The European Agency for the Evaluation of Medicinal Products
Press office

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EMEA PUBLIC STATEMENT

Efficacy and Safety concerns regarding the co-administration of tenofovir disoproxil fumarate (TDF, Viread[1]) and didanosine (ddI, Videx[2])

The European Medicines Agency (EMEA) and its Scientific Committee for human medicines (CHMP) have been made aware of new reports of virological failure and emergence of resistance following co-administration of tenofovir disoproxil fumarate and didanosine. These have been observed in several clinical studies[3-5] in which tenofovir disoproxil fumarate and didanosine were co-administered with a non-nucleoside reverse transcriptase inhibitor in HIV-infected treatment-naïve adult patients with high baseline viral load and low CD4 cell counts.

Similar reports have been previously observed with this dual combination in the context of triple combination therapy with a nucleoside/nucleotide reverse transcriptase inhibitor and were the subject of recommendations by the EMEA on 22 October 2003 (http://www.emea.eu.int/pdfs/human/press/pus/509403en.pdf). The precise nature of any interaction leading to non-response is still not known. The CHMP cannot exclude that the same findings can be observed in other contexts, as in antiretroviral experienced patients and/or in combination with protease inhibitors.

This co-administration was already considered as a safety concern due to the systemic over-exposure (40-60%) of didanosine resulting from a pharmacokinetic interaction with tenofovir. Such an over-exposure may increase the risk for didanosine-related adverse events (e.g. pancreatitis, lactic acidosis).

Based on the new clinical data the EMEA wishes to point out the following information:

- The co-administration of tenofovir disoproxil fumarate and didanosine is not recommended within any antiretroviral combination therapy, and particularly in patients with high viral load and low CD4 cell count.
- Rare, sometimes fatal, cases of pancreatitis and lactic acidosis have been reported with the co-adminstration of tenofovir and didanosine.
- If this combination is considered to be strictly necessary, patients should be closely monitored for efficacy and didanosine-related adverse events.

The Product Information for Viread has now been modified to reflect the above-mentioned information and is appended (Annex 2) to this Public Statement.

See **Annex 1** for Reference List

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ANNEX 1

REFERENCE LIST

[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] 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.

[3] **Podzamczer D**, Ferrer E, Gatell JM, Niubo J, Dalmau D, Leon A, Knobel H, Polo C, Iniguez D, Ruiz I. Early virologic failure with a combination of tenofovir, didanosine and efavirenz. Antiviral Therapy 10: 171-177, 2005.

[4] **Moyle G**, Maitland D, Hand J, Mandalia S, Nelson M, Gazzard B. Early virological failure in persons with viral loads >100000cps/ml and CD4 counts <200/mm3 receiving didanosine/tenofovir/efavirenz as initial therapy: 12 week results from a randomized comparative trial [poster]. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2004 October 30-November 2; Washington, DC, USA. Poster H-566.

[5] **Leon A**, Martinez E, Malloloas J, Laguno M, Blanco JL, Fumarola T, Gatell JM. Early virological failure in treatment-naive HIV-infected adults receiving didanosine and tenofovir plus efavirenz or nevirapine. AIDS 19(2): 213-215.

ANNEX 2

EXTRACT FROM VIREAD SPC INCLUDING CO-ADMINISTRATION WITH DIDANOSINE CHANGES HIGHLIGHTED AS ADOPTED BY THE CHMP ON 20 JANUARY 2005

4.4 Special warnings and special precautions for use

Co-administration of tenofovir disoproxil fumarate and didanosine results in a **40-60%** increase in systemic exposure to didanosine **that may increase the risk for didanosine-related adverse events (see 4.5). Rare cases of pancreatitis and lactic acidosis, sometimes fatal, have been reported.**

A reduced didanosine dose (250 mg) has been tested to avoid over-exposure to didanosine in case of co-administration with tenofovir disoproxil fumarate, but this has been associated with reports of high rate of virological failure and of emergence of resistance at early stage within several tested combinations. Co-administration of tenofovir disoproxil fumarate and didanosine is therefore not recommended, especially in patients with high viral load and low CD4 cell count. If this combination is judged strictly necessary, patients should be carefully monitored for efficacy and didanosine related adverse events.

4.5 Interaction with other medicinal products and other forms of interaction

When didanosine gastro-resistant capsules were administered 2 hours prior to or concurrently with tenofovir disoproxil fumarate, the AUC for didanosine was on average increased by 48% and 60% respectively. The mean increase in the AUC of didanosine was 44% when the buffered tablets were administered 1 hour prior to tenofovir. In both cases the pharmacokinetic parameters for tenofovir administered with a light meal were unchanged. **The co-administration of tenofovir disoproxil fumarate and didanosine is not recommended (see 4.4).**