd. Viread is approved for once-daily administration.

\(^2\) On 08 August 1996, the European Commission issued a marketing authorisation valid throughout the European Union for the medicinal product Epivir, which contains lamivudine. The marketing authorisation holder responsible for this medicinal product is GlaxoSmithKline. Epivir is approved for both once and twice-daily administration.

\(^3\) The medicinal product Videx, which contains didanosine, was authorised in France on 05 May 1992 and subsequently, in other European Concerned Member States, via mutual recognition procedure after 16 May 1997. The marketing authorisation holder responsible for this medicinal product is Bristol-Myers Squibb.
As a precautionary measure, until the nature of these interactions is further explored, the EMEA wishes to point out the following information:

**Information for physicians:**

- **When considering a new treatment regimen for treatment-naïve or previously treated patients:**
  
  Tenofovir in combination with didanosine and lamivudine should not be used when considering a new treatment regimen for therapy-naïve or experienced patients with HIV-infection and particularly, as a once a day regimen.

- **Patients well controlled on a tenofovir, didanosine and lamivudine regimen:**
  
  Any patient currently controlled on therapy with this combination should be frequently monitored with a sensitive viral load test (limit of quantification <50 copies/ml), and considered for modification of therapy at the first sign of viral load increase.

**Information for patients:**

If you are currently receiving, or if you are about to receive, an antiretroviral treatment including didanosine (Videx) and lamivudine (Epivir) in combination with tenofovir (Viread), you should inform your doctor as soon as you can.

Similar recommendations have been made by the EMEA on 30 July 2003 (http://www.emea.eu.int/pdfs/human/press/pus/2019403en.pdf) regarding a different once-daily triple combination containing abacavir, lamivudine and tenofovir (Gallant JE, et al., 2003⁴; Farthing et al., 2003⁵)

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ANNEX 1

In a 24-week, single-site, pilot study [(N=24) 20 males; 4 females; median age (range) of 39 (28 – 57) years] 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, the study was stopped.

Of 19 patients who had phenotyping results available, all samples showed susceptibility to TDF (<1.4X WT), while 5/10 patients with K65R showed reduced susceptibility to ddi (>1.7X WT).

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